Official Protocol Title:	A Phase 3 study of MK-4280A (coformulated favezelimab [MK-4280] plus pembrolizumab [MK-3475]) Versus Standard of Care in Previously Treated Metastatic PD-L1 positive Colorectal Cancer (KEYFORM-007)
NCT number:	NCT05600309
Document Date:	22-MAY-2023

TITLE PAGE

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Protocol Title: A Phase 3 study of MK-4280A (coformulated favezelimab [MK-4280] plus pembrolizumab [MK-3475]) Versus Standard of Care in Previously Treated Metastatic PD-L1 positive Colorectal Cancer (KEYFORM-007)

Protocol Number: 007-04

Compound Number: MK-4280A

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	Not applicable
EU CT	Not applicable
EudraCT	2021-001309-60
JRCT	Not applicable
WHO	Not applicable
UTN	Not applicable
IND	147726

Approval Date: 22 May 2023

Sponsor Signatory

Typed Name: Title:	Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 4	22-MAY-2023	This amendment was completed to address new data that emerged from external studies. CCI [redacted]
Amendment 3	18-AUG-2022	This amendment was completed in response to Health Authority requests and to clarify information.
Amendment 2	17-SEP-2021	This amendment was completed to adjust inclusion and exclusion criteria.
Amendment 1	23-JUL-2021	This amendment was completed in response to FDA comments.
Original Protocol	14-JUN-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 04

Overall Rationale for the Amendment:

The main reason for amendment is to address new data that emerged from external studies. CCI [redacted]

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
9 Statistical Analysis Plan	The SAP has been updated CCI [redacted]	This change was made to address new data that emerged from external studies. C CI [redacted]

Section Number and Name	Description of Change	Brief Rationale
Other Changes in Amendment		
Throughout Document	The structure of the protocol has been updated.	To comply with current industry regulations and guidelines. This restructuring does not affect the clinical or regulatory integrity of the protocol. All other relevant changes and their primary reasons are included for completeness.
Title Page 1.1 Synopsis	Added KEYFORM-007 to protocol title and acronym.	Revision to study branding.
2.3 Benefit/Risk Assessment	Language modified to explain that toxicity is caused by chemotherapy in previously treated mCRC.	To clarify the cause of toxicity.
4.2.1.1 Efficacy Endpoints	Added a reference CCI [redacted]	To incorporate recent study information C C I [redacted]
9.1 CCI [redacted]	CCI [redacted]	CCI [redacted]

Section Number and Name	Description of Change	Brief Rationale
CCI [redacted]		
Throughout Document	Minor administrative, formatting, grammatical, and/or typographical changes were made throughout the document.	To ensure clarity and accurate interpretation of the intent of the protocol.

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 study of MK-4280A (coformulated favezelimab [MK-4280] plus pembrolizumab [MK-3475]) Versus Standard of Care in Previously Treated Metastatic PD-L1 positive Colorectal Cancer (KEYFORM-007)

Short Title: MK-4280A (coformulation pembrolizumab plus favezelimab) Versus Standard of Care in Previously Treated Metastatic PD-L1 positive CRC

Acronym: KEYFORM-007

Hypotheses, Objectives, and Endpoints:

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Throughout this protocol, the term response evaluation criteria in solid tumors refers to the adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for further details.

In males and females with mCRC whose tumors are positive for PD-L1 CPS≥1, have pMMR status[redacted], and have progressed on or could not tolerate prior line(s) of therapy for mCRC:

Primary Objective	**Primary Endpoint**
• To compare MK 4280A to standard of care (regorafenib or TAS-102) with respect to overall survival. • Hypothesis (H1): MK-4280A is superior to standard of care with respect to overall survival.	• Overall survival: The time from randomization to death due to any cause.
Secondary Objectives	**Secondary Endpoints**
• To compare MK 4280A to standard of care with respect to progression free survival per RECIST 1.1 as assessed by BICR. • Hypothesis (H2): MK-4280A is superior to standard of care with respect to progression free survival per RECIST 1.1 by BICR.	• Progression-free survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.

• To compare MK 4280A to standard of care with respect to objective response rate per RECIST 1.1 as assessed by BICR • Hypothesis (H3): MK-4280A is superior to standard of care with respect to ORR per RECIST 1.1 by BICR.	• Objective response: complete response or partial response.
• To assess the efficacy of MK-4280A and standard of care with respect to duration of response per RECIST 1.1 by BICR.	• Duration of response: the time from first response (complete response or partial response) to subsequent disease progression or death from any cause, whichever occurs first.
• To determine the safety and tolerability of MK-4280A and standard of care.	• Adverse event • Study intervention discontinuation due to AEs
• To compare the change from baseline in global health status/QoL, physical functioning, appetite loss and bloating for MK-4280A versus standard of care.	• Score for the following Patient-Reported Outcomes scales/items: global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).
• To compare the time to deterioration in global health status/QoL, physical functioning, appetite loss and bloating for MK-4280A versus standard of care.	• Time-to-deterioration, defined as the time from baseline to the first onset of a ≥10-point deterioration from baseline in global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Colon cancer stage IV
Population	Participants with metastatic colorectal adenocarcinoma whose tumors are positive for PD-L1 CPS≥1, have pMMR status CCI [redacted], and have progressed on or could not tolerate prior line(s) of therapy. Participants must have measurable disease per RECIST 1.1 with Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-1
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active Control Without Placebo
Study Blinding	Unblinded open-label
Blinding Roles	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 36 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact. See country-specific requirements in Appendix 7.

Number of Participants:

Approximately 432 participants will be randomized. After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants from China have been enrolled to meet local regulatory requirements.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm A	MK-4280A	20 mg/mL favezelimab + 5 mg/mL pembrolizumab for a total protein content of 25 mg/mL	800 mg MK-4280 + 200 mg MK-3475	IV Infusion	Day 1, then Q3W, up to 35 infusions	Test Product
Arm B	regorafenib	40 mg/tablet	160 mg	Oral	4-week cycle: QD Days 1-21, no dose Days 22-28	Comparator
Arm B	TAS-102	15 mg trifluridine/6.14 mg tipiracil; 20 mg trifluridine/8.19 mg tipiracil	35 mg/m^2	Oral	4-week cycle: BID Days 1 to 5 and 8 to 12 of each 28-day treatment cycle (no dose days 6, 7, and 13-28)	Comparator

BID=twice daily; Exp=experimental; IV=intravenously; PD=progressive disease; PO=orally; Q3W=every 3 weeks; Q4W=every 4 weeks; QD=daily.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: NA.

Total Number of Intervention Groups/Arms	2
Duration of Participation	Each participant will participate in the study from the time that the participant provides documented informed consent through the final protocol-specified contact. After a screening phase of 28 days, each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. After the end-of-treatment, each participant will be followed for the occurrence of adverse events and spontaneously reported pregnancy. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

Executive Oversight Committee	Yes
Data Monitoring Committee	Yes
Clinical Adjudication Committee	No
Steering Committee	No

Study governance considerations are outlined in Appendix 1.

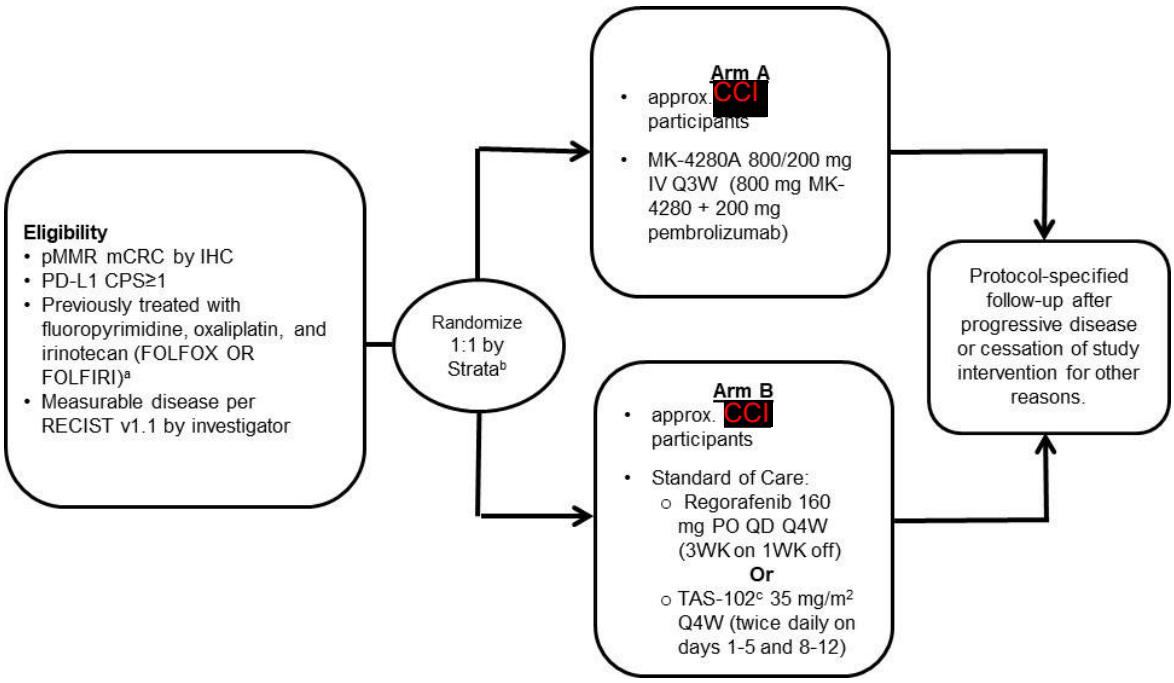
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 10.

1.2 Schema

The study design is depicted in Figure 1

Figure 1 MK-4280A-007 Study Design



CPS=combined positive score; EMEA=Europe, Middle East, Africa; FOLFIRI=folinic acid, fluorouracil, and irinotecan; FOLFOX=fluoropyrimidine, oxaliplatin, and irinotecan; IHC=immunohistochemistry; IV=intravenous; mCRC=metastatic colorectal cancer; PO=orally; PD-L1=programmed cell death ligand 1; pMMR=proficient mismatch repair; Q3W=every 3 weeks; Q4W=every 4 weeks; QD=daily; RECIST=Response Evaluation Criteria In Solid Tumors; WK=week.

[a] Capecitabine is acceptable as equivalent to IV fluoropyrimidine in prior therapy.

[b] Strata are 1) Geographic region (Asia Pacific; EMEA/Americas), 2) Presence of liver metastasis (Yes, No), and 3) Time from initial diagnosis of metastatic disease to randomization (≥18 months, <18 months).

[c] TAS-102 is a combination of trifluridine and tipiracil hydrochloride (tradename Lonsurf®).

1.3 Schedule of Activities

1.3.1 Arm A (MK-4280A)

Table 1 Arm A (MK-4280A)

Study Period	**Screening Phase**	**Intervention Phase (3-Week Cycles)**						**End of Treatment**	**Posttreatment**			**Notes**
Visit Number/Title	Screening	C1	C2	C3	C4	C5	C6-C35	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	1	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Administrative Procedures												
Informed Consent	X											If the investigator plans to treat beyond the initial radiologic disease progression per RECIST 1.1 verified by BICR, additional consent will be required prior to post-progression treatment (Section 8.1.1.1).
Informed Consent for FBR	X											Not required to participate in the study. To be obtained after consenting to the study.
Inclusion/Exclusion Criteria	X											
Participant ID Card Issued	X											At the time of Visit 1, site personnel should add the randomization number to the Participant ID card.
Medical History and Demographics	X											
CRC History	X											
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X			
Prior CRC Therapy Review	X											

Study Period	**Screening Phase**	**Intervention Phase (3-Week Cycles)**						**End of Treatment**	**Posttreatment**			**Notes**
Visit Number/Title	Screening	C1	C2	C3	C4	C5	C6-C35	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	1	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Treatment Eligibility Assessment (TEA)	X											Prior to randomization, the investigator must provide rationale for participants to receive regorafenib or TAS-102.
Randomization		X										
Poststudy Anticancer Therapy Status											X	
Survival Status		←									X	Collect for participants who have entered Survival Follow-up. Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Efficacy Assessments												
Tumor Scans (chest, abdomen, and pelvis; CT/MRI)	X	↔						X		X		The tumor scan schedule follows calendar days; do not adjust for cycle delays. Tumor scans should be performed at 9 weeks from the date of randomization (63 days ±7 days), then Q9W (63 days ±7 days) or more frequently if clinically indicated, and at discontinuation ±28-day window.
Clinical Procedures/Assessments												
MK-4280A Administration		X	X	X	X	X	X					
AE/SAE Review	X	X	X	X	X	X	X	X	X	X		Refer to Section 8.4.1 for details.
Full Physical Examination	X							X				
Directed Physical Exam		X	X	X	X	X	X					
Height	X											

Study Period	**Screening Phase**	**Intervention Phase (3-Week Cycles)**						**End of Treatment**	**Posttreatment**			**Notes**
Visit Number/Title	Screening	C1	C2	C3	C4	C5	C6-C35	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	1	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Weight	X	X	X	X	X	X	X	X				
Vital Signs	X	X	X	X	X	X	X	X				
12-Lead ECG	X		X			X	X	X	X			ECG at screening, C2D1, D1 of every third cycle (9 weeks) thereafter (eg, C5, C8, C11), EOT and Safety Follow-up Visits. Timing of ECG may be subject to local requirements.
ECOG Performance Status	X	X	X	X	X	X	X	X				Screening assessment must be within 10 days prior to first dose of study intervention. Subsequent assessments may be performed up to 72 hours prior to dosing.
LOCAL Laboratory Assessments												
RAS and BRAF Status	X											Only for participants whose RAS and BRAF status is unknown at the time of obtaining consent. The site should submit required samples to their local laboratory for testing and must provide status prior to randomization.
Urine or Serum Pregnancy Test (WOCBP only)	X	X	X	X	X	X	X	X	X			WOCBP require a negative test prior to randomization. If more than 24/72 hours have elapsed since urine/serum testing prior to first dose of study intervention, another pregnancy test is required.
Hematology	X	X	X	X	X	X	X	X	X			Screening: perform within 10 days prior to the first dose of study intervention. Perform up to 72 hours prior to dosing. If screening labs were within 72 hours of the first dose, repeat labs at Cycle 1 are not needed.
Chemistry	X	X	X	X	X	X	X	X	X			

Study Period	**Screening Phase**	**Intervention Phase (3-Week Cycles)**						**End of Treatment**	**Posttreatment**			**Notes**
Visit Number/Title	Screening	C1	C2	C3	C4	C5	C6-C35	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	1	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
PT/INR and aPTT	X											Perform within 10 days prior to the first dose of study intervention.
Urinalysis	X	X	X	X	X	X	X	X				At screening, perform within 10 days prior to the first dose of study intervention. Subsequent testing may be performed up to 72 hours prior to dosing. If urinalysis is unable to be performed, urine dipstick is acceptable. Timing of urinalysis may be subject to local requirements.
T3/FT3, T4/FT4, and TSH	X		X		X		X*	X	X			Screening: perform within 10 days prior to the first dose of study intervention. For subsequent cycles after C1D1, testing may be performed up to 72 hours prior to dosing, Participants may be dosed while thyroid function test results are pending. *After Cycle 6, perform testing on day 1 of every even number cycle.

Study Period	**Screening Phase**	**Intervention Phase (3-Week Cycles)**						**End of Treatment**	**Posttreatment**			**Notes**
Visit Number/Title	Screening	C1	C2	C3	C4	C5	C6-C35	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	1	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
ACTH/Cortisol		X1			X		X2	X	X			May perform centrally if unable to perform locally. 1At C1D1, ACTH/cortisol must be collected prior to the first dose of study intervention. Testing may be performed up to 72 hours prior to dosing. Participants may be dosed while ACTH/cortisol test results are pending. For subsequent cycles after C1D1, testing may be performed up to 72 hours prior to dosing. Participants may be dosed while ACTH/cortisol test results are pending. 2After Cycle 6, perform testing on day 1 of every even number cycle.
Serum Tumor Marker (CEA)		X	X	X	X	X	X	X	X			Perform within 72 hours prior to dosing at every cycle, Cycle 1 onwards.
HIV, Hepatitis B and C Testing	X											Not required unless mandated by local health authority.

Study Period	**Screening Phase**	**Intervention Phase (3-Week Cycles)**						**End of Treatment**	**Posttreatment**			**Notes**
Visit Number/Title	Screening	C1	C2	C3	C4	C5	C6-C35	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	1	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
CENTRAL Laboratory Assessments												
CCI [redacted]												

Study Period	**Screening Phase**	**Intervention Phase (3-Week Cycles)**						**End of Treatment**	**Posttreatment**			**Notes**
Visit Number/Title	Screening	C1	C2	C3	C4	C5	C6-C35	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	1	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
CCI [redacted]												

Study Period	**Screening Phase**	**Intervention Phase (3-Week Cycles)**						**End of Treatment**	**Posttreatment**			**Notes**
Visit Number/Title	Screening	C1	C2	C3	C4	C5	C6-C35	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	1	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Health Related Quality of Life (HRQoL)												
EQ-5D-5L EORTC QLQ-C30 EORTC QLQ-CR29		X	X	X	X	X	X*	X	X			ePROs should be done in the order in the table. It is strongly recommended that ePROs are completed prior to drug administration, adverse event evaluation and disease status notification. Collect at C1, C2, C3, C4, C5, and then every 4 cycles* thereafter (eg. C9, C13), until end of treatment or treatment discontinuation, whichever occurs first, and at the D30 posttreatment Safety Follow-up visit. A visit window of ±7 days will apply to every PRO visit assessment after C1.

ACTH= adrenocorticotrophic hormone; AE=adverse event; aPTT=activated partial thromboplastin time;CxDx=Cycle #, Day #; CEA=carcinoembryonic antigen; CRC=colorectal cancer; ctDNA=circulating tumor deoxyribonucleic acid; Discon=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30=EORTC Quality of Life Questionnaire – Core Questionnaire; EORTC QLQ-CR29=EORTC Colorectal 29; EOT=end of treatment; ePRO= electronic patient-reported outcome; EQ-5D-5L=EuroQoL 5D-5L; FBR=future biomedical research; FT3= free triiodothyronine; FT4=free thyroxine; HIV=human immunodeficiency virus; HRQoL=health related quality of life; ID=identification; MMR=mismatch repair; PD-L1=programmed cell death ligand 1;PK=pharmacokinetic; PT/INR=prothrombin time/international normalized ratio; Q9W=every 9 weeks; Q12W=every 12 weeks; QLQ=quality of life questionnaire; RECIST=response evaluation criteria in solid tumors; RNA=ribonucleic acid; SAE=serious adverse event; T3=triiodothyronine; T4=thyroxine; TEA=treatment eligibility assessment; TSH=thyroid-stimulating hormone; WOCBP=women of child bearing potential
See country-specific requirements in Appendix 7.

1.3.2 Arm B (Regorafenib)

Table 2 Arm B (Regorafenib)

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**								**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3	C4	C5	C6 Onward	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Administrative Procedures														
Informed Consent	X													
Informed Consent for FBR	X													Not required to participate in the study. To be obtained after consenting to the study.
Inclusion/Exclusion Criteria	X													
Participant ID Card Issued	X													At the time of Visit 1, site personnel should add the randomization number to the Participant ID card.
Medical History and Demographics	X													
CRC History	X													
Prior/Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X			
Prior CRC Therapy Review	X													

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**								**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3	C4	C5	C6 Onward	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Treatment Eligibility Assessment (TEA)	X													Prior to randomization, the investigator must provide rationale for participants to receive regorafenib or TAS-102.
Randomization		X												
Poststudy Anticancer Therapy Status													X	
Survival Status		←							→				X	Collect for participants who have entered Survival Follow-up. Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Efficacy Assessments														
Tumor Scans (chest, abdomen, and pelvis; CT/MRI)	X		←						→	X		X		The tumor scan schedule follows calendar days; do not adjust for cycle delays. Tumor scans should be performed at 9 weeks from the date of randomization (63 days ±7 days), then Q9W (63 days ±7 days) or more frequently if clinically indicated, and at discontinuation ±28-day window.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**								**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3	C4	C5	C6 Onward	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Clinical Procedures/Assessments														
Regorafenib Administration		←							→					Q4W: QD Days 1-21 (Weeks 1, 2, and 3), no dose Days 22-28 (Week 4). The C1D1 dose must be given to the participant at the site. Regorafenib should be dispensed to participants on day 1 of every cycle. After day 1 of each cycle, collect and record the number of regorafenib capsules returned at each visit, when applicable, for accountability and compliance purposes.
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X		Refer to Section 8.4.1 for details.
Full Physical Examination	X									X				
Directed Physical Exam		X	X	X	X	X	X	X	X					
Height	X													
Weight	X	X	X	X	X	X	X	X	X	X				

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**								**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3	C4	C5	C6 Onward	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Vital Signs	X	X	X	X	X	X	X	X	X	X				Weekly BP assessments are required from C1D1 through C2D15 and can be done at home. Arrange to have a communication (eg, telephone call) with the participant each week to receive and assess the measurement.
12-Lead ECG	X			X				X	X	X	X			ECG at screening, C2D1, D1 of every third cycle (12 weeks) thereafter (eg, C5, C8, C11), EOT and Safety Follow-up Visits. Timing of ECG may be subject to local requirements.
ECOG Performance Status	X	X	X	X	X	X	X	X	X	X				Screening assessment must be within 10 days prior to first dose of study intervention. Subsequent assessments may be performed up to 72 hours prior to dosing.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**								**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3	C4	C5	C6 Onward	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
LOCAL Laboratory Assessments														
RAS and BRAF Status	X													Only for participants whose RAS and BRAF status is unknown at the time of obtaining consent. The site should submit required samples to their local laboratory for testing and must provide status prior to randomization.
Urine or Serum Pregnancy Test (WOCBP only)	X	X		X		X	X	X	X	X	X			WOCBP require a negative test prior to randomization. If more than 24/72 hours have elapsed since urine/serum testing prior to first dose of study intervention, another pregnancy test is required.
Hematology	X	X	X	X	X	X	X	X	X	X	X			Perform within 10 days prior to the first dose of study intervention. Perform at C1 onwards: perform up to 72 hours prior to dosing at every cycle. Perform up to 72 hours prior to dosing. If screening labs were within 72 hours of the first dose, repeat labs at C1 are not needed.
Chemistry	X	X	X	X	X	X	X	X	X	X	X			

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**								**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3	C4	C5	C6 Onward	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
PT/INR and aPTT	X													Perform within 10 days prior to the first dose of study intervention.
Urinalysis	X	X		X		X	X	X	X	X				At screening, perform within 10 days prior to the first dose of study intervention. Subsequent testing may be performed up to 72 hours prior to dosing. If urinalysis is unable to be performed, urine dipstick is acceptable. Timing of urinalysis may be subject to local requirements.
T3/FT3, T4/FT4, and TSH	X			X			X		X*	X	X			Screening: perform within 10 days prior to the first dose of study intervention. For subsequent cycles after C1D1, testing may be performed up to 72 hours prior to dosing, Participants may be dosed while thyroid function test results are pending. *After Cycle 6, perform testing on day 1 of every even number cycle.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**								**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3	C4	C5	C6 Onward	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Serum Tumor Marker (CEA)		X		X		X	X	X	X	X	X			Perform within 72 hours prior to dosing at every cycle, C1 onwards.
HIV, Hepatitis B and C Testing	X													Not required unless mandated by local health authority.
CENTRAL Laboratory Assessments														
CCI [redacted]														

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**								**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3	C4	C5	C6 Onward	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Health Related Quality of Life (HRQoL)														
EQ-5D-5L EORTC QLQ-C30 EORTC QLQ-CR29		X		X		X	X		X*	X	X			ePROs should be done in the order in the table. It is strongly recommended that ePROs are completed prior to drug administration, adverse event evaluation and disease status notification. Collect at C1, C2, C3, C4, and then every 3 cycles* thereafter (eg, C7, C10), until end of treatment or treatment discontinuation, whichever occurs first, and at the D30 posttreatment Safety Follow-up visit. A visit window of ± 7 days will apply to every PRO visit assessment after C1.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**								**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3	C4	C5	C6 Onward	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	

AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; CxDx=Cycle #, Day #; CEA=carcinoembryonic antigen; CRC=colorectal cancer; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; Discon=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30=EORTC Quality of Life Questionnaire – Core Questionnaire; EORTC QLQ-CR29=EORTC Colorectal 29; EOT=end of treatment; ePRO= electronic patient-reported outcome; EQ-5D-5L=EuroQoL 5D-5L; FBR=future biomedical research; FT3=free triiodothyronine; FT4=free thyroxine; HIV=human immunodeficiency virus; HRQoL=health related quality of life; ID=identification; MRI=magnetic resonance imaging; PD-L1=programmed cell death ligand 1; PRO=patient-reported outcome; PT/INR= prothrombin time/international normalized ratio; Q9W=every 9 weeks; Q12W=every 12 weeks; QD=one a day; QLQ=Quality of Life Questionnaire; RNA=ribonucleic acid; SAE=serious adverse event; T3=triiodothyronine; T4= thyroxine; TEA=treatment eligibility assessment; TSH=thyroid-stimulating hormone; WOCBP=women of child bearing potential
See country-specific requirements in Appendix 7.

1.3.3 Arm B (TAS-102)

Table 3 Arm B (TAS-102)

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a, b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Administrative Procedures																		
Informed Consent	X																	
Informed Consent for FBR	X																	Not required to participate in the study. To be obtained after consenting to the study.
Inclusion/Exclusion Criteria	X																	
Participant ID Card Issued	X																	At the time of Visit 1, site personnel should add the randomization number to the Participant ID card.
Medical History and Demographics	X																	
CRC History	X																	
Prior/Concomitant Medication Review	X	X		X		X		X		X		X		X	X			

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a], [b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Prior CRC Therapy Review	X																	
Treatment Eligibility Assessment (TEA)	X																	Prior to randomization, the investigator must provide rationale for participants to receive regorafenib or TAS-102.
Randomization		X																
Poststudy Anticancer Therapy Status																	X	
Survival Status		←											→				X	Collect for participants who have entered Survival Follow-up. Upon Sponsor request, participants may be contacted for survival status at any time during the study.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a], [b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Efficacy Assessments																		
Tumor Scans (chest, abdomen, and pelvis; CT/MRI)	X	←											→	X		X		The tumor scan schedule follows calendar days; do not adjust for cycle delays. Scans should be performed at 9 weeks from the date of randomization (63 days ±7 days), then Q9W (63 days ±7 days) or more frequently if clinically indicated, and at discontinuation ±28-day window.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a], [b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Clinical Procedures/Assessments																		
TAS-102 Administration		←											→					Q4W: BID on Days 1-5 and on Days 8-12; no dose Days 6 and 7, and 13-28. The C1D1 dose must be given to the participant at the site. At subsequent cycles, TAS-102 is dispensed to participants on day 1 of every cycle. If for any reason both doses cannot be taken on Day 1 of each cycle (e.g., later morning or afternoon visit), the dosing schedule may be adjusted (ie, CxD1 one dose, CxD2 - CxD5 BID dosing, CxD6 one dose). After day 1 of each cycle, collect and record the number of TAS-102 capsules returned at each visit, when applicable, for accountability and compliance purposes.
AE/SAE Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Refer to Section 8.4.1 for details.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a, b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Full Physical Examination	X													X				
Directed Physical Exam		X		X		X		X		X		X						
Height	X																	
Weight	X	X		X		X		X		X		X		X				
Vital Signs	X	X		X		X		X		X		X		X				
12-Lead ECG	X			X						X		X		X	X			ECG at screening, C2D1, D1 of every third cycle (12 weeks) thereafter (eg, C5, C8, C11), EOT and Safety Follow-up Visits. Timing of ECG may be subject to local requirements.
ECOG Performance Status	X	X		X		X		X		X		X		X				Screening assessment must be within 10 days prior to first dose of study intervention. Subsequent assessments may be performed up to 72 hours prior to dosing.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a], [b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
LOCAL Laboratory Assessments																		
RAS and BRAF Status	X																	Only for participants whose RAS and BRAF status is unknown at the time of obtaining consent. The site should submit required samples to their local laboratory for testing and must provide status prior to randomization.
Urine or Serum Pregnancy Test (WOCBP only)	X	X		X		X		X		X		X		X	X			WOCBP require a negative text prior to randomization. If more than 24/72 hours have elapsed since urine/serum testing prior to first dose of study intervention, another pregnancy test is required.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a], [b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Hematology	X	X	X	X	Xc	X	X	X	X	X	X	X	X	X	X			Perform within 10 days prior to the first dose of study intervention. c C2D15 may be collected remotely.
Chemistry	X	X		X		X		X		X		X		X	X			Perform at C1 onwards: perform up to 72 hours prior to dosing at every cycle. If screening labs were within 72 hours of the first dose, repeat labs at C1 are not needed.
PT/INR and aPTT	X																	Perform within 10 days prior to the first dose of study intervention.
Urinalysis	X	X		X		X		X		X		X		X				At screening, perform within 10 days prior to the first dose of study intervention. Subsequent testing may be performed up to 72 hours prior to dosing. If urinalysis is unable to be performed, urine dipstick is acceptable. Timing of urinalysis may be subject to local requirements.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a], [b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
T3/FT3, T4/FT4, and TSH	X			X				X				X*		X	X			Screening: perform within 10 days prior to the first dose of study intervention. Participants may be dosed in subsequent cycles after C1D1 while thyroid function test results are pending. Testing may be performed up to 72 hours prior to dosing. *After Cycle 6, perform testing on day 1 of every even number cycle.
Serum Tumor Marker (CEA)		X		X		X		X		X		X		X	X			Perform within 72 hours prior to dosing at every cycle, C1 onwards.
HIV, Hepatitis B and C Testing	X																	Not required unless mandated by local health authority.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a], [b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
CENTRAL Laboratory Assessments																		
CCI [redacted]																		

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a, b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Health Related Quality of Life (HRQoL)																		
EQ-5D-5L EORTC QLQ-C30 EORTC QLQ-CR29		X		X		X		X				X*		X	X			ePROs should be done in the order in the table. It is strongly recommended that ePROs are completed prior to drug administration, adverse event evaluation and disease status notification. Collect at C1, C2, C3, C4, and then every 3 cycles* thereafter (eg, C7, C10), until end of treatment or treatment discontinuation, whichever occurs first, and at the D30 posttreatment Safety Follow-up visit. A visit window of ± 7 days will apply to every PRO visit assessment after C1.

Study Period	**Screening Phase**	**Intervention Phase (4-Week Cycles)**												**End of Treatment**	**Posttreatment**			**Notes**
Visit Number /Title	Screening	C1		C2		C3		C4		C5		C6 Onward		Discon	Safety Follow-up[a], [b]	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. [a] After Cycle 2, D15 visits are optional. [b] Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	15	1	15	1	15a	1	15a	1	15a	1	15a	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	+3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	

AE=adverse event; aPTT=activated partial thromboplastin time; CxDx=Cycle #, Day #; BID=twice daily; CEA=carcinoembryonic antigen; CRC=colorectal cancer; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; Discon=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EORTC=European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30=EORTC Quality of Life Questionnaire – Core Questionnaire; EORTC QLQ-CR29=EORTC Colorectal 29; EOT=end of treatment; ePRO=electronic patient-reported outcome; EQ-5D-5L=EuroQoL 5D-5L; FBR=future biomedical research; FT3=free triiodothyronine; FT4=free thyroxine; HIV=human immunodeficiency virus; ID=identification; MMR=mismatch repair; MRI=magnetic resonance imaging; PD-L1=programmed cell death ligand 1; PRO=patient-reported outcome; PT/INR=prothrombin time/international normalized ratio; Q4W=every 4 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; QLQ=Quality of Life Questionnaire; RNA=ribonucleic acid; SAE=serious adverse event; T3=triiodothyronine; T4= thyroxine; TEA=treatment eligibility assessment; TSH=thyroid-stimulating hormone; WOCBP=women of child bearing potential.
See country-specific requirements in Appendix 7.

2 INTRODUCTION

In the US, CRC is the third most common diagnosed cancer and the third leading cause of cancer death in both men and women [American Cancer Society 2014]. The American Cancer Society estimated that 149,500 adults would be diagnosed with CRC in 2021 in the US, with 52,980 deaths expect. The 5-year survival rate is 65% for all stages of CRC, but just 14% for patients with metastatic disease [Siegel, R. L., et al 2021]. Approximately 4.5% of men and women will be diagnosed with colon and rectum cancer at some point during their lifetime [Surveillance Research Program, NCI. 2015]. Based on the SEER Program data from 2008 to 2012, the age-adjusted incidence rate was 42.4 per 100,000 population; the incidence was higher in men (48.9 per 100,000 men) than in women (37.1 per 100,000 women). The incidence increased with age, from 0.1 per 100,000 in those between 10 and 14 years of age to 311.9 per 100,000 among those above 85 years of age [Surveillance, Epidemiology, and End Results Program 2015].

Globally, CRC represents 11% of all cancer diagnoses and is responsible for approximately 881,000 deaths worldwide [Rawla, P., et al 2019]. CRC death rates have increased in the EU from approximately 150,000 in 2015 to a projected 155,000 in 2021, in the UK alone, CRC deaths will have increased from about 20,000 to 21,000 in the same interval [Carioli, G., et al 2021]. Across all stages of disease, 95% of mCRC patients have tumors that are non-MSI-H/pMMR.

Similar to incidence patterns, mortality rates declined most rapidly in the past decade. The annual overall mortality for CRC was 15.5 per 100,000, and men had a higher mortality (18.6 per 100,000 men) than women (13.1 per 100,000 women) [Surveillance, Epidemiology, and End Results Program 2015]. On average, the 5-year survival was 65%, and survival was highest among those with localized lesions (90.1%), followed by those with regional lesions (70.8%), and was the lowest among those with distant lesions (13.1%) [Surveillance Research Program, NCI. 2015].

Despite recent advances, the intent of therapy for most mCRC participants is palliative with few patients achieving long-term survival [American Cancer Society 2017]. Current standard of care therapies for mCRC in the early-line setting include chemotherapy based on fluoropyrimidine, oxaliplatin, and irinotecan used in combination or sequentially, with option for monoclonal antibodies targeting VEGF (eg, bevacizumab, ziv-aflibercept) or its receptors (eg, ramucirumab), and in patients with RAS WT tumors, monoclonal antibodies targeting the EGFR (eg, cetuximab, panitumumab). However, therapeutic options for heavily pretreated patients beyond the second-line setting are especially limited and associated toxicities can be severe. Although regorafenib and TAS-102 are the 2 commonly accepted standard of care therapies for patients who have been treated with fluoropyrimidine-, irinotecan-, oxaliplatin-containing chemotherapies, anti-VEGF and an anti-EGFR agent (if KRAS WT), they offer minimal benefit as ORR is ≤2% for both agents [Grothey, A., et al 2013] [U.S. Prescribing Information 2012]. Minimal durability of clinical benefit is evidenced by a 6-month PFS rate of ~15%. Clearly, there is a high unmet medical need in developing novel combination regimens to improve the clinical outcome for patients with mCRC, especially in the later line treatment setting.

2.1 Study Rationale

Pembrolizumab and other anti-PD-1 agents produced durable clinical benefit in patients with mCRC with the deficient MMR/MSI-H phenotype [Le, D. T., et al 2015]. In the heavily treated mCRC setting, pembrolizumab produced high ORR, as well as evidence for durable clinical benefit [Le, D. T., et al 2015]. However, anticancer activity in CRC has been limited to cancers with the deficient MMR/MSI-H phenotype, which represents a minority (~5%) of the Stage IV mCRC population.

Because approximately 95% of mCRC patients have tumors that are neither dMMR nor MSI-H, there is a need to develop combination regimens that would provide durable clinical benefit. While high response rates from chemotherapy are reported in previously untreated mCRC population with current standard treatment, durability of clinical benefit is limited. Furthermore, therapy options for heavily pre-treated patients beyond the second-line setting are limited, and associated toxicities can be severe. Given that durable clinical benefit is the hallmark of pembrolizumab demonstrated in multiple tumor types with dMMR/MSI-H, addressing resistance to pembrolizumab in the patient population with neither dMMR nor MSI-H could improve the clinical outcome in this large segment of the population. As seen in the Phase 1 MK-4280-001 study (described below and refer to the MK-4280/MK-4280A IB for complete details), adding a LAG-3 inhibitor to pembrolizumab therapy may elicit responses in the pMMR/non-MSI-H population.

In this study, centralized testing by IHC of MMR proteins will be performed to separate the dMMR/MSI-H population from the pMMR/MSS population of colorectal cancer patients. Loss of MMR proteins correlate with abnormal microsatellite repeats [Cicek, M. S., et al 2011]. A large case series (N=3,824) from the Colon Cancer Family Registry (supplemental table 2) showed that of all patients who were evaluable for both IHC and MSI (excluding those with no IHC or equivocal IHC data, n=3,240), loss of IHC expression of at least 1 MMR protein occurred in 441 patients, of whom all but 1 met the definition of MSI-H disease (≥30% MSI markers). Conversely, 495 patients showed MSI-H genotype, but of these only 440 showed loss of IHC staining. Therefore, IHC may be more specific than PCR for selecting patients with pMMR/MSS colorectal cancer. Another study further showed concordance between MSI testing by PCR and MMR testing by IHC [Loughrey, M. B., et al 2021]. In this study, a cohort of 661 samples of Stage 2 and 3 colon cancers from a registry and biobank were tested for MMR proteins using the Ventana assay and by PCR. Of 593 cases able to be assessed by both methods, 97.1% of MSI-H cases demonstrated aberrant IHC, while 97.8% of cases with abnormal IHC were also MSI-H by PCR.

Emerging data suggest that combining PD-1/PD-L1 inhibitors with other immune modulatory agents might sensitize tumors to immunotherapy and/or provide additive efficacy. LAG-3 may be an appropriate target for coinhibition with PD-1. In a mouse model, LAG-3 appears to play an immunosuppressive role, helping to prevent autoimmunity [Topalian, S. L., et al 2012].

CD8+ T cells expressing both LAG-3 and PD-1 are the dominant TIL population in mice transplanted with CT26 colon carcinoma cells, in which LAG-3 was shown to control T-cell proliferation/cell cycle progression, resulting in a state of hypofunction [Waugh, K. A., et al

2016]. Consistent with the landmark finding that immune cells within human colorectal tumors predict clinical outcome [Galon, J., et al 2006], both in vitro and in vivo data indicate that dual blockade of LAG-3 and PD-1 potentially can have a synergistic impact on reversing tumor-specific anergy [Andrews, L. P., et al 2017]. In one example, using the MC-38 mouse model of colon derived tumor cells, PD-1 inhibition resulted in expression of LAG-3 on T cells [Beyrend, G., et al 2019]. In turn, combined PD-1 and LAG-3 blockade delayed tumor growth and enhanced survival.

In CRC patients, LAG-3 was overexpressed on colorectal immune cells, and correlated with poor differentiation, advanced stage, lymph node involvement, and invasion depth (T stage) [Chen, J. 2014]. Also, among MSI-H colon cancer patients, LAG-3 expression was associated with shorter relapse-free survival and correlated with tumor cell PD-L1 expression [Lee, S. J., et al 2017].

Favezelimab Alone and in Combination with Pembrolizumab in CRC

Clinical data in participants with MSS CRC treated with favezelimab alone and in combination with pembrolizumab in the first-in-human MK-4280-001 study is available (refer to the MK-4280/MK-4280A IB for complete details). Eligible participants with MSS PD-1/PD-L1-treatment-naïve mCRC that progressed on all prior therapies (3L+) were enrolled (Cohort A) to receive the recommended Phase 2 dose of 800 mg favezelimab alone, 800 mg favezelimab + 200 mg pembrolizumab, or 800 mg favezelimab + 200 mg pembrolizumab (MK-4280A) coformulation, all Q3W. Treatment continued for 35 cycles or until progression, unacceptable toxicity, or investigator/participant decision to withdraw from study intervention. Participants with confirmed progression per iRECIST 1.1 on favezelimab alone could crossover to 800 mg favezelimab + pembrolizumab.

A total of 20 participants received favezelimab monotherapy (Cohort A, Arm 1); 89 (including 9 crossover) received favezelimab + pembrolizumab (either as separate agents or as a coformulation; Cohort A, Arms 2C and 5). At data cutoff, median follow-up was 5.8 months in the favezelimab arm and 6.2 months in the favezelimab + pembrolizumab/MK-4280A arms. TRAEs were 65.0% with favezelimab and 65.2% with favezelimab + pembrolizumab/MK-4280A. Grade ≥3 TRAEs were 15.0% (favezelimab), and

20.2% favezelimab + pembrolizumab/MK-4280A). No Grade 5 TRAEs were reported. Common TRAEs (≥15.0%) included fatigue (20.0%) and nausea (15.0%) with favezelimab, and fatigue (16.9%) with favezelimab + pembrolizumab/MK-4280A [Garralda, E., et al 2021].

The efficacy population included 20 participants who received favezelimab monotherapy and 80 participants who received favezelimab + pembrolizumab, of which 12 and 36 participants, respectively, had PD-L1 CPS ≥1 tumors. Confirmed ORR was 0% in participants receiving favezelimab and 6.3% (4 PR, 1 CR) with favezelimab + pembrolizumab/MK-4280A. The ORR was 11.1%, 4 of 36 participants with tumors expressing PD-L1 CPS≥1 received favezelimab + pembrolizumab/MK-4280A. In the favezelimab + pembrolizumab/MK-4280A arms, median DOR was 10.6 months (range: 5.6-12.7 months). The median OS and 12-month OS rate in participants who received favezelimab + pembrolizumab/MK-4280A was 8.3 months (range: 5.5-12.9 months) and 40.8% in the ITT population, and 12.7 months (range: 4.5 months-NR) and 50.6% in participants with tumors expressing PDL-1 CPS≥1. The median PFS and 6-month PFS rate in participants receiving favezelimab + pembrolizumab/MK-4280A was 2.1 months (range: 1.9-2.2 months) and 16.2% in the ITT population, and 2.2 months (range: 1.8-4.2 months) and 25.4% in participants with tumors expressing PD-L1 CPS≥1 [Garralda, E., et al 2021].

Overall, favezelimab alone or in combination with pembrolizumab had a manageable safety profile, with no treatment-related deaths. Promising antitumor activity was observed with favezelimab + pembrolizumab/MK-4280A therapy compared with monotherapy and was enhanced in participants with PD-L1 CPS ≥1 tumors [Garralda, E., et al 2021].

Additional evidence for PD-L1 as a prognostic and potentially predictive biomarker comes from the IMblaze 370 study [Eng, C., et al 2019], where 3L MSS CRC participants were treated with either regorafenib (control arm) or atezolizumab ± cobimetinib (experimental arms). In a subgroup analysis, atezolizumab-treated participants showed a trend towards improved median OS in PD-L1 positive participants (HR 0.90; 95% CI: 0.58-1.41, median OS ~8.5 vs. 6.5 months on the Kaplan-Meier chart). In PD-L1 negative participants, conversely, the trend in OS favored regorafenib with a HR of 1.42 (95% CI: 0.94-2.14, median OS from the Kaplan-Meier graph is roughly 9 months for regorafenib treated participants vs approximately 7 months for atezolizumab-treated participants).

The MK-4280-001 and IMblaze 370 studies, therefore, suggest that an immunotherapeutic approach may be appropriate for participants with PD-L1 positive tumors. For this reason, the current study is designed to demonstrate an overall improvement in survival with MK-4280A, as compared to standard available therapy (regorafenib or TAS-102), among patients with PD-L1 positive MSS tumors refractory to cytotoxic chemotherapy.

Favezelimab Alone and in Combination With Pembrolizumab in Solid Tumors or Hematologic Malignancies

Safety data from MK-4280-001 as of 23-OCT-2020 included 38 participants treated with favezelimab monotherapy and 340 participants treated with favezelimab and pembrolizumab (administered separately or as a coformulation). In the favezelimab arm, 94.7% of

participants experienced an AE, and 63.2% experienced a TRAE. 10.5% of participants had a Grade 3-5 TRAE and 2.6% had an SAE that was considered treatment related. 1 participant (2.6%) discontinued due to a serious TRAE. In the favezelimab + pembrolizumab arms, 96.6% of participants experienced an AE, and 62.5% experienced a TRAE. 18.9% of participants had a Grade 3-5 TRAE and 6.6% had an SAE that was considered treatment related. 10.9% of participants discontinued due to a TRAE, 2.9% discontinued due to a serious TRAE. There were no treatment-related deaths on either favezelimab or favezelimab + pembrolizumab arms. The most common AEs for participants receiving favezelimab in combination with pembrolizumab (occurring in >20% of participants, excluding the chemotherapy arm) include fatigue (28.4%), nausea (23.8%), and decreased appetite (20.9%).

As of 23-OCT-2020, efficacy data are available for the participants treated in the dose escalation portion (Part A) of the study in participants with advanced solid tumors with no available therapy expected to benefit. These data include 18 participants treated with favezelimab monotherapy and 15 participants treated with favezelimab + pembrolizumab combination therapy at doses ranging from 7 mg to 700 mg. In participants treated on the combination arm at all favezelimab doses, the ORR was 26.7%, with 4 of 15 participants having confirmed partial responses. DCR was 40.0% (95% CI: 16.3, 67.7). By contrast, in participants treated on the monotherapy arm at all doses, the ORR was 5.6%, with 1 participant having a confirmed partial response. DCR was 16.7% (95% CI: 3.6, 41.4). Moreover, these data show improved efficacy for favezelimab given in combination with pembrolizumab over favezelimab alone in this cohort of mixed solid tumors [Lakhani, N., et al 2018].

MK-4280-001 also included assessment of the safety and biocomparability of separately administered 800 mg favezelimab and pembrolizumab with coformulated MK-4280A. Based on a preliminary population PK analysis as of 23-OCT-2020, favezelimab serum concentrations after MK 4280A coformulation product dosing (800 mg favezelimab + 200 mg pembrolizumab) overlapped predicted exposures from 800 mg favezelimab + pembrolizumab sequential dosing. The safety profile for participants receiving MK-4280A was consistent with the known safety profile of participants receiving sequential administration of 800 mg favezelimab and pembrolizumab. The efficacy was comparable between sequentially administered favezelimab + pembrolizumab (n=41) compared to coformulated MK-4280A (n=39) in participants with MSS CRC, ORR 7.3% (95% CI: 1.5, 19.9) and 5.1% (95% CI: 0.6, 17.3), respectively, and DCR was 24.4% (95% CI: 12.4, 40.3) and 30.8% (95% CI: 17.0, 47.6), respectively. Therefore, data available to date support that favezelimab and pembrolizumab administered separately or as MK-4280A show comparable PK, safety, and efficacy.

2.2 Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. Keytruda® (pembrolizumab) is indicated

for the treatment of patients across several indications. For more details on specific indications refer to the IB.

Favezelimab binds to the immune checkpoint receptor LAG-3 and blocks the interaction of LAG-3 with MHC Class II ligands. Favezelimab has also been shown to have an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. For more details, refer to the MK-4280/MK-4280A IB.

Given the Sponsor's observation of enhanced antitumor activity of anti-LAG-3 when combined with PD-1 blockade in nonclinical models, the Sponsor has developed a coformulated product of favezelimab and pembrolizumab (referred to as MK-4280A). MK-4280A is a fixed-dose combination of favezelimab and pembrolizumab antibodies. The single vial presentation could provide significant benefit to patients and providers, including simplified preparation and reduced infusion times compared with separate formulations. The Sponsor's ongoing Phase 1 study (MK-4280-001) will evaluate the safety, efficacy, and biocomparability of this coformulated product with that of the sequential administration of favezelimab and pembrolizumab.

2.2.1 Pharmaceutical and Therapeutic Background

2.2.1.1 Pembrolizumab Pharmaceutical and Therapeutic Background

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

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV-type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the

immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in colorectal cancer.

2.2.1.2 Favezelimab Pharmaceutical and Therapeutic Background

LAG-3 is an inhibitory immune modulatory receptor that regulates effector T-cell homeostasis, proliferation, and activation, and has a role in the suppressor activity of Tregs [Huang, C. T., et al 2004] [Baixeras, E., et al 1990] [Goldberg, M. V. 2011]. LAG-3 is expressed on activated CD8+ and CD4+ T cells, Tregs and the Tr1 regulatory T-cell population, as well as on natural killer cells and a subset of tolerogenic plasmacytoid dendritic cells [Huard, B., et al 1994] [Workman, C. J., et al 2009] [Gagliani, N., et al 2013]. Because of its proposed role on both effector T cells and Tregs, LAG-3 is one of several immune checkpoint molecules where simultaneous blockade of both cell populations has the potential to enhance antitumor immunity [Andrews, L. P., et al 2017].

LAG-3 is structurally related to CD4 and a member of the Ig superfamily. Like CD4, its ligand is MHC Class II molecules [Huard, B., et al 1995] [Triebel, F., et al 1990]. Interaction with its ligand leads to dimerization and signal transduction resulting in altered T-cell activation. Following T-cell activation, LAG-3 is transiently expressed on the cell surface. A large proportion of LAG-3 molecules are found in intracellular stores and can be rapidly translocated to the cell membrane upon T-cell activation [Woo, S. R., et al 2010]. LAG-3 expression is regulated at the cell surface by extracellular cleavage to yield a soluble form of LAG-3 (sLAG-3), which can be detected in serum [Li, N., et al 2007]. Expression of LAG-3 is tightly regulated and represents a self-limiting mechanism to counter uncontrolled T-cell activity.

LAG-3 is commonly coexpressed with PD-1 on anergic/exhausted T-cells, and both in vitro and in vivo data indicate that dual blockade of LAG-3 and PD-1 can have a synergistic impact on reversing tumor-specific anergy [Camisaschi, C., et al 2010] [Matsuzaki, J., et al 2010].

In samples collected from human patients, LAG-3 and PD-1 coexpression has been correlated with T-cell anergy/exhaustion. For example, tumor samples collected from patients with ovarian cancer contained NY ESO 1 specific CD8+ T cells that coexpressed high levels of PD-1 and LAG-3 [Matsuzaki, J., et al 2010]. In vitro dual blockade of these 2 pathways was able to improve the T cells' ability to produce IFN γ and proliferate, while blockade of either pathway on its own did not. Additionally, LAG-3 expression on Tregs has been shown to correlate with the production of cytokines traditionally thought to have an immunosuppressive role (eg, IL-10, TGF-β1) [Camisaschi, C., et al 2010]. LAG-3 expression has been identified on tumor-infiltrating Tregs in patients with head and neck squamous cell cancer and NSCLC as well as on tumor-infiltrating CD4+ Foxp3- (Tr1) cells in patients with

CRC [Jie, H. B., et al 2013] [Wei, T., et al 2015] [Chen, J. 2014]. In the patients with CRC, the presence of these LAG-3+ Tr1 cells expressing IL-10 was associated with disease progression [Scurr, M., et al 2014].

The use of favezelimab alone and in combination with other immune checkpoint inhibitors will be tested to potentially activate T-cells to enhance tumor killing in multiple human cancers that have not responded to other available therapies.

2.2.2 Preclinical and Clinical Studies

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other therapeutic modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and CRC. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [Ropponen, K. M., et al 1997] [Dudley, M. E., et al 2005] [Hunder, N. N., et al 2008] [Pölcher, M., et al 2010] [Okazaki, T., et al 2001] [Greenwald, R. J., et al 2005]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the pembrolizumab IB).

In the literature there are reports of co-blockade of PD-1 and LAG-3 with blocking antibodies in syngeneic mouse tumor models. Co-blockade was reported to result in greater tumor inhibition over either single agent in the Sal1N fibrosarcoma and MC38 colon adenocarcinoma tumor models [Woo, S. R., et al 2012]. However, co-blockade had little effect on the poorly immunogenic B16F10 melanoma model [Chen S, Lee LF, Fisher TS, Jessen B, 2015]. Blockade of LAG-3 alone had modest antitumor activity in the MBT-2 bladder syngeneic mouse tumor model, whereas coblockade of LAG-3 and PD-1 (with 28G10-mG1) resulted in greater numbers of animals with CRs and fewer numbers of animals with progressive disease compared to murinized anti-PD-1 alone in 2 independent studies. Loss of drug exposures over the course of therapy, preferentially in the combination therapy group, may underestimate the combination antitumor benefit. Curative murinized anti PD 1 therapy or murinized anti-PD-1 and anti-LAG-3 combination therapy resulted in the establishment of long-term immune memory to MBT-2 tumor rechallenge.

2.2.3 Ongoing Clinical Studies

2.2.3.1 Ongoing Pembrolizumab Clinical Studies

Clinical trials have shown pembrolizumab monotherapy efficacy in participants with many different indications including advanced melanoma, NSCLC, head and neck cancer, bladder cancer, Hodgkin Lymphoma, triple negative breast cancer, gastric adenocarcinoma, and MSI-H cancers.

In KEYNOTE-016, participants with progressive mCRC were treated with pembrolizumab at 10 mg/kg every 2 weeks. As of JAN-2015, the primary endpoint, immune-related ORR in Cohort A with dMMR was 40% (4 of 10 participants), and the immune-related PFS rate at 20 weeks was 78% (7 of 9 participants). In Cohort B, which included participants with non-MSI-H or MSS colorectal adenocarcinoma, the immune-related ORR was 0% (0 of 18 participants), and the immune-related PFS rate at 20 weeks was 11% (2 of 18 participants) [Le, D. T., et al 2015]. KEYNOTE-028 screened a cohort of 137 participants with mCRC, including 33 (24%) with PD-L1-positive tumors, of which 23 participants were enrolled and treated with pembrolizumab. As of the data cutoff 20-JUN-2016, there was only one PR (4%) from the only participant who had MSI-H CRC. The ORR in MSS CRC was 0% (0 of 22) from this study [O'Neil, B. H., et al 2017]. In summary, pembrolizumab monotherapy had no activity in either MSS or pMMR mCRC.

Ongoing clinical trials of pembrolizumab monotherapy or in combination are being conducted in advanced melanoma, nonsmall cell lung cancer, and a number of other advanced solid tumor indications and hematologic malignancies. For additional study details please refer to the pembrolizumab IB.

2.2.3.2 Ongoing Favezelimab Clinical Studies

Clinical studies for favezelimab or other mAb targeting LAG-3 are ongoing. Preliminary efficacy and safety data from the favezelimab first-in-human study (MK 4280-001) are provided in Section 2.1, as well as in the MK-4280/MK-4280A IB.

Several other ongoing clinical trials are examining pembrolizumab in combination with favezelimab in participants with various solid and hematologic malignancies. For details, please refer to the MK-4280/MK-4280A IB.

2.2.4 Information on Other Study-related Therapy

Regorafenib is a small molecule inhibitor with numerous targets, including VEGF receptors 1-3, platelet-derived growth factor receptor, tyrosine receptor kinase 2, fibroblast growth factor receptors, BRAF, KIT, and RET [Loree, J. M. 2017]. The Phase 3 CORRECT study has established regorafenib as a standard of care therapy for mCRC patients who are refractory to oxaliplatin and irinotecan-based therapy. In this study, median OS improved from 5.0 months with placebo to 6.4 months with regorafenib at a preplanned interim analysis (HR 0.77; 95% CI: 0.64–0.94; one-sided p=0.0052) [Grothey, A., et al 2013]. The CORRECT study results were confirmed in a broader Asian population in another Phase 3 study, CONCUR. Regorafenib resulted in a significantly longer OS (primary endpoint) and PFS compared with placebo (HR 0.55; 95%, median 8.8 vs 6.3 months; p=0.00016 and HR 0.31; median 3.2 vs 1.7 months; p<0.0001, respectively) [Li, J., et al 2015]. Regorafenib was approved by the FDA for patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with an anti-VEGF therapy, and, if KRAS WT, with an anti-EGFR therapy.

The recent REDOS study compared a dose-escalation strategy of regorafenib against standard dosing [Bekaii-Saab, T. S., et al 2019]. OS was 9.8 months with dose escalation,

compared to 6.0 months for standard dosing. However, the study was relatively small and consisted of only 123 participants randomized between the 2 groups. Thus, this study will allow investigators the option of either dosing strategy for participants treated with regorafenib.

TAS-102 is an orally administered combination of a thymidine-based nucleic acid analogue, trifluridine and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. Trifluridine is the active cytotoxic component of TAS-102; its triphosphate form is incorporated into DNA, with such incorporation appearing to result in antitumor effects [Tanaka, N., et al 2014]. Tipiracil hydrochloride is a potent inhibitor of thymidine phosphorylase and, when combined with trifluridine to form TAS-102, prevents the rapid degradation of the trifluridine, resulting in the maintenance of adequate plasma levels of the active drug.

The Phase 3 RECOURSE study of TAS-102 plus best supportive care versus placebo plus best supportive care in participants with metastatic CRC refractory to standard chemotherapies increased OS from 5.3 months to 7.1 months compared with placebo (HR 0.68; 95% CI: 0.58–0.81, $p<0.001$) in treatment-refractory mCRC [Mayer, R. J., et al 2015]. From these results, both regorafenib and TAS-102 have been recognized as standard treatments for refractory mCRC.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

Extended duration of clinical benefit coupled with favorable tolerability and toxicity have been the hallmark of pembrolizumab monotherapy in many tumor types including MSI-H/dMMR mCRC. Based on the available preclinical and clinical information, including the unmet medical need for heavily pretreated patients, who have neither dMMR nor MSI-H tumors, the benefit/risk of the MK-4280A appear reasonable to evaluate in a Phase 3 clinical study.

Thus, the coformulation regimen being examined in the current trial has the potential to provide improvement of efficacy without toxicity of chemotherapy in previously treated mCRC.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

Hypotheses are aligned with objectives in the Objectives and Endpoints table.

Throughout this protocol, the term response evaluation criteria in solid tumors refers to the adjustment of RECIST 1.1 to include a maximum of 10 target lesions and a maximum of 5 target lesions per organ. Refer to Section 4.2.1.1 for further details.

In males and females with mCRC whose tumors are positive for PD-L1 CPS≥1, have pMMR status based on IHC testing at screening, and have progressed on or could not tolerate prior line(s) of therapy for mCRC:

Primary Objective	**Primary Endpoint**
• To compare MK 4280A to standard of care (regorafenib or TAS-102) with respect to overall survival. • Hypothesis (H1): MK-4280A is superior to standard of care with respect to overall survival.	• Overall survival: The time from randomization to death due to any cause.
Secondary Objectives	**Secondary Endpoints**
• To compare MK 4280A to standard of care with respect to progression free survival per RECIST 1.1 as assessed by BICR. • Hypothesis (H2): MK-4280A is superior to standard of care with respect to progression free survival per RECIST 1.1 by BICR.	• Progression-free survival: The time from randomization to the first documented disease progression or death due to any cause, whichever occurs first.
• To compare MK 4280A to standard of care with respect to objective response rate per RECIST 1.1 as assessed by BICR • Hypothesis (H3): MK-4280A is superior to standard of care with respect to ORR per RECIST 1.1 by BICR.	• Objective response: complete response or partial response.
• To assess the efficacy of MK-4280A and standard of care with respect to duration of response per RECIST 1.1 by BICR.	• Duration of response: the time from first response (complete response or partial response) to subsequent disease progression or death from any cause, whichever occurs first.
• To determine the safety and tolerability of MK-4280A and standard of care.	• Adverse event • Study intervention discontinuation due to AEs

• To compare the change from baseline in global health status/QoL, physical functioning, appetite loss and bloating for MK-4280A versus standard of care.	• Score for the following Patient-Reported Outcomes scales/items: global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).
• To compare the time to deterioration in global health status/QoL, physical functioning, appetite loss and bloating for MK-4280A versus standard of care.	• Time-to-deterioration, defined as the time from baseline to the first onset of a ≥10-point deterioration from baseline in global health status/QoL (EORTC QLQ-C30 items 29 and 30), physical functioning (EORTC QLQ-C30 items 1-5), appetite loss (EORTC QLQ-C30 item 13) and bloating (EORTC QLQ-CR29 item 37).
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
CCI [redacted]	

4 STUDY DESIGN

4.1 Overall Design

This is a Phase 3, randomized, active-controlled, parallel-group, multi-site, open-label, safety and efficacy study of MK-4280A (Arm A) versus standard of care (Arm B) in approximately 432 participants with metastatic (Stage IV as defined by AJCC, NCCN Guidelines Version 2.2018: Colon Cancer [National Comprehensive Cancer Network 2018]) colorectal adenocarcinoma whose tumors are positive for PD-L1 CPS≥1, have pMMR status based on IHC testing at screening, and have progressed on or could not tolerate previous treatment with fluoropyrimidine (or capecitabine), oxaliplatin, and irinotecan, ±VEGF agent, ±EGFR agent (if RAS WT left-sided tumor), and +RAF inhibitors (if BRAF V600E mutated). Participants must have measurable disease per RECIST 1.1, as determined by the investigator, and an ECOG PS of 0 to 1 at enrollment.

Participants may enroll regardless of RAS status; participants with no RAS mutations and left-sided tumors must have been treated with anti-EGFR agents as this subgroup is known to benefit from this therapy. Likewise, participants with and without BRAF mutations may enroll, though the efficacy of RAF inhibitors in patients with V600E mutations argues for the requirement that participants have progressed on this therapy before enrolling in this study.

After obtaining documented informed consent, candidate participants will be screened against all the eligibility criteria. Eligible participants will be randomly assigned to study intervention in a 1:1 ratio.

Randomization will be stratified by geographic region of the enrolling site (Asia Pacific; EMEA/Americas), presence of liver metastasis (yes, no), and time from initial diagnosis of metastatic disease to randomization (≥18 months, <18 months).

The study will be conducted in conformance with Good Clinical Practices (GCPs).

The primary endpoint of the study is OS. Secondary endpoints include PFS, OR, DOR per RECIST 1.1, safety and tolerability and PRO endpoints. On-study imaging assessments performed Q9W will be calculated from the date of randomization and independent of treatment delays for both treatment arms.

For participants in the study, all disease assessments, including expedited verification of PD by BICR, will be made using RECIST 1.1. Tumor imaging showing site-assessed PD will be submitted for verification by BICR. In Arm A, treatment beyond centrally verified PD per RECIST 1.1 may be permitted at the discretion of the investigator (if, eg, no new symptoms, stable or decreasing tumor markers CEA) after consultation with the Sponsor. Updated documented informed consent for continuing treatment on Arm A must be obtained prior to receiving the next study treatment (Section 8.1.1.1). Participants in Arm B may not crossover to Arm A intervention.

Participants on Arm A may receive up to 35 cycles of MK-4280A (approximately 2 years) in the Intervention Phase.

Participants receiving MK-4280A who attain locally confirmed CR per RECIST 1.1 by 2 tumor scans at least 4 weeks apart and who have received at least 8 cycles (approximately 6 months) with MK-4280A may discontinue intervention at the discretion of the investigator after receiving at least 2 cycles beyond the initial determination of a CR.

Adverse events will be monitored throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0 (Section 10.3.4). Each participant will be monitored for AEs and SAEs (refer to Section 8.4.1 for details). Because neither pembrolizumab monotherapy, nor favezelimab have activity as monotherapies in MSS CRC, if study intervention is discontinued for toxicity, single-agent therapy will not be offered.

Participants may undergo resection of the primary tumor and/or metastasectomy with curative intent after achieving a response to study intervention that converts previously unresectable disease to resectable disease, if deemed eligible per investigator's discretion in a multidisciplinary approach according to his/her institutional standard, and with Sponsor consultation. After surgery, when clinically appropriate and after the surgical wound is fully healed participant may resume the same therapy they were receiving pre-operatively starting at least 4 weeks and no more than 12 week post-surgery, unless approved by the Sponsor. Post-operative therapy may continue until verified progression by BICR, intolerability, or for Arm A, have received up to 35 cycles of MK-4280A.

The first post-operative tumor scan should be performed at a minimum of no less than 4 weeks after surgery and no more than 8 weeks after surgery and prior to the start of the next treatment cycle (Section 8.2.1.2). If treatment does not resume within 12 weeks after surgery, the investigator should consult with the Sponsor. In addition, participants who discontinue study intervention for reasons other than radiographic disease progression will have posttreatment follow-up for disease status Q9W (± 7 days) from date of randomization until disease progression (verified in an expedited manner by BICR per RECIST 1.1), start of a non-study anticancer therapy, consent withdrawal, becoming lost to follow-up, death, or end of the study.

While off study intervention, participants who undergo surgical resection of visible disease may demonstrate disease progression in non-surgical sites. In this instance, disease progression might not necessarily reflect resistance to study intervention. Accordingly, participants from both study arms who develop isolated lesion/tumor growth postoperatively (eg, while off study intervention) may resume the previously assigned study intervention. The investigator must assess overall clinical benefit to the participant and consult the Sponsor prior to resuming study intervention.

The sample size is estimated based on the primary endpoint OS, and the required target events to detect the superiority of MK-4280A versus standard of care in the comparison of OS.

Details regarding IA are provided in Section 9.7. An eDMC will serve as the primary reviewer of the treatment-level results and will make recommendations for discontinuation or modification of the study. These recommendations will be made to an executive oversight

committee of the Sponsor. The eDMC responsibilities and review schedules will be outlined in the eDMC charter.

After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants in China has been enrolled to meet local regulatory requirements. This extension portion of the study will be identical to the global study, (eg, inclusion and exclusion criteria, study endpoints, primary and secondary objectives, and study procedures).

Details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and ICF documents.

Specific procedures to be performed during the study, including prescribed times and associated visit windows, are outlined in Section 1.3 of the SoA. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

MK-4280A is being developed to treat solid tumors and hematologic malignancies.

Randomization will be performed to avoid bias in the assignment of participants to study intervention, to increase the likelihood that known and unknown participant attributes (geographic region and presence of liver metastasis) are balanced across intervention arms, and to ensure the validity of statistical comparisons between intervention arms.

The study will be an open-label trial, as chemotherapy refractory patients have short overall survival and as OS is a concrete endpoint that will limit any bias. The paucity of alternative therapies will also serve to limit bias from lack of blinding. Moreover, the frequency of hand-foot syndrome seen in regorafenib, and the frequency of cytopenias seen with TAS-102 would render any attempt at blinding effectively futile.

In the landmark CORRECT study, subgroup analysis of OS significantly favored regorafenib versus placebo for participants from North America and Western Europe, but not Asia or Eastern Europe [Grothey, A., et al 2013]. In contrast, subgroup analysis of PFS significantly favored regorafenib compared with placebo, except for patients from Eastern Europe, for

whom the difference was not significant. Thus, it is important to investigate whether patients from different geographic region will respond differently to pembrolizumab plus favezelimab versus regorafenib.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

OS will serve as the primary endpoint for this study. OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. In 3L therapy of mCRC, OS is the most important endpoint, as standard of care regorafenib and TAS-102 are associated with median OS of only 6.4 and 7.1 months, respectively [Grothey, A., et al 2013] [Mayer, R. J., et al 2015]. A more recent estimate from the SUNLIGHT study [Tabernero, J., et al 2023] showed a median survival of 7.5 months.

The secondary efficacy endpoints will include PFS, OR, and DOR per RECIST 1.1 as assessed by BICR. These endpoints are commonly accepted endpoints by both regulatory authorities and the oncology community.

RECIST 1.1 will be used by the BICR when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.4 for additional detail.

4.2.1.2 Safety Endpoints

The safety and tolerability of MK-4280A and of standard of care will be characterized in this study. See country-specific requirements in Appendix 7.

Safety parameters frequently used for evaluating investigational-systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs, and changes in vital signs and laboratory values. AEs will be assessed as defined by CTCAE, Version 5.0.

4.2.1.3 Patient-reported Outcomes

CCI

CCI

[redacted]

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[redacted]

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[redacted]

4.2.2 Rationale for the Use of Comparator

Regorafenib and TAS-102 are selected as the comparators included in this study since they are the globally accepted standard of care for mCRC that are refractory to fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, as recommended by formal guidelines (NCCN, ESMO, and JSCCR). Moreover, as both regorafenib and TAS-102 are not available in all regions and standard of care will be locally sourced, both options will be allowed in this study.

4.3 Justification for Dose

4.3.1 Justification of Favezelimab Dose

The planned dose of favezelimab in this study is 800 mg Q3W. Preliminary PK data from participants treated on MK-4280-001 in participants receiving favezelimab alone and in combination with pembrolizumab in advanced solid tumors at doses from 7 to 800 mg showed that serum favezelimab exposures increased in a dose-dependent manner. Preliminary PK profiles of favezelimab exposures suggest that target receptor-mediated clearance (reflecting target engagement of membrane LAG-3) of favezelimab was more likely to stay saturated at ≥700 mg dose compared with lower doses considering PK C_{trough} variability observed. Additionally, efficacy data from a randomized dose-finding study in participants with gastric cancer in MK-4280-001 suggested possible trend towards better efficacy at higher doses. Favezelimab given alone and in combination with pembrolizumab has been tolerable at all dose levels tested from 7 to 800 mg with no clear dose dependence in the type or frequency of AEs. For more detailed information, please refer to the MK-4280/MK-4280A IB. Therefore, based on the totality of preliminary data accumulated so far, the Sponsor has elected 800 mg dose of favezelimab in this Phase 3 study.

4.3.2 Justification of Pembrolizumab Dose

The planned dose of pembrolizumab for this study is 200 mg Q3W.

Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W representing an approximate 5- to 7.5-fold exposure range (refer to the pembrolizumab IB)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 participants were enrolled with melanoma and NSCLC, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched, and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W versus 10 mg/kg Q3W (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg Q3W versus 10 mg/kg Q2W (KN001 Cohort B3, KN001 Cohort F2 and KN006). All of these studies showed flat dose- and E-R relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-E-R relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating TMDD conclusively showed saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Second, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other participant covariates on exposure, has shown that the fixed dosing provides similar control of PK variability as weight-based dosing, with considerable overlap

in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed dose was selected for evaluation across all pembrolizumab protocols.

4.3.3 Justification of the Coformulation MK-4280A

Given the Sponsor's observation of limited favezelimab monotherapy activity and the observed efficacy and tolerability of favezelimab when used in combination with pembrolizumab in the ongoing Phase 1 clinical study of MK-4280-001, the Sponsor developed MK-4280A, a coformulated product of favezelimab in combination with pembrolizumab. PK, safety, and efficacy are comparable in MSS CRC participants treated with MK-4280A compared to separately administered favezelimab and pembrolizumab on MK-4280-001 (see MK-4280/MK-4280A IB for details). Compared with sequential administration of separate formulations, the single coformulation vial could provide significant benefit to patients and providers, including simplified preparation, reduced infusion times, and reduction of potential errors in drug administration.

4.3.4 Justification of Regorafenib and TAS-102 Doses

Doses and regimens for standard of care chemotherapy were selected based on standard clinical practice and should be prepared per local and institutional guidelines according to the approved product labels.

4.4 Beginning and End-of-Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

5 STUDY POPULATION

Male/female participants with histologically confirmed diagnosis of PD-L1 CPS≥1 metastatic colorectal adenocarcinoma who are pMMR by IHC and are at least 18 years of age will be enrolled in this study.

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

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

5.1 Inclusion Criteria

A participant will be eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. The participant must have a histologically confirmed colorectal adenocarcinoma that is metastatic and unresectable (Stage IV as defined by AJCC eighth edition) [National Comprehensive Cancer Network 2018].

   Note: upon providing documented informed consent, the participants tissue sample will be sent for central testing of PD-L1 expression and MMR status. Participants who test positive for PD-L1 (CPS≥1) and who have IHC consistent with pMMR tumors will qualify to participate in the study.

   Note: RAS and RAF mutation status must be known.
2. Have measurable disease per RECIST 1.1 as assessed by the local site investigator. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
3. Has been previously treated for their disease and radiographically progressed on or after or could not tolerate standard treatment, which must include ALL of the following agents if approved and locally available in the country where the participant is randomized:
   Note: Adjuvant chemotherapy is regarded as prior systemic therapy if there is documented disease progression within 6 months of chemotherapy completion
   Note: A participant who has withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of treatment and precluding retreatment with the same agent prior to progression of disease will also be eligible to enter the study. If a participant is determined to be intolerant to a prior line of therapy, the participant must have had a minimum of 2 cycles of that therapy.
   a. Fluoropyrimidine, irinotecan and oxaliplatin.
      Note: Capecitabine is acceptable as equivalent to fluorouracil in prior therapy (XELOX/CAPOX and XELIRI are considered equivalent to FOLFOX and FOLFIRI, respectively).

Note: Participants who have previously received fluoropyrimidine, oxaliplatin, and irinotecan as part of the same and only chemotherapy regimen, eg, FOLFOXIRI or FOLFIRINOX, may participate the study.

b. With or without an anti-VEGF monoclonal antibody (eg, bevacizumab)

c. At least one of the anti-EGFR monoclonal antibodies (cetuximab or panitumumab) for RAS WT participants with left sided tumors.
Note: For participants with ctDNA RAS mutant but RAS mutation negative in tissue, enrollment into the study before anti-EGFR administration is allowed.

d. Participants with BRAF v600E mutations must have been treated with a RAF inhibitor with or without binimetinib. Participants with BRAF mutations that are not v600E are not required to have received RAF inhibitor therapy.

4. Submit an archival (≤ 5 years) or newly obtained tumor tissue sample that has not been previously irradiated to enable central laboratory testing of PD-L1 and MMR status. FFPE blocks are preferred to slides.
5. Have an ECOG PS of 0 to 1 within 10 days prior to first dose of study intervention.
6. Have a life expectancy of at least 3 months, based on the investigator assessment.
7. Have the ability to swallow and retain oral medication and not have any clinically significant gastrointestinal abnormalities that might alter absorption.
8. Have adequate organ function as defined in the following table (Table 4). Specimens must be collected within 10 days prior to the start of study intervention.
Note: Participants may have their blood retested if they do not meet criteria greater than 10 days prior to the anticipated first dose of study intervention.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine OR Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN OR ≥60 mL/min for participant with creatinine levels >1.5 × institutional ULN
Urinalysis	Urine Protein <1g/24h or <2 (<100mg/dL) on a urine dipstick test[c]
Hepatic	
Total bilirubin	≤1.5 ×ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
INR or PT aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); ANC=Absolute neutrophil count; aPTT=Activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); CrCl=creatinie clearance; GFR=glomerular filtration rate; INR=International normalized ratio; pRBC=packed red blood cell; PT=prothrombin time; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without pRBC transfusion within last 2 weeks.

[b] CrCl should be calculated per institutional standard.

[c] Participants with proteinuria ≥2+ (≥100 mg/dL) on urinalysis or urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria

Note: This table includes eligibility-defining laboratory value requirements for intervention; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

Demographics

9. Is male or female, ≥18 years of age at the time of obtaining the documented informed consent.
10. Male or Female Participants

Male Participants

Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for

each study intervention is as follows: TAS-102 (90 days) and regorafenib (90 days). No contraception requirements are needed for males receiving MK-4280A.

- Refrain from donating sperm

PLUS either:

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

OR

- Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause Appendix 5) as detailed below:
  - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: 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-vaginal penetration.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Female Participants

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

Is not a WOCBP

OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows: MK-4280A (120 days), TAS-102 (180 days), and regorafenib (180 days).

The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 or 72 hours, respectively, before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.
- Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Informed Consent

11. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study. The participant may also provide consent/assent for FBR. However, the participant may participate in the study without participating in FBR.

Refer to Appendix 7 for country-specific requirements.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant meets any of the following criteria:

Medical Conditions

1. Has previously been found to have dMMR/MSI-H tumor status determined by either IHC or PCR.
2. Has known active CNS metastases and/or carcinomatous meningitis or leptomeningeal disease. Participants with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 28 days by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid intervention for at least 14 days prior to first dose of study intervention.

3. Has a history of acute or chronic pancreatitis.
4. Has neuromuscular disorders associated with an elevated creatine kinase (eg, inflammatory myopathies, muscular dystrophy, amyotrophic lateral sclerosis, spinal muscular atrophy).
5. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability.

   Note: Participants with cardiac failure NYHA Class II, III and IV are not permitted to receive treatment with regorafenib for Arm B.

   Note: Medically controlled arrhythmia would be permitted.
6. Has urine protein ≥1 g/24h.

   Note: Participants with proteinuria ≥2+ (≥100 mg/dL) on urinalysis or urine dipstick testing will undergo 24-hour urine collection for quantitative assessment of proteinuria.
7. A WOCBP who has a positive urine/serum pregnancy test within 24/72 hours prior to the first dose of study intervention (Appendix 5). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

   Note: If 72 hours have elapsed between the screening pregnancy test and the first dose of study intervention, another pregnancy test (urine or serum) must be performed and must be negative in order for the participant to start receiving study intervention.

Prior/Concomitant Therapy

8. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, anti-LAG-3 antibody, with a TKI (eg, lenvatinib) other than RAF inhibitors (binimetinib is permitted if combined with a RAF inhibitor), or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137).
9. Has previously received regorafenib or TAS-102.
10. Has received prior systemic anticancer therapy including investigational agents within 28 days before randomization.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with ≤Grade 2 neuropathy may be eligible.

    Note: If the participant had a major operation, the participant must have recovered adequately from the procedure and/or any complications from the operation before starting study intervention.
11. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.
12. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a given country is allowed in the study as long as they are mRNA vaccines, adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy. Refer to Section 6.5 for information on COVID-19 vaccines.

Note: Investigational vaccines (ie, those not licensed or approved for emergency use) are not allowed.

Prior/Concurrent Clinical Study Experience

13. Is currently participating in or has participated in a study of an investigational agent or has used an investigational device within 28 days before the first dose of study intervention.

    Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been 28 days after the last dose of the previous investigational agent.

Diagnostic Assessments

14. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 10 days prior the first dose of study medication.
15. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.
16. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
17. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
18. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
19. Has an active infection requiring systemic therapy (eg, tuberculosis, known viral or bacterial infections).

    Note: No testing for active infections is required unless mandated by local health authority.
20. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.
21. Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
    Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by local health authority.

22. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.
23. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

Other Exclusions

24. Has had an allogenic tissue/solid organ transplant.
    Refer to Appendix 7 for country-specific requirements.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

No restrictions are required.

5.3.3 Activity Restrictions

No restrictions regarding activity and exercise are required for this study.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

Rescreening information is provided in Section 8.12.1.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention or withdraws from the study will not be replaced.

6 STUDY INTERVENTION

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

Clinical supplies provided by the Sponsor will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 5.

Table 5 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/Treatment Period/Vaccination Regimen	Use	IMP or NIMP/AxMP	Sourcing
Arm A	Experimental	MK-4280A	Drug	Solution	20 mg/mL favezelimab + 5 mg/mL pembrolizumab for a total protein content of 25 mg/mL	800 mg MK-4280 + 200 mg MK-3475	IV Infusion	Day 1, then Q3W, up to 35 infusions	Test Product	IMP	Sponsor
Arm B	Active Comparator	regorafenib	Drug	Tablet	40 mg/tablet	160 mg	Oral	4-week cycle: QD Days 1-21, no dose Days 22-28	Comparator	IMP	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Arm B	Active Comparator	TAS-102	Drug	Tablet	15 mg trifluridine/6.14 mg tipiracil; 20 mg trifluridine/8.19 mg tipiracil	35 mg/m^2	Oral	4-week cycle: BID Days 1 to 5 and 8 to 12 of each 28-day treatment cycle (no dose days 6, 7, and 13-28)	Comparator	IMP	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee

BID=twice daily; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q3W=every 3 weeks; QD=daily.
The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 5 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the study site, subsidiary, or designee, every attempt will be made to source these supplies from a single lot/batch number. The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

Refer to Section 8.1.8 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

6.2.1.1 MK-4280A

Details on preparation and administration of MK-4280A are provided in the Pharmacy Manual.

6.2.1.2 Regorafenib

Regorafenib will be prepared and administered as per the approved product label and should follow local therapeutic guidelines. It is recommended that participants start with 80 mg regorafenib QD on days 1 to 7, then 120 mg QD on days 8 to 14, followed by 160 mg QD on days 15 to 21, and 160 mg QD on subsequent cycles (days 1 to 21) [Bekaii-Saab, T. S., et al 2018], although investigators are allowed to follow local/institutional guidelines for regorafenib.

6.2.1.3 TAS-102

TAS-102 will be prepared and administered as per the approved product label and should follow local therapeutic guidelines.

6.2.2 Handling, Storage, and Accountability

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

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions 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 (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention randomization will occur centrally using an IRT system. There are 2 study intervention arms. Participants will be assigned randomly in a 1:1 ratio to MK-4280A study intervention and standard of care study intervention, respectively.

The SOC study intervention to be used, regorafenib or TAS-102, must be chosen by the investigator before randomization and reasons for selection of one or the other treatment will be documented (refer to Section 8.1.6.1).

6.3.2 Stratification

Intervention randomization will be stratified according to the following factors:

1. Geographic region (Asia Pacific; EMEA/Americas)
2. Presence of liver metastasis (Yes, No)
3. Time from initial diagnosis of metastatic disease to randomization (≥18 months, <18 months)

6.3.3 Blinding

This is an open-label study; therefore, the Sponsor, investigator, and participant will know the study intervention administered.

6.4 Study Intervention Compliance

If there are interruptions in the study intervention schedule, the details of and reason for any interruption of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.1 for dose modification and toxicity management for irAEs associated with MK-4280A and for other allowed dose interruption of MK-4280A.

When participants are dosed MK-4280A at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant ID will be confirmed at the time of dosing by a member of the study-site staff other than the person administering the study intervention.

For Arm B, the first dose of Cycle 1 of standard of care must be given to the participant at the site and will be witnessed by the investigator and/or study staff, and/or qualified designee per institutional guidelines and procedures. For medication taken at home, site staff will make tablet counts at regular intervals during the Intervention Phase. Compliance will be calculated by the Sponsor based on drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100% compliance, and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

6.5 Concomitant Therapy

The following medications and vaccinations are prohibited during the study:

- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.

Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use

- Intraarticular joint use

- For inhalation in the management of asthma or chronic obstructive pulmonary disease

If there is a clinical indication for any medications or vaccinations prohibited, the investigator must discuss any questions regarding this with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, and the Sponsor.

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study intervention period, study intervention (if combination, specify all) must be discontinued:

- Systemic antineoplastic chemotherapy, immunotherapy, or biological therapy not specified in this protocol

- Investigational agents other than those specified in the protocol

- Radiation therapy

- Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion

- Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed

The investigator must refer to the up-to-date regorafenib or TAS-102 product label, for guidance on prescribing information for regorafenib or TAS-102, for Arm B. The investigator should be knowledgeable of prohibited medications or medications to be used with precaution. Specific to the use of regorafenib, avoid concomitant use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and inhibitors of CYP3A4 activity (eg, clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole). CYP3A4 inhibitors and inductors may impact mean exposure of regorafenib. UGT1A9 inhibitors (eg, phenytoin, fosphenytoin, diflunisal) should also be avoided.

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the eCRF including all prescription, OTC products, herbal supplements, and IV medications, and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded.

All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

See country-specific requirements in Appendix 7.

6.5.1 Rescue Medications and Supportive Care

Participants should receive appropriate supportive care measures as deemed necessary by the treating investigator.

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6. See country-specific requirements in Appendix 7.

6.6 Dose Modification (Escalation/Titration/Other)

CTCAE v5.0 must be used to grade the severity of AEs (Section 10.3.4). If appropriate, the investigator may attribute each toxicity event for Arm A to MK-4280A and use dose modification table (Table 6). For Arm B, management of toxicity events attributed by the investigator to regorafenib or TAS-102 should be consistent with local dose modification guidelines and/or local regulations, if more stringent than FDA and/or SMPC guidelines.

All AEs should be followed as clinically appropriate until stabilization or resolution. The drug to which the investigator is attributing to the AE must be documented (ie, associated eCRFs, patient notes). Exceptional circumstances to following the dose modification tables below should be consulted with the Sponsor.

Dose modifications are always based on the previous cycle.

For Arm B, study intervention may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks (21 days) of the originally scheduled dose, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the participant's study record.

6.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab monotherapy, coformulation, or IO combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO

combination administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy, coformulations, or IO combinations, pembrolizumab monotherapy, coformulations, or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy, coformulations, or IO combinations should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab monotherapy, coformulations, or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy, coformulations, or IO combinations as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for irAEs, pembrolizumab monotherapy, coformulations, or IO combinations may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 6.

Table 6 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	**Toxicity Grade (CTCAE v5.0)**	**Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations**	**Corticosteroid and/or Other Therapies**	**Monitoring and Follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		
AST or ALT Elevation or Increased Bilirubin	Grade 2[a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3[b] or 4[c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of b-cell failure	Withhold[d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue[d]		
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (which was previously myocarditis Grade 1 using CTCAE v4.0)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event[e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up

AE(s)=adverse event(s); ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome;
T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to 5.0 ´ ULN if baseline normal; >3.0 to 5.0 ´ baseline, if baseline abnormal;
bilirubin: >1.5 to 3.0 ´ ULN if baseline normal; >1.5 to 3.0 ´ baseline, if baseline abnormal.

[b] AST/ALT: >5.0 to 20.0 ´ ULN if baseline normal; >5.0 to 20.0 ´ baseline, if baseline abnormal;
bilirubin: >3.0 to 10.0 ´ ULN if baseline normal; >3.0 to 10.0 ´ baseline, if baseline abnormal.

[c] AST/ALT: >20.0 ´ ULN if baseline normal; >20.0 ´ baseline, if baseline abnormal;
bilirubin: >10.0 ´ ULN if baseline normal; >10.0 ´ baseline, if baseline abnormal.

[d] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[e] Events that require discontinuation include, but are not limited to, encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose Modification and Toxicity Management of Infusion Reactions Related to MK-4280A

MK-4280A may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on MK-4280A associated infusion reaction are provided in Table 7.

Table 7 MK-4280A Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	Stop Infusion Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg, from 100 mL/h to 50 mL/h). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug intervention.	Participant may be premedicated 1.5 h (±30 min) prior to infusion of study intervention with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing
IV=intravenous; NSAID=nonsteroidal anti-inflammatory drug; PO=orally. Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

Other Allowed Dose Interruption for MK-4280A

MK-4280A may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 9 weeks of the originally scheduled dose and within 12 weeks of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.7 Intervention After the End of the Study

There is no study-specified intervention after the end of the study.

6.8 Clinical Supplies Disclosure

This study is open-label; therefore, the participant, the study-site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

6.9 Standard Policies

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.12.4.3 unless the participant has withdrawn from the study Section 7.2.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons.

A participant must be discontinued from study intervention, but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.1, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Radiographic disease progression outlined in Section 8.2.1.5 (after obtaining informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond disease progression).
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.

- The participant requires any prohibited concomitant medications as described in Section 6.5.
- Arm A: Discontinuation of intervention may be considered for participants who have attained a confirmed CR and have been treated for at least 8 cycles (at least 24 weeks), receiving 2 cycles of MK 4280A beyond the date when the initial CR was declared.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of study intervention.

For participants who are discontinued from study intervention, but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

Discontinuation from study intervention is "permanent." Once a participant is discontinued from study intervention, they shall not be allowed to restart study intervention.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from FBR, are outlined in Section 8.1.9.

Refer to Section 8.12.4.3 for details regarding Survival Follow-up. See country-specific requirements in Appendix 7. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.
- Refer to Section 8.12.4.3 for details regarding Survival Follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- 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 (eg, blood count) and obtained before signing of ICF may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The maximum amount of blood collected from each participant over the duration of the study can be found in the Laboratory Manual or Procedures Document.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented informed consent from each potential participant (or their legally acceptable representative) prior to participating in this clinical study or FBR. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

8.1.1.1 General Informed Consent

Informed consent given by the participant or their legally acceptable representative must be documented on a consent form. The form must include the study protocol number, study protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the participant (or their legally acceptable representative) before participation in the study.

The initial ICF, any subsequent revised ICF, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's or the participant's legally acceptable representative's dated signature.

If the investigator recommends continuation of study intervention beyond disease progression, the participant or their legally acceptable representative will be asked to provide documented informed consent.

Specifics about the study and the study population are to be included in the study informed consent form.

Informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or medically qualified designee will explain the FBR consent to the participant, or the participant's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to FBR. A copy of the informed consent will be given to the participant before performing any procedure related to FBR.

The participant may participate in the study without participating in FBR.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator, who is a qualified physician, to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study-site contact information (including direct

telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant ID card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically important. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

If a medical condition is diagnosed at the time of screening due to the physical examination, laboratory tests, radiologic assessment, other assessment, and/or a combination of these evaluations, the medical condition is to be recorded as a baseline condition along with the participant's other medical history unless due to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in).

8.1.4.1 Colorectal Cancer History

The investigator or qualified designee (consistent with local requirements) will obtain prior and current details regarding the participant's CRC. All prior historical information must be reviewed (eg, prior surgeries, radiation, other oncologic therapies).

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before starting the study. Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication.

8.1.5.1.1 Prior Colorectal Cancer Therapy Review

The investigator or qualified designee (consistent with local requirements) will review all prior anticancer therapies including systemic therapies, radiation, and surgeries.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through the Safety Follow-up Visit.

Concomitant medication review is to continue post the Safety Follow-up visit if related to an AE/SAE that is being followed.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur before randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be reused for different participants.

Any participant who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.12.1.

8.1.6.1 Treatment Eligibility Assessment Form

A TEA form is included in this study to document the investigator assessment of participant suitability for potential treatment in Arm B with regorafenib or TAS-102 and the rationale. These data may be required to support reimbursement efforts for MK-4280A.

The investigator must complete this form and provide rationale to document the choice of regorafenib or TAS-102 before randomization.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment randomization. Once a treatment/randomization number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or study staff according to the specifications within the Pharmacy Manual.

It is strongly preferred that participants receive first dose of study intervention on day of randomization.

The first dose of Cycle 1 of oral study drug (regorafenib or TAS-102) must be taken by the participant while at the site.

Refer to the Pharmacy Manual for MK-4280A administration for Arm A.

Refer to the regorafenib or TAS-102 product label, respectively, for guidance on administration procedures for regorafenib or TAS-102, for Arm B.

Study intervention should begin within 3 days of randomization.

See country-specific requirements in Appendix 7.

8.1.8.1 Timing of Dose Administration

8.1.8.1.1 MK-4280A Administration (Arm A)

MK-4280A 800/200 mg will be administered as a 30-minute IV infusion Q3W. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min). Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

All subsequent MK-4280A doses may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgment.

8.1.8.1.2 Regorafenib Administration (Arm B)

Participants are to take regorafenib at the same time each day on Days 1 to 21 of each cycle. Participants are advised to swallow the tablet whole with water following a low-fat meal. Any missed dose of regorafenib should be taken on the same day, as soon as the participant remembers, although 2 doses of regorafenib should not be taken on the same day to make up for a missed dose from the previous day. Participants are not to take any doses of regorafenib on Days 22 to 28 of each cycle. Refer to the regorafenib product label for current prescription information.

8.1.8.1.3 TAS-102 Administration (Arm B)

Participants are to take TAS-102 twice daily on Days 1 through 5 and Days 8 through 12 of each 28-day cycle. Participants are to swallow the tablets whole with water after a meal. Participants are not to take 2 doses of TAS-102 at once to make up for a missed dose. Participants are not to take any doses of TAS-102 on Days 6 and 7 and 13 to 28 of each cycle. Refer to the TAS-102 package insert for current prescription information. For calculation of TAS-102 dosing based on weight/BSA, refer to the website https://www.lonsurfhcp.com/dosing.

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.12.3.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the End-of-Treatment/Discontinuation visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4.

8.1.9.1 Withdrawal From Future Biomedical Research

Participants may withdraw their consent for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@MSD.com). Subsequently, the participant's consent for FBR will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the participant of completion of withdrawal. Any analyses in progress at the time of request for withdrawal or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for specimen withdrawal cannot be processed.

8.1.10 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study. The emergency unblinding call center will be available so that a health care provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.11 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained are reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.1.12 Tumor Tissue for Biomarker Status

During the screening period, a tumor sample for each participant is required and is to be:

- A newly obtained tissue sample of a tumor lesion, which was not previously irradiated

Or

- An archival tumor tissue sample if a new biopsy is unavailable (depending on protocol requirements)

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

Details pertaining to tumor tissue submission can be found in the Procedures Manual.

The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic test is identical to the US FDA-approved PD-L1 IHC 22C3 pharmDx diagnostic kit except it is labeled IUO. The PD-L1 IHC 22C3 pharmDx assay kit is currently approved to assess PD-L1 status.

The MMR status must be determined by central laboratory testing prior to randomization and the participant must have pMMR status based on IHC testing. Colorectal tumor MMR status is determined by IHC, while MSI status is determined by PCR. Tumors are classified as dMMR in the absence of at least 1 of 4 MMR proteins (MLH1/MSH2/MSH6/PMS2).

See country-specific requirements in Appendix 7.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

Throughout this section, the term ‘scan’ refers to any medical imaging data used to assess tumor burden and may include cross-sectional imaging (such as CT or MRI), medical photography, or other methods as specified in this protocol.

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into survival follow-up. The process for scan collection and transmission to the iCRO can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. The same scan technique should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

Note: For the purposes of assessing tumor scans, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer at the site or at an offsite facility.

Participant eligibility will be determined using investigator assessment based on RECIST 1.1. While on study, scheduled imaging studies scans for each participant should be submitted for BICR. Unscheduled imaging studies scans obtained for assessment of disease progression or other reasons, but capturing radiologic progression or used in response assessments, should also be submitted for BICR.

If brain scans are performed, magnetic resonance imaging is preferred; however, CT imaging will be acceptable, if MRI is medically contraindicated.

Bone scans may be performed to evaluate bone metastases. Any supplemental scans performed to support a positive or negative bone scan, such as plain x-rays acquired for correlation, should also be submitted to the iCRO.

Other imaging modalities that may be collected, submitted to the iCRO, and included in the response assessment include chest X-rays, PET-CT, etc . Other types of medical imaging (such as ultrasound) should not be submitted to the iCRO and will not be included in response assessment.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days prior to the date of randomization. Any scans obtained after Cycle 1 Day 1 cannot be included in the screening assessment. The site must review screening scans to confirm the participant has measurable disease per RECIST 1.1.

8.2.1.2 Tumor Scans During the Study

The first on-study scan should be performed at 9 weeks (63 days ±7 days) from the date of randomization. Subsequent tumor scans should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 9 weeks (63 days ±7 days), participants who remain on treatment will have scans performed every 9 weeks (63 days ±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts. Scans are to be performed until disease progression is identified by the investigator and verified by the BICR, or until the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Objective response should be confirmed by a repeat scan performed at least 4 weeks after the first indication of a response is observed. Participants will then return to the regular scan schedule, starting with the next scheduled time point. Participants who receive additional scans for confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

On-study brain or bone scans should be performed if clinically indicated or to confirm CR (if other lesions indicate CR and brain or bone lesions existed at baseline).

Treatment beyond centrally verified PD per RECIST 1.1 may be permitted at the discretion of the investigator after consultation with the Sponsor and receiving documented informed consent. Participants who continue treatment beyond centrally verified PD must continue tumor assessments as described in the SoA (Section 1.3). Investigator assessments are to be documents on the eCRF, but scans are not to be submitted to the iCRO. Further progression and discontinuation of study intervention are to be determined by the investigator.

When the investigator identifies radiographic progression per RECIST 1.1, the iCRO will perform expedited verification of radiologic disease progression and communicate the results to the study site and Sponsor via email. In clinically stable participants, scans should continue until disease progression has been verified by BICR (if initial site-assessed disease progression was not verified by BICR, each subsequent scan must be submitted to iCRO with verification of disease progression request until disease progression has been verified by BICR). Once disease progression is verified centrally, subsequent scans (if acquired) should not be submitted to the iCRO.

For participants who have surgery with curative intent during the study, scans must be performed at a minimum of no less than 4 weeks after surgery and no more than 8 weeks prior to the next treatment cycle. The last set of scans prior to restart of treatment will be used to establish a new baseline of tumor burden. Subsequent scans will be compared to this new baseline and the visit responses will be limited to PD, non-PD, or NE (not evaluable); these new postoperative images will be assessed every 9 weeks (63 days ± 7 days) for 12 months and every 12 weeks (84 days ± 7 days) thereafter.

For those participants who did not achieve a confirmed curative outcome, a new baseline is not required. Participants will continue on study as planned using RECIST 1.1 (refer to data entry guidelines).

8.2.1.3 End-of-treatment and Follow-up Tumor Scans

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation. If participants discontinue study intervention due to documented disease progression, this is the final required tumor scan.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of randomization, refer to Section 8.2.1.2.

Scans are to be continued until one of the following conditions are met:

- disease progression as defined by RECIST 1.1 verified by BICR
- the start of a new anticancer treatment
- pregnancy
- death
- withdrawal of consent
- the end of the study

8.2.1.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be used by BICR as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (eg, discontinuation of study intervention). Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, this protocol allows a maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden.

Upon investigator-assessed disease progression, the indicative scan(s) are to be submitted immediately to iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

If disease progression is not verified, the process continues as follows:

- If participant is clinically stable, continue study intervention per protocol
  - resume imaging per protocol schedule (≥4 weeks to next scan)
  - send scans to iCRO
  - continue local assessment
  - do not change investigator assessment of progression
  - if subsequent scan(s) indicate progression, submit scan(s) to iCRO to request verification
- If the participant is not clinically stable, best medical practice is to be applied

Before stopping study intervention or imaging or starting new anti-cancer therapy in a participant who is clinically stable, communication with the Sponsor is required.

If disease progression is verified, the process continues as follows:

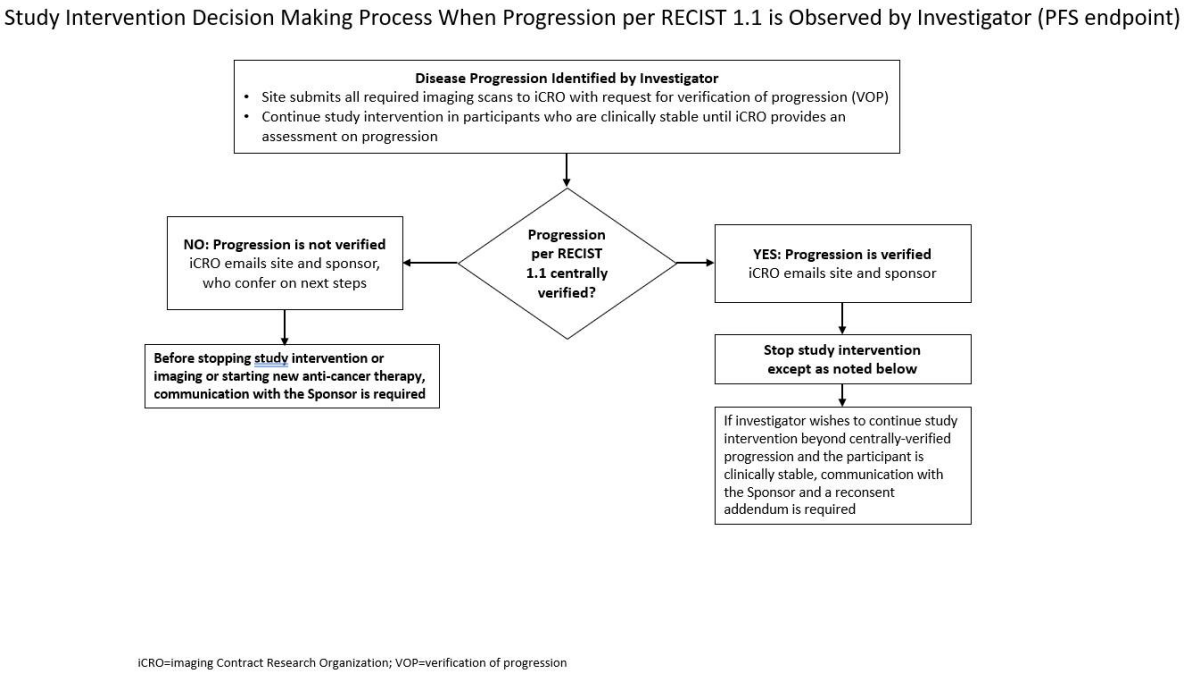
- investigator judgement will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the sponsor is required and a reconsent addendum must be signed
- obtain scans locally per original protocol schedule
- do not send scans to iCRO

Figure 2 illustrates the study intervention decision process involving verification of disease progression for participants.

- For the purpose of this decision process, lack of clinical stability is defined as:
  - unacceptable toxicity
  - clinical signs or symptoms indicating clinically significant disease progression
  - decline in performance status

- rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

Figure 2 Study Intervention Decision Making Process When Progression per RECIST 1.1 is Observed by Investigator (PFS Endpoint)



RECIST= response evaluation criteria in solid tumors ; PFS= progression-free survival

8.2.2 Patient-reported Outcomes

CCI

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the Laboratory or Study Procedures Manual.

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

8.3.1 Physical Examinations

8.3.1.1 Full Physical Examination

The investigator or qualified designee (consistent with local requirements) will perform a complete physical examination during the Screening period per institutional standard. Height and weight will also be measured and recorded. Clinically significant abnormal findings should be recorded as medical history.

Time points for full physical examinations are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical exam as defined in Section 1.3, the investigator or qualified designee (consistent with local requirements) will perform a brief directed physical examination (per institutional standard) as clinically indicated prior to study intervention administration. Weight will also be measured and recorded. New clinically significant abnormal findings should be recorded as AEs.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

- Temperature, pulse rate, RR, and BP will be assessed by institutional standard.

- BP and pulse measurements will be assessed per institutional standard with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Note: Participants in Arm B receiving regorafenib treatment are required to measure BP weekly. Weekly BP assessments can be done at home.

- BP and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

- Vital Signs will be measured in a semisupine or sitting position after 5 minutes rest and will include temperature, systolic and diastolic BP, and pulse and RR.

8.3.3 Electrocardiograms

Single 12-lead ECG will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3) using an ECG machine that automatically calculates the HR and measures pulse rate, QRS, QT, and QTc intervals.

8.3.4 Performance Assessments

8.3.4.1 Eastern Cooperative Oncology Group Performance Status

The ECOG PS is standardized criteria to measure how cancer impacts level of functioning (performance status) in terms of ability to care for oneself, daily activity, and physical ability (walking, working, etc) with Grades 0 to 5.

The investigator or qualified designee (consistent with local requirements) will assess ECOG status (Appendix 9) at screening, before the administration of each dose of study intervention, at the End-of-Treatment Visit, and at the 30 day Safety Follow-up Visit, as specified in the SoA (Section 1.3).

8.3.5 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual or Procedures Document and the SoA.
- If laboratory values from nonprotocol-specified laboratory assessments performed at the institution's local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation In the study or within 90 days for Arm A and 30 days for Arm B after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant can be found in the Laboratory Manual or Procedures Document. Refer to the SoAs (Section 1.3) for the timing of laboratory assessments.

8.3.5.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis are specified in Appendix 2.

8.3.6 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at every cycle during intervention and safety follow-up (Section 1.3 SoA).
  - Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure.
  - Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

See country-specific requirements in Appendix 7.

8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Progression of the cancer under study is not considered an AE as described in Section 8.4.6 and Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant’s legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3. The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity, and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention randomization, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event cause the participant to be excluded from the study, or is the result of a protocol-specified intervention, including, but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

- All AEs from the time of intervention randomization through 30 days after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.
- All pregnancies and exposure during breastfeeding, from the time of intervention randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.5, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 8.

Exception: A positive pregnancy test at the time of initial screening is not a reportable event unless the participant has received study intervention.

Table 8 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
NSAE	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/ Lactation Exposure	Report if: - participant has been exposed to any protocol-specified intervention (eg, procedure, washout or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential DILI - require regulatory reporting	Not required	Within 24 hours of learning of event

Type of Event	Reporting Time Period: Consent to Randomization/ Allocation	Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period	Reporting Time Period: After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
ECI (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; SAE=serious adverse event.

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events, including pregnancy and exposure during breastfeeding, ECIs, cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities toward 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 and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

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

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee), including the pregnancy of a male participant's female partner, that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy.

Any pregnancy complication will be reported as an AE or SAE.

The medical reason (example: maternal health or fetal disease) for an elective termination of a pregnancy will be reported as an AE or SAE. Prenatal testing showing fetus will be born with severe abnormalities/congenital anomalies that leads to an elective termination of a pregnancy will be reported as an SAE for the fetus.

Pregnancy outcomes of ectopic pregnancy, spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as an AE.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

Selected serious and nonserious AEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An overdose of Sponsor's product, as defined in Section 8.5.

2. An elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing*.

*Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For this study, an overdose of pembrolizumab will be defined as any dose of 1000 mg or greater.

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

MK-4280A

For this study, an overdose of MK-4280A will be defined as exceeding the prescribed dose by ≥100%.

No specific information is available on the treatment of overdose of MK 4280A. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive intervention should be provided if clinically indicated.

Regorafenib and TAS-102

For this study, refer to the regorafenib and TAS-102 product labels for current overdose information, frequently observed adverse drug reactions, and guidelines.

8.6 RAS and BRAF Status

All participants in the trial must be tested for RAS and BRAF status, unless at the time of obtaining consent the participant already has a documented RAS and BRAF status.

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[redacted]

8.11 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all participants throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

All-cause hospitalizations and emergency department visits must be reported in the eCRF, from the time of treatment randomization through 90 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier.

8.12 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.12.1 Screening

Documented informed consent must be provided before performing any protocol-specific procedure. Results of a test performed before the participant signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days before the first dose of study intervention. Except for the following:

- Archival tumor tissue sample should be from ≤5 years prior to screening. Newly obtained tumor tissue may be obtained within 28 days of treatment initiation.
- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention.
- Evaluation of ECOG is to be performed within 10 days prior to the first dose of study intervention.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 24 or 72 hours, respectively, prior to the first dose of study intervention. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study-site laboratory).

Participants may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Participants who are rescreened will retain their original screening number.

8.12.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1.

8.12.3 Discontinued Participants Continuing to be Monitored in the Study

When a participant discontinues study intervention in the Intervention Phase, procedures for discontinuation will be performed.

The discontinuation visit should occur at the time study intervention is discontinued for any reason. If the discontinuation visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up visit, the discontinuation visit procedures and any additional safety follow-up procedures should be performed. Visit requirements are outlined in Section 1.3. Additional details regarding participant withdrawal and discontinuation are presented in Section 7.

8.12.4 Posttreatment Visit

8.12.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of study intervention or before initiation of a new anticancer treatment, whichever comes first. The Safety Follow-up Visit should occur before initiation of a new anticancer

treatment if the new treatment occurs before 30 days post last dose and may be conducted by telephone.

8.12.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up. Follow-up visits after treatment discontinuation must coincide with the imaging schedule until disease progression, death, or end-of-study. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, end-of-study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated.

8.12.4.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The first survival follow-up assessment should be scheduled as described below:

- For participants who discontinue treatment intervention and who will not enter Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the Discontinuation Visit and/or Safety Follow-up Visit (whichever is last).
- For participants who completed assessments in Efficacy Follow-up, the first survival follow-up contact will be scheduled 12 weeks after the last efficacy assessment follow-up visit has been performed.

8.12.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, an eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined period will be contacted for their vital status.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any unblinding/final database lock, changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding/final database lock, will be documented in a sSAP and referenced in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will be included in the sSAP.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase 3 study of MK-4280A Versus Standard of Care in Previously Treated Metastatic Colorectal Cancer.
Treatment Assignment	Approximately 432 participants will be randomized in a 1:1 ratio between 2 treatment groups: (1) the MK-4280A arm (Arm A) and (2) the standard of care (regorafenib or TAS-102) arm (Arm B). Stratification factors are: Geographic region (Asia Pacific; EMEA/Americas), presence of liver metastasis (Yes, No) and time from initial diagnosis of metastatic disease to randomization (≥18 months, <18 months). This is an open-label study.
Analysis Populations	Efficacy: ITT Safety: APaT
Primary Endpoint(s)	Overall survival
Key Secondary Endpoints	Progression-free survival per RECIST 1.1 as assessed by BICR. Objective response rate per RECIST 1.1 as assessed by BICR.
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary hypothesis testing for OS and secondary hypothesis testing for PFS will be evaluated by comparing the experimental group to the control group using a stratified log-rank test. The HR will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method. The stratified M&N method with strata weighted by sample size will be used for secondary hypothesis testing of ORR [Miettinen, O. and Nurminen, M. 1985]
Statistical Methods for Key Safety Analyses	For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	**Efficacy** One interim analysis is planned in this study. Results will be reviewed by an eDMC. Details are provided in Section 9.7. • Interim Analysis: o Timing: to be performed after both ~309 OS events have been observed and ~ 10 months after last participant randomized o Primary purpose: interim efficacy analysis for OS, final analysis for PFS and ORR • Final Analysis: o Timing: to be performed after both ~386 OS events have been observed and ~12 months after interim analysis o Primary purpose: final analysis for OS **Safety** An interim safety analysis will be performed and reviewed by the eDMC 6 months after first participant is randomized or 2 months after 60th participant is randomized, whichever comes first. Afterwards, the eDMC will review safety data periodically in the study. Details will be specified in the DMC charter.
Multiplicity	The overall type I error over the primary and secondary hypotheses is strongly controlled at 2.5% (1-sided), with 2.5% initially allocated to OS (H1), 0% to PFS (H2), and 0% to ORR (H3). By using the graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013], if one hypothesis is rejected, the alpha will be shifted to other hypotheses.
Sample Size and Power	The planned sample size is approximately 432 participants. It is estimated that there will be ~ 386 OS events at the final analysis. With 386 OS events, the study has 93.5% power for detecting a HR of 0.7 at an initially assigned 0.025 (1-sided) significance level.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the Sponsor.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment as appropriate in this protocol, and the allocation will be implemented in IRT.

Although the study is open-label, analyses or summaries generated by randomized intervention assignment, or actual intervention received will be limited and documented.

Blinding issues related to the planned interim analyses are described in Section 9.7.

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

9.4.1 Efficacy Endpoints

Primary

- Overall Survival

OS is defined as the time from randomization to death due to any cause.

Secondary

- **Progression-free survival**

PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

- **Objective Response Rate**

The ORR is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR.

- **Duration of Response**

For participants who demonstrate confirmed CR or PR, duration of response is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

9.4.2 Safety Endpoints

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, SAEs, fatal AEs, laboratory tests. Furthermore, specific events will be collected and designated as ECIs as described in Section 8.4.7.

9.4.3 PRO Endpoints

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[redacted]

9.5 Analysis Populations

See country-specific requirements in Appendix 7.

9.5.1 Efficacy Analysis Populations

The ITT population will serve as the primary population for the analysis of efficacy data in this study. The ITT population consists of all randomized participants. Participants will be analyzed in the treatment arm to which they are randomized. Details of the approach to handling missing data are provided in Section 9.6.1.4.

9.5.2 Safety Analysis Populations

Safety Analyses will be conducted in the APaT population, which consists of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized except for participants who take incorrect study treatment for the entire treatment period; such participants will be included in the treatment group corresponding to the study treatment actually received.

At least one laboratory or vital sign measurement obtained after at least one dose of study treatment is required for inclusion in the analysis of the respective safety parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 PRO Analysis Populations

The PRO analyses are based on the PRO FAS population, defined as all randomized participants who have at least one PRO assessment available for the specific endpoint and have received at least one dose of the study intervention. Participants will be analyzed in the treatment group to which they are randomized.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 9.8, Multiplicity. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives will be described in the supplemental SAP.

The stratification factors used for randomization (Section 6.3.2) will be applied to all stratified analyses, in particular, the stratified log-rank test, stratified Cox model, and stratified M&N method [Miettinen, O. and Nurminen, M. 1985]. In the event, that there are small strata, for the purpose of analysis, strata will be combined to ensure sufficient number of participants, responses and events in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP prior to the database lock for the first analysis when each applicable endpoint will be analyzed, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

9.6.1.1 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR). The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.1.2 Progression-Free Survival

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the earlier of the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR and the date of death. Death is always considered a PD event.

For the primary analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment prior to the missed visits. In addition, any participant who initiates new anticancer therapy prior to documented progression will be censored at the last disease assessment prior to the initiation of new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease

assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to reasons other than complete response, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for the primary and sensitivity analyses are summarized in Table 9. Details regarding PFS analysis for surgical participants will be provided in the sSAP.

Table 9 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	**Primary Analysis**	**Sensitivity Analysis 1**	**Sensitivity Analysis 2**
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments, or after new anticancer therapy	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on-study treatment or completed study treatment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
PD=progressive disease; PFS=progression-free survival.			

9.6.1.3 Objective Response Rate

The stratified M&N method will be used for the comparison of ORR between 2 treatment groups [Miettinen, O. and Nurminen, M. 1985]. The difference in ORR and its 95% CI from the stratified M&N method with strata weighting by sample size will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to the analysis.

The point estimate of ORR will be provided by treatment group, together with 95% CI using exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934].

9.6.1.4 Analysis Strategy for Key Efficacy Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 10.

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
OS	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at the date participant last known to be alive
Key Secondary Analyses			
PFS per RECIST 1.1 by BICR	Testing: stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored according to rules in Table 9
ORR per RECIST 1.1 by BICR	Testing and estimation: stratified M&N method	ITT	Participants with missing data are considered non-responders

BICR=blinded independent central review; ITT=intent-to-treat; M&N=Miettinen & Nurminen; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors.

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs and laboratory tests.

The analysis of safety results will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as

system organ class terms) and events that meet predefined limits of change in laboratory and vital signs are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on the observed proportion of participants with events.

Tier 1 Events

Safety parameters or AEs of special interest that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. There are no Tier 1 events for this protocol. Adverse events that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab clinical development program, and determination of statistical significance is not expected to add value to the safety evaluation. The coformulated MK-4280A has not been found to be associated with any new safety signals. Finally, there are no known AEs associated with participants with CRC for which determination of a p-value is expected to impact the safety assessment.

Tier 2 Events

Tier 2 parameters will be assessed via point estimates with 95% CIs provided for differences in the proportion of participants with events using the M&N method, an unconditional, asymptotic method [Miettinen, O. and Nurminen, M. 1985].

Membership in Tier 2 requires that at least 10% of participants in any treatment group exhibit the event; all other AEs and predefined limits of change will belong to Tier 3. The threshold of at least 10% of participants was chosen for Tier 2 events because the population enrolled in this study is in critical condition and usually experiences various AEs of similar types regardless of treatment; events reported less frequently than 10% of participants would obscure the assessment of the overall safety profile and add little to the interpretation of potentially meaningful treatment differences. In addition, Grade 3 to 5 AEs (≥5% of participants in 1 of the treatment groups) and SAEs (≥5% of participants in 1 of the treatment groups) will be considered Tier 2 endpoints. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in safety review, not as a formal method for assessing the statistical significance of the between-group differences.

Tier 3 Events

Safety endpoints that are not Tier 1 or 2 events are considered Tier 3 events. The broad AE categories consisting of the proportion of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3-5 AE, a drug-related Grade 3-5 AE, and discontinuation due to an AE will be considered Tier 3 endpoints. Only point estimates by treatment group are provided for Tier 3 safety parameters.

Continuous Safety Measures

For continuous measures such as changes from baseline in laboratory parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Grade 3-5 AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	Serious AE (incidence ≥5% of participants in one of the treatment groups)	X	X
	AEs (incidence ≥10% of participants in one of the treatment groups)	X	X
Tier 3	Any AE		X
	Any Grade 3-5 AE		X
	Any Serious AE		X
	Any Drug-Related AE		X
	Any Serious and Drug-Related AE		X
	Any Grade 3-5 and Drug-Related AE		X
	Discontinuation due to AE		X
	Death		X
	Specific AEs, system organ class (incidence <10% of participants in all of the treatment groups)		X
	Change from Baseline Results (laboratory toxicity shift)		X

AE=adverse events; CI=confidence interval.

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

This section describes the planned analyses for the PRO endpoints.

Change from Baseline

The time point for the change from baseline will be determined based on blinded data review prior to the database lock for any PRO analysis and documented in the sSAP.

To assess the treatment effects on the PRO score change from baseline in the global health status/QoL, physical, appetite loss and bloating, a constrained longitudinal data analysis

model proposed by Liang and Zeger [Liang, Kung-Yee and Zeger, Scott L. 2000] will be applied, with the PRO score as the response variable, and treatment, time, the treatment by time interaction, and the stratification factors used for randomization (Section 6.3.2) as covariates. The treatment difference in terms of least square mean change from baseline will be estimated from this model together with 95% CI. Model-based least square mean with 95% CI will be provided by treatment group for PRO scores at baseline and post-baseline time point.

Time-to-Deterioration

The Kaplan-Meier method will be used to estimate the TTD curve for each treatment group. The estimate of median time-to-deterioration and its 95% confidence interval will be obtained from the Kaplan-Meier estimates. The treatment difference in TTD will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling and with a single treatment covariate will be used to assess the magnitude of the treatment difference (ie, HR). The HR and its 95% CI will be reported. The stratification factors used for randomization (Section 6.3.2) will be used as the stratification factors in both the stratified log-rank test and the stratified Cox model.

Details of PRO analyses will be described in the sSAP.

9.6.4 Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened and randomized and the primary reasons for screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

9.7 Interim Analyses

The eDMC will serve as the primary reviewer of the results of the IAs and will make recommendations for discontinuation of the study or modification to the executive oversight committee of the Sponsor. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee and potentially other limited Sponsor personnel may be unblinded to the treatment-level results in order to act on these recommendations. The extent to which individuals are unblinded with respect to results of IAs will be documented by the unblinded statistician. Additional logistic details will be provided in the eDMC Charter.

Treatment-level results of the interim analysis will be provided by the unblinded statistician to the eDMC. Prior to final study unblinding, the unblinded statistician will not be involved in any discussions regarding modifications to the protocol or statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

9.7.1 Efficacy Interim Analysis

One IA is planned in addition to the FA for this study. For the IA and FA, all randomized participants will be included. Results of the IA will be reviewed by the eDMC. Details of the boundaries for establishing statistical significance with regard to efficacy are discussed further in Section 9.8.

The analyses planned, endpoints evaluated, and drivers of timing are summarized in Table 12.

Table 12 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA	OS (PFS and ORR if OS is rejected)	Both ~309 OS events have been observed and ~ 10 months after last participant randomized	~ 21 months	• Interim OS analysis • Final PFS and ORR analysis
FA	OS	Both ~386 OS events have been observed and ~12 months after IA	~ 33 months	• Final OS analysis

FA=final analysis; IA=interim analysis; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Note that for FA, if the OS events accrue slower than expected and the final targeted OS events cannot be reached by ~33 months after the first participant randomized, the Sponsor may conduct the analysis with up to additional ~4 months of follow-up, or the specified number of events is observed, whichever occurs first.

9.7.2 Safety Interim Analysis

The eDMC will be responsible for periodic interim safety reviews as specified in the eDMC charter. An interim safety analysis will be performed 6 months since first participant is randomized or 2 months after 60th participant is randomized, whichever comes first. Afterwards, the eDMC will review safety data periodically in the study. Interim safety analyses will also be performed at the time of interim efficacy analyses. Details will be specified in the eDMC charter.

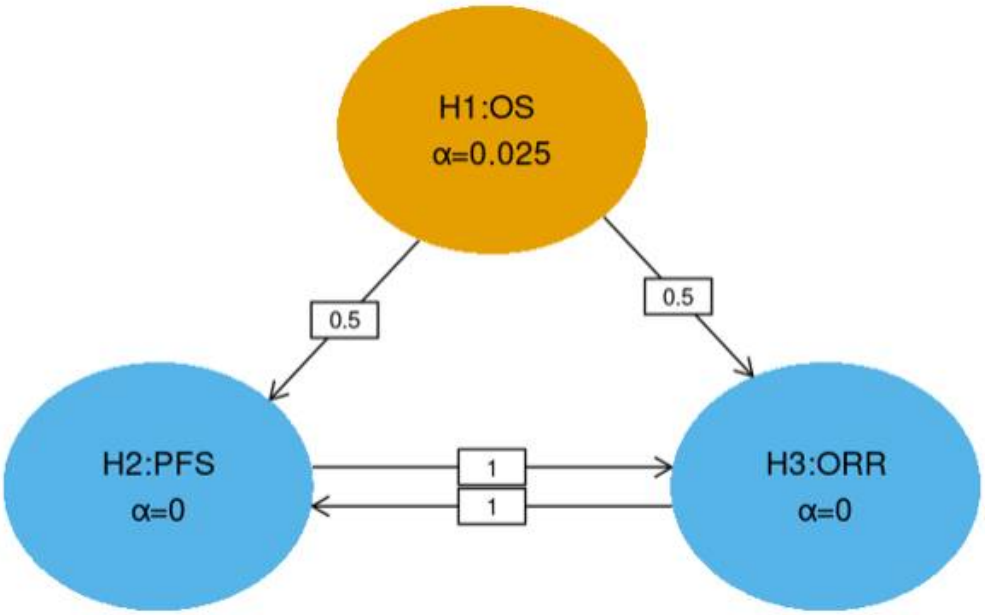
9.8 Multiplicity

The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] to provide strong multiplicity control for multiple hypotheses as well as interim analyses. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Note that if the OS null hypothesis is rejected at FA of the study, the previously computed PFS and ORR test statistics at IA may be used for inferential testing

with its updated bounds considering the α reallocation from the OS hypothesis. Figure 3 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses.

The initial α assigned to OS, PFS and ORR will be 0.025, 0 and 0, respectively. If OS hypothesis is rejected, the corresponding alpha can be reallocated equally to PFS and ORR. If the PFS hypothesis is rejected, the corresponding alpha can be reallocated to ORR. If the ORR hypothesis is rejected, the corresponding α can be reallocated to PFS.

Figure 3 Multiplicity Diagram for Type I Error Control



ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

Note: If OS null hypothesis is rejected, the allocation strategy allows testing of PFS and ORR at α = 0.0125, separately.

9.8.1 Overall Survival

The study will test OS at IA and FA. Following the multiplicity strategy as outlined in Figure 3, the OS hypothesis will be tested at α=0.025. Table 13 shows the bounds and boundary properties for OS hypothesis testing derived using a Lan-DeMets spending function approximating O'Brien-Fleming bounds.

Table 13 Efficacy Boundaries and Properties for Overall Survival Analyses

Analysis	**Value**	**α=0.025**
IA: 80%* N: 432 Events: 309 Month: 21	Z	2.2504
	p (1-sided)[a]	0.0122
	HR at bound[b]	0.7738
	P(Cross) if HR=1[c]	0.0122
	P(Cross) if HR=0.7[d]	0.8123
FA N: 432 Events: 386 Month: 33	Z	2.0249
	p (1-sided)[a]	0.0214
	HR at bound[b]	0.8135
	P(Cross) if HR=1[c]	0.0250
	P(Cross) if HR=0.7[d]	0.9350

HR=hazard ratio; IA=interim analysis, FA=final analysis.
The number of events and timings are estimated.
* Percentage of total planned events at the interim analysis.
[a] *p* (1-sided) is the nominal α for group sequential testing.
[b] HR at bound is the approximate HR required to reach an efficacy bound.
[c] P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis.
[d] P (Cross if HR=0.7) is the probability of crossing a bound under the alternative hypothesis.

The bounds provided in the table above are based on the assumptions that the expected number of events at IA and FA are 309 and 386, respectively. At the time of an analysis, the observed number of events may differ substantially from the expected. To avoid overspending at an IA and leave reasonable α for the FA, the minimum α spending strategy will be adopted. At an IA, the information fraction used in Lan-DeMets spending function to determine the alpha spending at the IA will be based on the minimum of the expected information fraction and the actual information fraction at each analysis. Specifically,

- In the scenario that the events accrue slower than expected and the observed number of events is less than the expected number of events at a given analysis, the information fraction will be calculated as the observed number of events at the IA over the target number of events at FA.
- In the scenario that the events accrue faster than expected and the observed number of events exceeds the expected number of events at a given analysis, then the information fraction will be calculated as the expected number of events at the IA over the target number of events at FA.

The final analysis will use the remaining Type I error that has not been spent at the earlier analysis.

Of note, while the information fraction used for alpha spending calculation will be the minimum of the actual information fraction and the expected information fraction, the correlations required for deriving the bounds will still be computed using the actual information fraction based on the observed number of events at each analysis over the target number of events at FA.

The minimum spending approach assumes timing is not based on any observed Z-value and thus the Z test statistics used for testing conditioned on timing are multivariate normal. Given the probabilities derived with the proposed spending method, the correlations based on actual event counts are used to compute bounds that control the Type I error at the specified alpha level for a given hypothesis conditioned on the interim analysis timing. Since this is true regardless of what is conditioned on, the overall Type I error for a given hypothesis unconditionally is controlled at the specified level. By using more conservative spending early in the study, power can be retained to detect situations where the treatment effect may be delayed.

9.8.2 Progression-free Survival

The study will test PFS at IA only if the OS null hypothesis is rejected. Following the multiplicity strategy as outlined in Figure 3, the PFS hypothesis may be tested at α=0.0125 (if the OS null hypothesis is rejected, but not the ORR hypothesis) or at α= 0.025 (if both the OS and ORR null hypotheses are rejected). Table 14 shows the boundary properties for each of these α levels for the PFS analysis. Note that the final row indicates the total power to reject the null hypothesis for PFS at each α level.

Table 14 Efficacy Boundaries and Properties for Progression-Free Survival Analysis

Analysis	Value	α=0.0125	α=0.025
IA N = 432 Events*: 419 Month: 21	Z	2.2414	1.9600
	p (1-sided) [a]	0.0125	0.025
	HR at bound[b]	0.8032	0.8256
	P(Cross) if HR=1[c]	0.0125	0.025
	P(Cross) if HR=0.65[d]	0.9850	0.9929

HR=hazard ratio; IA=interim analysis.

*The number of events and timing are estimated.

[a] *p* (1-sided) is the nominal α for group sequential testing.

[b] HR at bound is the approximate HR required to reach an efficacy bound.

[c] P (Cross if HR=1) is the probability of crossing a bound under the null hypothesis.

[d] P(Cross if HR=0.65) is the probability of crossing a bound under the alternative hypothesis.

Note that if the OS null hypothesis is rejected, the PFS test statistics computed at IA will be used for inferential testing with its corresponding alpha levels.

9.8.3 Objective Response Rate

The study will test ORR only once at the IA if the OS null hypothesis is rejected. Following the multiplicity strategy as outlined in Figure 3, the ORR hypothesis may be tested at α=0.0125 (if the OS null hypothesis is rejected, but not the PFS hypothesis) or at α= 0.025 (if both the OS and PFS null hypothesis is rejected). Power at the possible α-levels as well as the approximate treatment difference required to reach the bound (ΔORR) are shown in Table 15, assuming underlying 2% and 12% response rates in the control and experimental groups, respectively.

Table 15 Possible α Levels and Approximate Observed ORR Difference Required to Demonstrate Efficacy for Objective Response at IA

α	~Δ ORR	Power (ΔORR=0.1)
0.0125	0.0550	0.970
0.025	0.0481	0.984
IA=interim analysis; ORR=Objective Response Rate.		

Note that if the OS null hypothesis is rejected, the ORR test statistics computed at IA will be used for inferential testing with its corresponding alpha levels.

9.8.4 Safety Analysis

The eDMC has responsibility for assessment of overall risk/benefit. When prompted by safety concerns, the eDMC can request corresponding efficacy data. eDMC review of efficacy data to assess the overall risk/benefit to study participants will not require a multiplicity adjustment typically associated with a planned efficacy IA. However, to account for any multiplicity concerns raised by the eDMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for ORR, PFS, and OS adopting a conservative multiplicity adjustment will be prespecified in the sSAP.

9.9 Sample Size and Power Calculations

The study will randomize 432 participants in a 1:1 ratio into the MK-4280A arm (Arm A) and the standard of care arm (Arm B). OS is the primary endpoint for the study, with PFS and ORR as the key secondary endpoints.

For the OS endpoint, based on a target number of 386 events and 1 IA at approximately 80% of the target number of events, the study has approximately 93.5% power to detect a HR of 0.7 at the initially allocated α=0.025 (1-sided).

For the PFS endpoint, based on a target number of 419 events at the IA (final PFS analysis), the study has approximately 99% power to detect a HR of 0.65 at the reallocated α=0.0125 (1-sided) if only OS hypothesis is rejected.

Based on the 432 participants with at least approximately 10 months of follow-up, the power of the ORR testing at the reallocated α=0.0125 (1-sided) if only OS hypothesis rejected is approximately 97% to detect a 10-percentage point difference between an underlying 2% ORR in the control arm (Arm B) and a 12% ORR in the experimental arm (Arm A).

Note that the above OS and PFS power calculations are based on a constant HR assumption.

Based on CORRECT, RECOURSE, and SUNLIGHT studies, the above sample size and power calculations for OS and PFS assume the following:

- OS follows an exponential distribution with a median of 7.5 months for the control group.
- PFS follows an exponential distribution with a median of 2 months for the control group.
- Enrollment period of 12 months with enrollment ramp-up over first 2 months.
- An annual dropout rate of 2% and 5% for OS and PFS, respectively
- A follow-up period of 22 and 10 months and for OS and PFS, respectively, after the last participant is randomized.

The sample size and power calculations were performed using R ("gsDesign" package).

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect for OS (with a nominal 95% CI) will be estimated and plotted by treatment group within each category of the following subgroup variables:

- Geographic region (Asia Pacific; EMEA/Americas)
- Geographic region (Western Europe/North America, Asia, Rest of the World)
- Time from initial diagnosis of metastatic disease to randomization (≥18 months, <18 months)
- ECOG PS (0, 1)
- Age category (<65 years, ≥65 years)
- Sex (female, male)
- Race (white, all others)
- Primary tumor sidedness (left-sided, right-sided)

- Number of prior treatments (0-3, ≥4)
- Presence of liver metastasis (Yes, No)
- RAS (WT, mutant)
- Investigators' choice of standard of care chemotherapy prior to randomization (regorafenib versus TAS-102)

The consistency of the treatment effect will be assessed using descriptive statistics for each category of the subgroup variables listed above. If the number of participants in a category of a subgroup variable is less than 10% of the ITT population, the subgroup analysis will not be performed for this category of the subgroup variable, and this subgroup variable will not be displayed in the forest plot. The subgroup analyses for OS will be conducted using an unstratified Cox model.

9.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

9.12 Extent of Exposure

Extent of Exposure for a participant is defined as the number of cycles and number of days for which the participant receives the study intervention. Summary statistics will be provided on the extent of exposure for the overall study intervention for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data

protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing; in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary,

authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

See country-specific requirements in Appendix 7.

10.1.2 Financial Disclosure

Financial disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for financial disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, frequently known as a financial disclosure form, provided by

the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

The Sponsor will conduct this study in compliance with all applicable data protection regulations.

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 that 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.

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.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee, affiliated institution, and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution, and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules, and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets

regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 External Data Monitoring Committee

To supplement the routine study monitoring outlined in this protocol, an external DMC will monitor the interim data from this study. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the study in any other way (eg, they cannot be study investigators) and must have no competing interests that could affect their roles with respect to the study.

The DMC will make recommendations to the EOC regarding steps to ensure both participant safety and the continued ethical integrity of the study. Also, the DMC will review interim study results, consider the overall risk and benefit to study participants (Section 9.7 Interim Analysis) and recommend to the EOC whether the study should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the study governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in the DMC charter that is reviewed and approved by all the DMC members.

10.1.4.2 Executive Oversight Committee

The EOC is comprised of members of Sponsor Senior Management. The EOC will receive and decide on any recommendations made by the DMC regarding the study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. 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.

If publication activity is not directed by the Sponsor, 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.

Authorship will be determined by mutual agreement and in line with ICMJE authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study-site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of GCP (eg, ICH GCP: Consolidated Guideline and other generally accepted standards of GCP), and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Trials.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor’s studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator’s knowledge, threatened.

For investigators located in countries with serious breach reporting requirements, investigator will promptly report to the Sponsor any serious breach or suspected serious breach that occurs in compliance with those requirements. Unless more specifically defined in the applicable requirements, a serious breach is any breach of the applicable clinical trial regulation or of the clinical trial protocol which is likely to affect to a significant degree: (i) the safety or rights of a trial participant, or (ii) the reliability and robustness of the data generated in the clinical trial.

10.1.8 Data Quality Assurance

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

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion 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.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

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

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study-site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor or designee will promptly notify that study site's IRB/IEC as specified by applicable regulatory requirement(s).

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- See country-specific requirements in Appendix 7.

Table 16 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices[a] MCV MCH % Reticulocytes[b]	WBC count with Differential[b]: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN[c]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	CO2 or Bicarbonate[a]	Chloride	Phosphorous
	Creatinine[d]	Sodium	ALT/SGPT	Total Protein
	Glucose nonfasting	Calcium	Alkaline phosphatase	Magnesium
	Amylase/Lipase[e]		LDH	
Routine Urinalysis[f]	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick. Dry chemical method may be used to evaluate leukocyte esterase as per institutional standard. See country-specific requirements in Appendix 7. • Microscopic examination (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine pregnancy test (as needed for WOCBP)[g]			

Laboratory Assessments	**Parameters**
Screening Only Tests	• PT/INR and aPTT/PTT[h] • FSH (as needed in WONCBP only)[i] • Serology (HIV antibody, HBsAg, and Hepatitis C Virus antibody). NOTE: certain ex-US sites require testing for HIV and Hepatitis B and C during screening. Consult with regional health authorities and institutional standards to confirm if such testing is applicable[j]. • See country-specific requirements in Appendix 7
Other Tests	• Thyroid panel: TSH, T3/FT3, and T4/FT4[k] • ACTH/Cortisol • Serum Tumor Marker (CEA)

ACTH=adrenocorticotrophic hormone; ALT=alanine aminotransferase; aPTT/PTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C1D1=Cycle 1 Day 1; CEA=Carcinoembryonic antigen; CO2=carbon dioxide; EOT=end of treatment; FSH=follicle-stimulating hormone; FT3=free triiodothyronine; FT4=free thyroxine; GFR=glomerular filtration rate; HBsAg=Hepatitis B surface antigen; HBV DNA=Hepatitis B virus deoxyribonucleic acid; HCV=Hepatitis C virus; HCV RNA=Hepatitis C virus ribonucleic acid; HIV=human immunodeficiency virus; INR=international normalization ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; T3=triiodothyronine; T4thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; US=United States; WBC=white blood cells; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

a. Performed only if considered local standard of care.
b. Absolute or % acceptable per institutional standard.
c. Urea is acceptable if BUN is not available as per institutional standard.
d. GFR (measured or calculated) or creatinine clearance can be used in place of creatinine.
e. Obtain lipase and amylase test for screening, EOT and 30-day follow-up.
f. If urine dipstick is abnormal, urinalysis must be performed. Perform on WOCBP only 24 hours before first dose.
g. Pregnancy tests must be repeated before every cycle.
h. Performed as part of the screening assessment and as clinically indicated for participants taking anticoagulants.
i. If necessary, to check menopausal status.
j. HBsAg or HBV DNA. HCV RNA (qualitative) or HCV antibody.
k. Participants may be dosed in subsequent cycles after C1D1 while thyroid function tests are pending. Free T3/T4 is acceptable when total T3/T4 cannot be determined.

The investigator or medically qualified designee (consistent with local requirements) must document their review of each laboratory safety report.

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication Error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic intentional, excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a 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 a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 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.

An 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
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant 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 (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect
   - In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events
   - 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 1 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.

10.3.4 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same time frame as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not the cancer under study) as noted in Section 8.4.1.
- Is associated with an overdose.

10.3.5 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- 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 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 blinded on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.
  - 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.
  - Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
  - Grade 4: Life threatening consequences; urgent intervention indicated.
  - Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?
- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**
  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?
  - **Likely Cause**: Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.
  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?
    - If yes, did the AE resolve or improve?
    - If yes, this is a positive dechallenge.
    - If no, this is a negative dechallenge.

(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

  - **Rechallenge**: Was the participant re-exposed to the Sponsor's product in this study?
    - If yes, did the AE recur or worsen?
    - If yes, this is a positive rechallenge.
    - If no, this is a negative rechallenge.

(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL, AND IF REQUIRED, THE INIRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.
- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:
    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)
- 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 follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.
- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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.
- New or updated information will be recorded in the CRF.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.6 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- 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 EDC 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 EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure email of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Medical Device and Drug–Device Combination Products: Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

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

Women in the following categories are not considered WOCBP:

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

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

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal 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.

10.5.2 Contraceptive Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency Failure rate of <1% per year when used consistently and correctly.
• See country-specific requirements in Appendix 7. • Progestogen-only subdermal contraceptive implant[b] • IUS[c] • Non-hormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This 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. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
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 intervention. 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.
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research[3, 4]

The specimens consented and/or collected in this study as outlined in Section 8.8 will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways with which drugs/vaccines may interact
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

3. Summary of Procedures for Future Biomedical Research[3, 4]

a. Participants for Enrollment
All participants enrolled in the clinical study will be considered for enrollment in future biomedical research.

b. Informed Consent
Informed consent for specimens (ie, DNA, RNA, protein, etc) will be obtained during screening for protocol enrollment from all participants or legal guardians, at a study visit by the investigator or his or her designate. Informed consent for future biomedical research should be presented to the participants on the visit designated in the SoA. If delayed, present consent at next possible Participant Visit. Consent forms signed by the participant will be kept at the clinical study site under secure storage for regulatory reasons.

A template of each study site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens
Documentation of participant consent for future biomedical research will be captured in the eCRFs. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen(s)
Collection of specimens for future biomedical research will be performed as outlined in the SoA. In general, if additional blood specimens are being collected for future biomedical research, these will usually be obtained at a time when the participant is having blood drawn for other study purposes.

4. Confidential Participant Information for Future Biomedical Research[3, 4]

In order to optimize the research that can be conducted with future biomedical research specimens, it is critical to link participants' clinical information with future test results. In fact, little or no research can be conducted without connecting the clinical study data to the specimen. The clinical data allow specific analyses to be conducted. Knowing participant characteristics like sex, age, medical history, and intervention outcomes is critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for future biomedical research, the Sponsor has developed secure policies and procedures. All specimens will be single coded per ICH E15 guidelines as described below.

At the clinical study site, unique codes will be placed on the future biomedical research specimens. This code is a random number that does not contain any personally identifying information embedded within it. The link (or key) between participant identifiers and this unique code will be held at the study site. No personal identifiers will appear on the specimen tube.

5. Biorepository Specimen Usage[3, 4]

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses using the future biomedical research specimens may be performed by the Sponsor, or an additional third party (eg, a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third-party analyses will conform to the specific scope of analysis outlined in future biomedical research protocol and consent. Future biomedical research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

6. Withdrawal From Future Biomedical Research[3, 4]

Participants may withdraw their consent for FBR and ask that their biospecimens not be used for FBR. Participants may withdraw consent at any time by contacting the study investigator. If medical records for the study are still available, the investigator will contact the Sponsor using the designated mailbox

(clinical.specimen.management@MSD.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to study use only. If specimens were collected from study participants specifically for FBR, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed before the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

If the medical records for the study are no longer available (eg, if the investigator is no longer required by regulatory authorities to retain the study records) or the specimens have been completely anonymized, there will no longer be a link between the participant's personal information and their specimens. In this situation, the request for withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens[3, 4]

Future biomedical research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not used in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility, which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3, 4]

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated study administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards to protect against unauthorized access.

9. Reporting of Future Biomedical Research Data to Participants[3, 4]

No information obtained from exploratory laboratory studies will be reported to the participant, family, or physicians. Principle reasons not to inform or return results to the participant include lack of relevance to participant health, limitations of predictive capability, and concerns regarding misinterpretation.

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and participants. Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population[3, 4]

Every effort will be made to recruit all participants diagnosed and treated on Sponsor clinical studies for future biomedical research.

11. Risks Versus Benefits of Future Biomedical Research[3, 4]

For future biomedical research, risks to the participant have been minimized and are described in the future biomedical research informed consent.

The Sponsor has developed strict security, policies, and procedures to address participant data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation, there is risk that the information, like all medical information, may be misused.

12. Questions

Any questions related to the future biomedical research should be emailed directly to clinical.specimen.management@MSD.com.

13. References

1. National Cancer Institute [Internet]: Available from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45618
2. International Council on Harmonisation [Internet]: E15: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available from http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/definitions-for-genomic-biomarkers-pharmacogenomics-pharmacogenetics-genomic-data-and-sample-cod.html
3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group [Internet]: Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

10.7 Appendix 7: Country-specific Requirements

10.7.1 China-specific Requirements

Biomarker sample collection and analysis for participants enrolled in China will be dependent on approval by the HGRAC. Please see Section 5.1 Inclusion Criteria for eligibility.

Section 8.1.12 Tumor Tissue for Biomarker Status

In China, the below samples, including tumor tissue or slides, will be collected for the participants who enrolled after HGRAC approval of the biomarker testing:

- Tumor tissue blocks or slides for PD-L1
- Tumor tissue blocks or slides for MMR

Section 9.5 Analysis Populations:

The Chinese participants randomized after the enrollment of the global portion is closed if any will not be included in the primary analysis population which is based on the global portion. The China portion will also be analyzed separately per local regulatory requirement.

Appendix 2: Clinical Laboratory Tests

For the urinalysis, Leucocytes Esterase may be substituted using Leucocyte, as per institutional standard.

10.7.2 Czech Republic-specific Requirements

Section 1.3 Schedule of Activities

HBV, HCV, HIV, and tuberculosis (if applicable) testing at screening is mandatory.

Section 5.1 Inclusion Criteria

Inclusion Criterion: Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows: TAS-102 (180 days) and regorafenib (90 days). No contraception requirements are needed for males receiving MK-4280A.

Section 5.2 Exclusion Criteria

- Exclusion Criterion: Has a known history of HIV infection. Testing for HIV is required at screening.
- Exclusion Criterion: has active tuberculosis (if applicable).

- Exclusion Criterion: Has a known history of Hepatitis B (defined as Hepatitis B surface antigen reactive) or known active Hepatitis C virus (defined as Hepatitis C virus RNA [qualitative] is detected) infection.

Note: Testing for Hepatitis B and Hepatitis C is required at screening.

Section 6.5 Concomitant Therapy

Investigators must refer to the up-to-date SmPCs of registered products used in this study, regarding forbidden medications or medications to be used with precaution. Specific to the use of regorafenib, avoid concomitant use of strong CYP3A4 inducers (eg, rifampin, phenytoin, carbamazepine, phenobarbital, and St. John's Wort) and inhibitors of CYP3A4 activity (eg, clarithromycin, grapefruit juice, itraconazole, ketoconazole, posaconazole, telithromycin, and voriconazole). CYP3A4 inhibitors and inductors may impact mean exposure of regorafenib. UGT1A9 inhibitors (eg, phenytoin, fosphenytoin, diflunisal) should also be avoided.

Section 6.5.1 Rescue Medications and Supportive Care

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered within 30 days prior to the first dose of study intervention, while participating in the study, and for 120 days after the last dose of study intervention.

Section 10.5 Appendix 5: Contraceptive Guidance

Ovulation-blocking oral hormonal contraception to be included as a highly reliable contraception method.

10.7.3 France-specific Requirements

Section 1.3 Schedule of Activities

Pregnancy testing must be performed at each cycle during study intervention as well as at the end-of-study intervention and at Safety FU.

Section 5.1 Inclusion Criteria

Inclusion Criteria: Patients will be included according to the renal function requirement below:

Renal	
Creatinine AND/OR Measured or calculateda creatinine clearance (GFR can also be used in place of creatinine or CrCl) [a]CrCl should be calculated per institutional standard.	≤1.5 × ULN AND/OR ≥60 mL/min for participant with creatinine levels >1.5 × institutional ULN

Inclusion Criteria: Male participants to use contraception for 180 days (6 months) after completing TAS-102 treatment.

Section 8.1.8 Study Intervention Administration

Investigators should refer to http://base-donnees-publique.medicaments.gouv.fr for updated SmPC of the marketing authorization of commercially available products used during the study for patient management, particularly regarding safety monitoring, product contraindications, and precautions.

Section 8.3.6 Pregnancy Testing

Monthly urine pregnancy testing is required during treatment as well as up to 120 days (4 months) for WOCBP in Arm A (MK-4280A) and 180 days (6 months) for WOCBP in Arm B (TAS-102 plus regorafenib).

Section 10.5 Appendix 5: Contraceptive Guidance

Pregnancy testing must be performed at each cycle during study intervention as well as at the end-of-study intervention and at Safety FU.

10.7.4 Germany-specific Requirements

Legally Acceptable Representative

Persons of legal age, who are incapable of comprehending the nature, significance and implications of the clinical trial and of determining their will, are excluded from the trial at German sites; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Section 1.3 Schedule of Activities

Monthly urine pregnancy testing is required during study intervention as well as at the end-of-study intervention and at Safety FU.

Section 5.2 Exclusion Criteria

Exclusion Criterion: HIV testing is required for participants.

Exclusion Criterion: Hepatitis B and C testing is required for participants.

Section 10.5 Appendix 5: Contraceptive Guidance

Monthly urine pregnancy testing after randomization is required during study intervention as well as at the end-of-study intervention and at Safety FU.

10.7.5 Italy-specific Requirements

Section 1.3 Schedule of Activities

- Monthly urine pregnancy testing is required during treatment as well as up to 120 days for WOCBP in Arm A (MK-4280A) and 180 days for WOCBP in Arm B (TAS-102 plus regorafenib)

- HBV, HCV, HIV and tuberculosis testing at Screening is mandatory.

Section 5.2: Exclusion Criteria

- Has an active infection requiring systemic therapy (eg, tuberculosis, known viral or bacterial infections).

Note: Testing for tuberculosis is requested at screening.

- Has a known history of HIV infection. HIV testing is required at screening.

- Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: Testing for Hepatitis B and Hepatitis C is required for screening.

Section 8.3.6 Pregnancy Testing

- Monthly urine pregnancy testing is required during treatment as well as up to 120 days for WOCBP in Arm A (MK-4280A) and 180 days for WOCBP in Arm B (TAS-102 plus regorafenib).

Section 10.5 Appendix 5: Contraceptive Guidance

- Monthly urine pregnancy testing is required during treatment as well as up to 120 days for WOCBP in Arm A (MK-4280A) and 180 days for WOCBP in Arm B (TAS-102 plus regorafenib).

10.7.6 Japan-specific Requirements

Section 1.3 Schedule of Activities

Hepatitis B virus test (HBs antigen, HBc antibody, and HBs antibody) at screening is mandatory.

1.3.1 Arm A (MK-4280A)

In addition to all study procedures and assessments listed, the following procedure should be performed as indicated for subjects in Japan.

Table 17 Japan-specific Trial Flow Chart

Study Period	Screening Phase	Intervention Phase (3-Week Cycles)						End of Treatment	Posttreatment			Notes
Visit Number /Title	Screening	C1	C2	C3	C4	C5	C6-C35	Discon	Safety Follow-up*	Efficacy Follow-up	Survival Follow-up	All assessments should be performed prior to treatment administration unless otherwise indicated. If discontinuation visit occurs ≥30 days from last dose of study intervention, a separate Safety Follow-up Visit is not required, and all Safety Follow-up procedures will be performed at the discontinuation visit. *Refer to Section 8.12.4.1 for details.
Cycle Day	Up to 28 days prior to first dose	1	1	1	1	1	1	At Discon	30 days from last dose			
Scheduled Days	-28 to -1	+3	±3	±3	±3	±3	±3	+7	+7	Q9W ±7	Q12W ±7	
Clinical Procedures/Assessments												
Pulse Oximetry (SpO_2)		X	X	X	X	X	X	X	X			At C1D1, collect prior to first dose of study intervention.

C1D1=Cycle 1, Day 1; Discon=discontinuation; Q9W=every 9 weeks; Q12W=every 12 weeks

For subjects in Japan only, pulse oximetry will be performed using local standard procedures by the investigator or qualified designee at the time points outlined in Table 17 above.

Section 5.2 Exclusion Criteria

- Exclusion Criterion: Has a known history of Hepatitis B (defined as HBsAg) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: Testing for Hepatitis B and Hepatitis C is required at screening.

Patients who are HBc antibody positive or HBs antibody positive will be excluded from the study.

Subjects who are positive for HBs antibody but negative for HBc antibody and HBs antigen and have a known history of HBV vaccination are eligible.

10.7.7 Korea-specific Requirements

Section 1.3 Schedule of Activities

HBV, HCV, and HIV testing at screening is mandatory.

Section 5.2 Exclusion Criteria

- Exclusion Criterion: Has a known history of HIV infection. Testing for HIV is required at screening.

- Exclusion Criterion: Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: Testing for Hepatitis B and Hepatitis C is required at screening.

10.7.8 South Africa-specific Requirements

Section 5.2 Exclusion Criteria

- Exclusion Criterion: Has a known history of HIV infection. Testing for HIV is required at screening.

- Exclusion Criterion: Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: Testing for Hepatitis B and Hepatitis C is required at screening.

10.7.9 Spain-specific Requirements

Section 1.3 Schedule of Activities

Pregnancy testing must be performed at each cycle during study intervention as well as at the end-of-study intervention and at Safety FU.

Section 5.2 Exclusion Criteria

- Exclusion Criterion: Has a known history of HIV infection. Testing for HIV is required at screening.

- Exclusion Criterion: has active tuberculosis (if applicable).

- Exclusion Criterion: Has a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.

Note: Testing for Hepatitis B and Hepatitis C is required at screening.

Section 6.5 Concomitant Therapy

Investigators must refer to the up-to-date SmPCs of registered products used in this study, regarding forbidden medications or medications to be used with precaution.

Section 10.5 Appendix 5: Contraceptive Guidance

Pregnancy testing must be performed at each cycle during study intervention as well as at the end-of-study intervention and at Safety FU.

10.7.10 Sweden-specific Requirements

Section 4.2.1.2 Safety Endpoints

Safety parameters commonly used for evaluating investigational systemic anticancer treatments are included as safety endpoints including, but not limited to, the incidence of, causality, and outcome of AEs/SAEs; and changes in vital signs and laboratory values. Adverse events will be assessed as defined by CTCAE,v5.0.

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

10.1.1 Code of Conduct for Clinical Trials

III. Participant Protection

A. Ethics Committee Review (IRB/IEC) and Health Authorities

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents must be submitted to and approved by the applicable Competent Authority and IRB/IEC before the study is initiated in accordance with EU Directive 2001/20/EC, Article 10 (a) and/or local requirements. Any amendments to the protocol will require IRB/IEC and Competent Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants [2001/20/EC, Article 10 (c)].

- Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

In the EU [CT-1 (2010/C 82/01)], the Sponsor must send immediate end-of-study notification to the national competent authority and the Ethics Committee of the Member State concerned. The end-of-study notification must be sent within 15 days after the study is halted to clearly describe the reasons and follow-up measures, if any, taken for safety reasons. The 15-day notification applies only for early termination of the study. Otherwise the time window to send end-of-study notification is 90 days in the EU.

10.7.11 United Kingdom-specific Requirements

Section 5.1 Inclusion Criteria

Inclusion Criterion: Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows: TAS-102 (180 days) and regorafenib (90 days). No contraception requirements are needed for males receiving MK-4280A.

Section 6.5.1 Rescue Medications and Supportive Care

Listed below are specific concomitant therapies or vaccinations that are prohibited during the study (exceptions noted):

- Live vaccines must not be administered for 90 days after the last dose of study intervention.

- Males are to be advised to seek counseling on sperm storage before starting treatment with pemetrexed, etoposide, and/or platinum-based therapy as per respective SmPCs.

- Monthly urine pregnancy testing is required during treatment as well as at the end-of-study treatment.

10.8 Appendix 8: Description of the iRECIST Process for Assessment of Disease Progression

Not applicable.

10.9 Appendix 9: Eastern Cooperative Oncology Group Performance Status

Grade	Performance Status
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but ambulatory. 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	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

[ECOG ACRIN Cancer Research Group 2016]

10.10 Appendix 10: Abbreviations

Abbreviation	Expanded Term
3L	third-line
3L+	third-line or beyond
ACTH	adrenocorticotrophic hormone
ADA	antidrug antibodies
ADL	activities of daily living
AE	adverse event
AJCC	American Joint Committee on Cancer
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APaT	All-Participants-as-Treated
aPTT/PTT	activated partial thromboplastin time
AR	adverse reaction
ART	antiretroviral therapy
AST	aspartate aminotransferase
BICR	blinded independent central review
BID	twice daily
BP	blood pressure
BUN	blood urea nitrogen
C	cycle
CAPOX	capecitabine and oxaliplatin
C30	cancer-specific 30 items
CD	cluster of differentiation
CD28	cluster of differentiation 28
CD3ζ	CD3 zeta
CEA	carcinoembryonic antigen
CF	compact flash
CG	Cockcroft-Gault
CI	confidence interval
CL	clearance
C_{max}	maximum concentration
C_{min}	minimum concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disease
CPS	combined positive score
CR	complete response
CR29	colorectal cancer-specific 29 items
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report

Abbreviation	Expanded Term
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
C_{trough}	minimum concentration
D	day
DCR	disease control rate
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
ECOG PS	ECOG performance status
eCRF	electronic Case Report Form
EDC	electronic data collection
eDMC	external data monitoring committee
EEA	European Economic Area
EGFR	epidermal growth factor receptor
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EMEA	Europe, Middle East, Africa
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
EOT	end of treatment
ePRO	electronic patient-reported outcome
EQ-5D-5L	EuroQoL 5D-5L
ESMO	European Society for Medical Oncology
EU	European Union
FA	final analysis
FAS	full analysis set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed paraffin-embedded
FOLFIRI	folinic acid, fluorouracil, and irinotecan
FOLFIRINOX	folinic acid, fluorouracil, irinotecan, and oxaliplatin
FOLFOX	fluoropyrimidine, oxaliplatin, and irinotecan
FOLFOXIRI	folinic acid, fluorouracil, irinotecan, and oxaliplatin
FSH	follicle-stimulating hormone

Abbreviation	Expanded Term
FT3	free triiodothyronine
FT4	free thyroxine
FU	follow-up
GFR	glomerular filtration rate
GI	gastrointestinal
H1	Hypothesis 1
H2	Hypothesis 2
H3	Hypothesis 3
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HGRAC	Human Genetic Resources Administration of China
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HR	hazard ratio
HRQoL	health related quality of life
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
iCRO	imaging contract research organization
ID	identification
IEC	independent ethics committee
Ig	immunoglobulin
IgG4	humanized immunoglobulin G4
IgV-type	Ig-variable–type
IHC	Immunohistochemistry
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IO	immuno-oncology
irAE	immune-related AE
IRB	institutional review board
iRECIST	response evaluation criteria in solid tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
ITT	intention-to-treat
IUD	intrauterine device
IUO	investigational use only
IUS	intrauterine hormone-releasing system
IV	intravenous

Abbreviation	Expanded Term
IVD	in vitro diagnostic
JSCCR	Japanese Society for Cancer of the Colon and Rectum
LAG-3	lymphocyte activation gene 3
LAM	lactational amenorrhea method
M&N	Miettinen and Nurminen
mAb	monoclonal antibody
MCH	mean corpuscular hemoglobin
mCRC	metastatic colorectal cancer
MCV	mean corpuscular volume
MHC	major histocompatibility complex
MMR	mismatch repair
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NIMP	non-investigational medicinal product
non-MSI-H	non-microsatellite instability-high
NSAE	nonserious adverse event
NSAID	nonsteroidal anti-inflammatory drug
NSCLC	nonsmall cell lung cancer
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
OS	overall survival
PBPK	physiologically based pharmacokinetic
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic
PKCθ	protein kinase C-theta
pMMR	proficient mismatch repair
PO	orally
PR	partial response
pRBC	packed red blood cell
PRO	patient-reported outcome
PT	prothrombin time

Abbreviation	Expanded Term
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
Q9W	every 9 weeks
QD	daily
QLQ	Quality of Life Questionnaire
QoL	quality of life
RBC	red blood cells
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
ROW	rest of world
SAE	serious adverse event
SEER	Surveillance, Epidemiology, and End Results
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SIM	Site Imaging Manual
sLAG-3	soluble Lymphocyte activation gene-3
SmPC	Summary of Product Characteristics
SoA	schedule of activities
SOC	standard of care
sSAP	supplemental statistical analysis plan
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TB	tuberculosis
TEA	treatment eligibility assessment
TIL	tumor-infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
TMDD	target-mediated drug disposition
TRAE	treatment-related adverse event
Tregs	regulatory T cells
TSH	thyroid-stimulating hormone
TTD	time to deterioration
UK	United Kingdom
ULN	upper limit of normal
US	United States
V	volume of distribution
VEGF	vascular endothelial growth factor
WBC	white blood cells
WOCBP	woman/women of childbearing potential
WT	wild type

Abbreviation	Expanded Term
XELIRI	capecitabine plus irinotecan
XELOX	capecitabine plus oxaliplatin
ZAP70	zeta-chain-associated protein kinase

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