Official Title of Study:

Phase 1/2 Open-label Study of BMS-986466 in Combination with Adagrasib with or without Cetuximab in Participants with KRAS G12C-mutant Advanced Solid Tumors

NCT Number: NCT06024174

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CLINICAL PROTOCOL CA1260015

Phase 1/2 Open-label Study of BMS-986466 in Combination with Adagrasib with or without Cetuximab in Participants with KRAS G12C-mutant Advanced Solid Tumors

Compound: BMS-986466 (BBP-398, IACS-15509)

Brief Title:

A Study of BMS-986466 with Adagrasib with or without Cetuximab in Participants with KRAS G12C-mutant Solid Tumors

Protocol Amendment 01

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REGULATORY AGENCY IDENTIFIER NUMBER(S)

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DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Protocol Amendment 01	07-Jul-2023	The purpose of this protocol amendment is to elaborate on the inclusion criteria for participants harboring actionable mutations, [redacted] to include the criterion of having received an approved targeted therapy for that particular mutation, if any, to be considered eligible to participate in this study.
Administrative Letter 01	22-May-2023	The purpose of this Administrative Letter is to correct a typographical error in Table 2-1: Cycle 1 Day 15 (changed to Day 18) and Day 22 (deleted). Updates were made to align with Table 2-3.
Original Protocol	16-May-2023	Not applicable.

OVERALL RATIONALE FOR PROTOCOL AMENDMENT 01:

The purpose of this protocol amendment is to elaborate on the inclusion criteria for participants harboring actionable mutations, [redacted] to include the criterion of having received an approved targeted therapy for that particular mutation, if any, to be considered eligible to participate in this study.

This amendment also incorporates changes from the approved Administrative Letter 01, which are detailed in the Document History, but not listed in the Summary of Key Changes below.

SUMMARY OF CHANGES FOR PROTOCOL AMENDMENT 01		
Section Number & Title	**Description of Change**	**Brief Rationale**
Table 2-1: Procedural Outline (Part 1 DDI Cohort Only; CA1260015)	Deleted footnote "h" "Other targetable mutations, including ALK, ROS1, RET, NTRK, MET amplification, MET exon 14 skipping mutations, and other non-KRAS mutations, should be documented if available." As a result of the deletion, footnote "h" was updated to "g" for the "Participants with PDAC and BTC: EGFR, GFFR2, IDH1, BRAF non-V600X, and Other Mutations."	To address redundancy of footnote "h" with "g"
Section 6.1: Inclusion Criteria	Added inclusion criterion 2)d)iii) regarding participants with known actionable mutations.	[redacted] to clarify prior treatments with targeted therapies for tumors with actionable mutations.
All	Minor formatting and typographical corrections	Minor, therefore, have not been summarized

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1 PROTOCOL SUMMARY

Protocol Title	Phase 1/2 Open-label Study of BMS-986466 in Combination with Adagrasib with or without Cetuximab in Participants with KRAS G12C-mutant Advanced Solid Tumors	
Brief Title	A Study of BMS-986466 with Adagrasib with or without Cetuximab in Participants with KRAS G12C-mutant Solid Tumors	
Study Intervention	BMS-986466 in combination with adagrasib in participants with KRAS G12C-mutant non-small cell lung cancer, pancreatic duct adenocarcinoma, and biliary tract cancer, and BMS-986466 in combination with adagrasib with or without cetuximab in participants with KRAS G12C-mutant colorectal cancer.	
Background and Rationale	BMS-986466 is a potent, selective, orally active allosteric inhibitor of SHP2, a ubiquitously expressed scaffolding protein and tyrosine phosphatase that transduces signaling from multiple RTKs to activate the small GTPase, RAS, and MAPK signaling pathway and can dephosphorylate and deactivate several negative regulators of the RAS/MAPK pathway. Adagrasib is a potent, orally available, small molecule, covalent inhibitor of KRAS G12C [redacted] Since SHP2 is a central node in downstream RTK activation, BMS-986466 may be beneficial as a component of combination therapy in cancers driven by constitutive MAPK pathway mutations to maximize the therapeutic potential of adagrasib with or without cetuximab.	
Objectives and Endpoints	**Objectives**	**Endpoints**
Primary		
	• To characterize the safety and tolerability; to establish the MTD, if reached; to evaluate the MAD if MTD is not reached; and to identify dose level(s) for expansion of: – Part 1A: BMS-986466 administered in combination with adagrasib to participants with KRAS G12C-mutant NSCLC, CRC, PDAC, and BTC – Part 1B: BMS-986466 administered in combination with adagrasib with cetuximab to participants with KRAS G12C-mutant CRC	• Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and deaths
	• To evaluate anti-tumor activity: – Part 2A: BMS-986466 in combination with adagrasib vs adagrasib in participants with KRAS G12C-mutant (G12Ci treatment-naïve) NSCLC – Part 2B: BMS-986466 in combination with adagrasib with or without cetuximab vs adagrasib with cetuximab in participants with KRAS G12C-mutant (G12Ci treatment-naïve) CRC	• ORR per RECIST v1.1 by BICR

Secondary		
	• Parts 1 and 2: To characterize the PK profile of BMS-986466 following first dose and at steady state in combination with adagrasib with or without cetuximab	• Summary measures of BMS-986466 PK parameters in plasma including Cmax, Tmax, and AUC(0-T), from concentration-time data
	• To evaluate the preliminary efficacy of: – Part 2A: BMS-986466 in combination with adagrasib vs adagrasib in participants with KRAS G12C-mutant (G12Ci treatment-naïve) NSCLC – Part 2B: BMS-986466 in combination with adagrasib with or without cetuximab vs adagrasib with cetuximab in participants with KRAS G12C-mutant (G12Ci treatment-naïve) CRC	• PFS, DCR, DOR, and TTR per RECIST v1.1 by BICR
	• To assess the safety and tolerability of: – Part 2A: BMS-986446 in combination with adagrasib in participants with KRAS G12C-mutant (G12Ci treatment -naïve) NSCLC – Part 2B: BMS-986446 in combination with adagrasib with or without cetuximab in participants with KRAS G12C-mutant (G12Ci treatment-naïve) CRC	• Incidence of AEs, SAEs, AEs leading to discontinuation, and deaths
	• To assess the PD profile of BMS-986466	• Summary measures of target engagement such as, but not limited to, pERK.
Overall Design	This is a Phase 1/2 multi-center, open-label study of BMS-986466 in combination with adagrasib in participants with KRAS G12C-mutant NSCLC, PDAC, BTC, and BMS-986466 in combination with adagrasib with or without cetuximab in KRAS G12C-mutant CRC. **Part 1 (DDI Cohort and Dose Escalation):** The potential DDI between BMS-986466 and adagrasib will be evaluated. A minimum of 6 PK-evaluable participants will be treated with a single dose of BMS-986466 10 mg PO on C1D1 followed by continuous dosing of adagrasib 400 mg BID starting on [redacted] and another single dose of BMS-986466 10 mg on [redacted]. Starting on C3D1, participants will be treated daily with the combination of BMS-986466 10 mg QD and adagrasib 400 mg BID. The PK evaluation from the DDI cohort will inform the subsequent dose levels of BMS-986466 in combination with adagrasib. Based on the data from this DDI cohort, dose levels will be evaluated to achieve exposures approximately comparable to or less than BMS-986466 [redacted] and [redacted] mg QD monotherapy from Study NAV-1001 in combination with adagrasib (Part 1A) or adagrasib plus cetuximab (Part 1B). **Part 2 (Randomized Dose Expansion):** A randomized, open-label dose expansion with comparator cohorts to assess preliminary efficacy, optimal dose level(s), safety, and tolerability of BMS-986466 in combination with adagrasib with or without cetuximab. The doses to be administered in Parts 2A and 2B will not exceed doses determined to be tolerable from Parts 1A and 1B of the study, respectively.	
Number of Participants	A total of approximately 410 evaluable participants will be treated in this study. A minimum of 6 PK-evaluable participants will be treated in Part 1 DDI cohort. In Parts 1A and 1B (excluding the DDI cohort), approximately 3 to 9 DLT-evaluable participants will be tested per dose level	

	up to approximately 54 participants. In Parts 2A and 2B, approximately 150 and 200 response-evaluable participants will be treated, respectively.	
Study Population	Key Inclusion Criteria	**Part 1:** • Participants must have histologically documented, locally advanced and unresectable, or metastatic NSCLC, PDAC, BTC (DDI, Part 1A), or CRC (DDI, Parts 1A and 1B) with KRAS G12C mutation, whether naïve to KRAS G12C inhibitor treatment or not. • For NSCLC and CRC: Participants must have a documented KRAS G12C mutation from a NYS-approved or FDA-approved/cleared or CE-marked test or, when such result is not available, positive KRAS G12C mutation status should be confirmed by a central laboratory (Guardant360 CDx) in liquid biopsy samples collected at the time of screening. • For PDAC and BTC: Participants must have a documented KRAS G12C mutation from an NYS-approved, FDA-approved/cleared, or CE-marked test and liquid biopsy samples collected only for retrospective testing. • Have progression or are intolerant or have disease recurrence on or after available standard of care treatments. **Part 2:** • Participants must have histologically documented, locally advanced and unresectable, or metastatic KRAS G12C-mutant NSCLC (Part 2A) or CRC (Part 2B), naïve to treatment with KRAS G12C inhibitor. • Participants must have a documented KRAS G12C mutation from a NYS-approved or FDA-approved/cleared or CE-marked test or, when such result is not available, positive KRAS G12C mutation status should be confirmed by a central laboratory (Guardant360 CDx) in liquid biopsy and/or tumor samples collected at the time of screening or from archival biopsies (less than 1 year old). • Have progression or disease recurrence or are intolerant after at least 1 prior line of systemic therapy.
	Key Exclusion Criteria	• Have tumors harboring known activating mutations in BRAF V600X, PTPN11 (SHP2), or KRAS Q61X. • Uncontrolled or significant cardiovascular disease. • Interstitial lung disease or pneumonitis (previous Grade 1 or 2 immune-mediated pneumonitis is permitted if completely resolved).
Study Intervention Administration and Duration	In the DDI cohort, a single dose of BMS-986466 10 mg PO will be given on C1D1 and [redacted] with continuous dosing of adagrasib 400 mg BID starting on [redacted]. Starting on C3D1, participants will be treated daily with the combination of BMS-986466 10 mg QD and adagrasib 400 mg BID. Based on the data from this DDI cohort, dose levels will be evaluated to achieve exposures approximately comparable to or less than BMS-986466 [redacted] mg QD monotherapy from Study NAV-1001 in combination with adagrasib (Part 1A) or adagrasib plus cetuximab (Part 1B). Decisions for dose escalation and to continue enrollment according to the outlined study protocol will be made by the Sponsor in collaboration with the investigators, and take into consideration all available safety, PK, and PD data. Part 2 is a randomized, open-label dose expansion with comparator cohorts to assess preliminary efficacy, safety, and tolerability of optimal dose level(s) of BMS-986466 in combination with adagrasib with or without cetuximab. The doses to be administered in Parts 2A and 2B will not exceed doses determined to be tolerable from Parts 1A and 1B of the study, respectively. The treatment period will last approximately 2 years or until confirmed disease progression, unacceptable AE, withdrawal by participant, or death. In the follow-up period, safety and survival follow-up will occur concurrently. The safety follow-up period is 30 days (± 7 days) after the	

	EOT visit. Survival follow-up every 3 months (± 15 days) for all parts will begin at EOT and last for a period of 2 years, or until death, lost to follow-up, withdrawal of consent, conclusion of the study, or study termination, whichever comes first. The survival follow-up visits can be conducted in person or via telephone.
Statistical Methods	Decisions to dose escalate or de-escalate in the dose escalation Parts 1A and 1B will be guided by the TITE-BOIN method, where ≥ 3 participants are treated per dose cohort. [redacted] The primary endpoint for Part 1 is to assess safety based on incidence of AEs, SAEs, AEs leading to discontinuation, and deaths. In addition, the selected tolerable dose levels of BMS-986466 in combination with adagrasib (Part 1A) and BMS-986466 in combination with adagrasib and cetuximab (Part 1B) will be determined using the DLT rate within the 28-day window among DLT-evaluable participants in Parts 1A and 1B. The incidence of DLTs will be calculated and compared to the actions recommended by the TITE-BOIN design to guide the dose escalation/stay/de-escalation decision for the BMS-986466 plus adagrasib treatment and for the BMS-986466 plus adagrasib plus cetuximab treatment. The primary endpoint for Part 2 is ORR of BMS-986466 plus adagrasib compared to adagrasib control (Part 2A), and ORR of BMS-986466 in combination with adagrasib plus cetuximab compared to adagrasib plus cetuximab control (Part 2B), in the randomized population. Bayesian continuous safety monitoring framework will be utilized to monitor toxicity and detect safety signals affecting conduct of the study. ORR is defined as the proportion of participants who achieve a best response of CR or PR using the RECIST v1.1 criteria.
Data Monitoring or Other Committee	Bristol-Myers Squibb Company (BMS) has developed a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team (SMT), and this will be employed in this study.

Abbreviations: AE, adverse event; AUC (0-T), area under the concentration-time curve from time zero to time of last quantifiable concentration; BICR, Blinded Independent Central Review; BID, twice daily; BMS, Bristol-Myers Squibb Company; BRAF, proto-oncogene B-Raf; C, cycle; CE, conformité européenne; Cmax, maximum (or peak) concentration; CR, complete response; CRC, colorectal cancer; D, day; DCR, disease control rate; DDI, drug-drug interaction; DLT, dose-limiting toxicity; DOR, duration of response; EOT, end of treatment; FDA, Food and Drug Administration; G12Ci, G12C inhibitor; KRAS, Kirsten rat sarcoma viral oncogene; MAD, maximum administered dose; MAPK, mitogen-activated protein kinase; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; NYS, New York State; ORR, overall response rate; PD, pharmacodynamic; pERK, phosphorylation of extracellular signal-regulated kinase; PFS, progression-free survival; PK, pharmacokinetic; PO, orally; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RTK, receptor tyrosine kinase; SAE, serious adverse event; SHP2, Src homology-2 phosphatase; SMT, Safety Management Team; TITE-BOIN, time-to-event Bayesian optimal interval; Tmax, time at which maximum concentration (Cmax) occurs; TTR, time to response; WWPS, Worldwide Patient Safety.

Brief Summary:

The purpose of this study is to find a safe, tolerable, and efficacious dose of BMS-986466 when given orally, in combination with adagrasib with or without cetuximab in participants with advanced KRAS G12C-mutant non-small cell lung cancer, pancreatic duct adenocarcinoma, biliary tract cancer, or colorectal cancer. The safety and tolerability will be assessed by the incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and deaths, whereas the efficacy will be assessed by ORR per RECIST v1.1 by BICR.

Study Duration: Approximately 4 years.

Study Intervention Duration: Approximately 2 years or until progression.

Study Visit Frequency: Approximately every 2 weeks (more frequent in first 2 cycles).

2 SCHEDULE OF ACTIVITIES

Table 2-1: Procedural Outline (Part 1 DDI Cohort Only; CA1260015)

Procedure[a,b]	Screening	Cycle 1 (1 Cycle = 28 Days)								Cycle 2		Cycle 3+		EOT[c]	Follow-up	
Visit		**D1**	**D2**	**D3**	**D4**	**D9**	**D10**	**D12**	**D18**	**D1**	**D15**	**D1**	**D15**		**FU1**	**Survival FU (Q3M)**
Visit Window (Days)	**(-28 to -1)**									**± 2**	**± 2**	**± 3**	**± 3**	**± 2**	**(± 7)**	**(± 15)**
Eligibility Assessments																
Informed Consent	X															
Inclusion/ Exclusion Criteria	X															
Medical History	X															
Safety Assessments (Section 9.4)																
Physical Examination (Section 9.4.1)	X	X								X		X		X	X	
Targeted PE			X	X	X	X	X	X	X		X		X			
Physical Measurements (Height, Weight, and BMI)	X															
Body Weight	X	X								X		X				
Vital Signs and Oxygen Saturation (Section 9.4.2)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance Status (ECOG; Appendix 5)	X	X								X		X		X	X	

Table 2-1: Procedural Outline (Part 1 DDI Cohort Only; CA1260015)

Procedure[a,b]	Screening	Cycle 1 (1 Cycle = 28 Days)								Cycle 2		Cycle 3+		EOT[c]	Follow-up	
Visit		**D1**	**D2**	**D3**	**D4**	**D9**	**D10**	**D12**	**D18**	**D1**	**D15**	**D1**	**D15**		**FU1**	**Survival FU (Q3M)**
Visit Window (Days)	**(-28 to -1)**									**± 2**	**± 2**	**± 3**	**± 3**	**± 2**	**(± 7)**	**(± 15)**
Prior/Concomitant Medication Use (Section 7.7.1)	Prior medication including previous cancer treatment	Continuously throughout the study.													Subsequent cancer treatment	
Single 12-lead ECG (Section 9.4.3)	X									X		X				
Triplicate ECG[d] (Section 9.4.3)		X			X	X										
2-D ECHO/MUGA (Section 9.4.4)	X									X		Odd cycles		X		
Laboratory Tests																
Clinical Laboratory Assessments (Table 9.4.5-1)	X	X			X	X				X	X	X	X	X	X	
Urinalysis (Table 9.4.5-1)	X	X								X		X		X	X	
Pregnancy Testing (WOCBP only)[e]	X	X								X		X		X	X	

Table 2-1: Procedural Outline (Part 1 DDI Cohort Only; CA1260015)

Procedure[a,b]	Screening	Cycle 1 (1 Cycle = 28 Days)								Cycle 2		Cycle 3+		EOT[c]	Follow-up	
Visit		**D1**	**D2**	**D3**	**D4**	**D9**	**D10**	**D12**	**D18**	**D1**	**D15**	**D1**	**D15**		**FU1**	**Survival FU (Q3M)**
Visit Window (Days)	**(-28 to -1)**									**± 2**	**± 2**	**± 3**	**± 3**	**± 2**	**(± 7)**	**(± 15)**
FSH (for post-menopausal women under 55 years of age)	X															
Serology (HBV, HCV, HIV; see Table 9.4.5-1)	X															
KRAS G12C Mutation Status[f]	X															
Participants with NSCLC: PD-L1 (TPS), STK11, and Other Known Mutation Status[g]	If available															
Participants with CRC: MSI, MMR, and TMB Status	If available															
Participants with PDAC and BTC: EGFR, FGFR2, IDH1, BRAF non-V600X, and Other Mutations[g]	If available															

Table 2-1: Procedural Outline (Part 1 DDI Cohort Only; CA1260015)

Procedure[a,b]	Screening	Cycle 1 (1 Cycle = 28 Days)								Cycle 2		Cycle 3+		EOT[c]	Follow-up	
Visit		**D1**	**D2**	**D3**	**D4**	**D9**	**D10**	**D12**	**D18**	**D1**	**D15**	**D1**	**D15**		**FU1**	**Survival FU (Q3M)**
Visit Window (Days)	**(-28 to -1)**									**± 2**	**± 2**	**± 3**	**± 3**	**± 2**	**(± 7)**	**(± 15)**
PK Assessments (Section 9.5)																
PK Collections[d]	See Table 2-3.															
Biomarker Assessments (Section 9.7)																
Biomarker Sample Collection	See Section 9.7 and Table 2-6.															
Fresh Tumor Biopsy (Table 2-6)	Optional									Op-tional				Op-tional		
Archival Tumor Biopsy	Required, if available															
AE Reporting (Section 9.2)																
Monitor for Serious and Non-serious AEs	Continuously throughout the study from the time of consent until 30 days post discontinuation of study intervention (Section 9.2).															
Disease/Efficacy Assessment (Section 9.1)																
Body Imaging (Section 9.1.2)	X	Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from date of first dose for the first 48 weeks, then every 12 weeks (± 7 days) until disease progression or discontinuation of all study intervention, whichever occurs later.													X See Section 9.1.2	
Brain Imaging (Section 9.1.2)	X NSCLC - Mandatory Optional for all other indications	Participants with a brain metastasis at baseline should have surveillance MRIs (without and with contrast) per standard of care (approximately every 12 weeks [± 7 days] or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated.													X See Section 9.1.2	

Table 2-1: Procedural Outline (Part 1 DDI Cohort Only; CA1260015)

Procedure[a,b]	Screening	Cycle 1 (1 Cycle = 28 Days)								Cycle 2		Cycle 3+		EOT[c]	Follow-up	
Visit		**D1**	**D2**	**D3**	**D4**	**D9**	**D10**	**D12**	**D18**	**D1**	**D15**	**D1**	**D15**		**FU1**	**Survival FU (Q3M)**
Visit Window (Days)	**(-28 to -1)**									**± 2**	**± 2**	**± 3**	**± 3**	**± 2**	**(± 7)**	**(± 15)**
Assessment of Participant Survival Status (Section 5.1.5)															X	X
Study Intervention (Section 7.1)																
Contact IRT (Section 7.2)	X	X														
Dispense BMS-986466 10 mg		X				X						X				
Dispense Adagrasib 400 mg[h]					X						X					
Study Intervention Compliance									X	X	X	X	X	X		

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BMI, body mass index; BRAF, proto-oncogene B-Raf; BTC, biliary tract cancer; C, cycle; CE, conformité européenne; CRC, colorectal cancer; CT, computed tomography; D, day; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic Case Report Form; EGFR, epidermal growth factor receptor; EOT, end of treatment; FDA, Food and Drug Administration; FGFR2, fibroblast growth factor receptor 2; FSH, follicle-stimulating hormone; FU, follow-up; HBV, hepatitis B virus; hCG, human chorionic gonadotrophin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDH1, isocitrate dehydrogenase 1; IRT, Interactive Response Technology; IU, international units; KRAS, Kirsten rat sarcoma viral oncogene; M, month; MET, mesenchymal to epithelial transition; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI, microsatellite instability; MUGA, multigated acquisition; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; NYS, New York State; PDAC, pancreatic duct adenocarcinoma; PD-L1, programed death ligand 1; PE, physical examination; PK, pharmacokinetic; Q3M, every 3 months; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1; STK11, serine/threonine kinase 11; TMB, tumor mutational burden; TPS, tumor proportion score; WOCBP, women of childbearing potential.

[a] If all components of study intervention are delayed, the procedures scheduled for that same time point should be delayed to coincide with when the time point's dosing actually occurs (except tumor imaging assessments).

[b] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[c] EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be made prior to study discharge for the participants who are permanently discontinued.

[d] See Table 2-3 for exact PK and triplicate ECG time points.

[e] Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) to be done at screening visit and repeated within 24 hours prior to the start of study intervention. WOCBP must have a negative pregnancy test within 24 hours prior to the start of study intervention and results also must be evaluated prior to study intervention administration. If pregnancy test is taken within 24 hours of dosing (C1D1), a further pregnancy test is not required. An extension up to 72 hours prior to the start of study intervention is permissible in situations where results cannot be obtained within standard 24-hour window.

[f] Participants must have a documented KRAS G12C mutation from an NYS-approved, FDA-approved/cleared or CE-marked test or, when such result is not available, positive KRAS G12C mutation status should be confirmed by a central laboratory in liquid biopsy samples collected at the time of screening.

[g] Other targetable mutations, including EGFR, ALK, ROS1, RET, NTRK, MET amplification, MET exon 14 skipping mutations, and non-KRAS G12C, should be documented if available.

[h] Dispense adagrasib every 42 days (± 3 days).

Table 2-2: Procedural Outline (All Parts Excluding Part 1 DDI Cohort; CA1260015)

Procedure[a,b]	Screening	Cycle 1 (1 Cycle = 28 Days)			Cycle 2			Cycle 3+		EOT[c]	Follow-up	
Visit		**D1**	**D2**	**D15**	**D1**	**D2[d]**	**D15**	**D1**	**D15**		**FU1**	**Survival FU (Q3M)**
Visit Window (Days)	**(-28 to -1)**				**± 2**		**± 2**	**±3**	**± 3**	**± 2**	**(± 7)**	**(± 15)**
Eligibility Assessments												
Informed Consent	X											
Inclusion/Exclusion Criteria	X											
Medical History	X											
Safety Assessments (Section 9.4)												
Physical Examination	X	X			X			X		X	X	
Targeted PE			X	X		X	X		X			
Physical Measurements (Height, Weight, and BMI)	X											
Body Weight	X	X			X			X				
Vital Signs and Oxygen Saturation	X	X	X	X	X	X	X	X	X	X	X	
Performance Status (ECOG; Appendix 5)	X	X			X			X		X	X	
Prior/Concomitant Medication Use	Prior medication including previous cancer treatment	Continuous throughout the study.									Subsequent cancer treatment	
Single 12-lead ECG[e]	X	X			X			X				
Triplicate ECG (Part 1A and 1B only)		X			X							
2-D ECHO/MUGA[f]	X				X			Odd cycles[f]		X		

Table 2-2: Procedural Outline (All Parts Excluding Part 1 DDI Cohort; CA1260015)

Procedure[a,b]	Screening	Cycle 1 (1 Cycle = 28 Days)			Cycle 2			Cycle 3+		EOT[c]	Follow-up	
Visit		**D1**	**D2**	**D15**	**D1**	**D2[d]**	**D15**	**D1**	**D15**		**FU1**	**Survival FU (Q3M)**
Visit Window (Days)	**(-28 to -1)**				**± 2**		**± 2**	**±3**	**± 3**	**± 2**	**(± 7)**	**(± 15)**
Laboratory Tests												
Clinical Laboratory Assessments (Table 9.4.5-1)	X	X		X	X		X	X	X	X	X	
Urinalysis (Table 9.4.5-1)	X	X			X			X		X	X	
Pregnancy Testing (WOCBP only)[g]	X	X			X			X		X	X	
FSH (for post-menopausal women only)	X											
Serology (HBV, HCV, HIV) (Table 9.4.5-1)	X											
KRAS G12C Mutation Status[h]	X											
Participants with NSCLC: PD-L1 (TPS), STK11, and Other Mutation Status[i]	If available											
Participants with CRC: MSI, MMR, and TMB Status	If available											
Participants with PDAC and BTC (Part 1A only): EGFR, FGFR2, IDH1, BRAF non-V600X, and Other Mutations[i]	If available											
PK Assessments (Section 9.5)												
PK Collections		See Table 2-4 for Parts 1A and 1B and Table 2-5 for Parts 2A and 2B.										

Table 2-2: Procedural Outline (All Parts Excluding Part 1 DDI Cohort; CA1260015)

Procedure[a,b]	Screening	Cycle 1 (1 Cycle = 28 Days)			Cycle 2			Cycle 3+		EOT[c]	Follow-up	
Visit		**D1**	**D2**	**D15**	**D1**	**D2[d]**	**D15**	**D1**	**D15**		**FU1**	**Survival FU (Q3M)**
Visit Window (Days)	**(-28 to -1)**				**± 2**		**± 2**	**±3**	**± 3**	**± 2**	**(± 7)**	**(± 15)**
Biomarker Assessments (Section 9.7)												
Biomarker Sample Collection	See Section 9.7 and Table 2-7.											
Fresh Tumor Biopsy (Parts 1A and 1B)	Optional				Op-tional					Op-tional		
Fresh Tumor Biopsy (Part 2) (Section 9.7.4)	X				X					Op-tional		
Archival Tumor Biopsy	Required if available											
AE Reporting												
Monitor for Serious and Non-serious AEs	Continuously throughout the study from the time of consent until 30 days post discontinuation of study intervention (see Section 9.2).											
Disease/Efficacy Assessment (Section 9.1)												
Body Imaging (Section 9.1.2)	X	Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur every 8 weeks (± 7 days) starting from date of first dose for the first 48 weeks, then every 12 weeks (± 7 days) until disease progression or discontinuation of all study intervention, whichever occurs later.									X	
Brain Imaging (Section 9.1.2)	X NSCLC - Mandatory Optional for all other indications	Participants with brain metastasis at baseline should have surveillance MRIs (without and with contrast) per standard of care (approximately every 12 weeks) (± 7 days) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated.									X	
Assessment of Participant Survival Status (Section 5.1.5)											X	X

Table 2-2: Procedural Outline (All Parts Excluding Part 1 DDI Cohort; CA1260015)

Procedure[a,b]	Screening	Cycle 1 (1 Cycle = 28 Days)			Cycle 2			Cycle 3+		EOT[c]	Follow-up	
Visit		**D1**	**D2**	**D15**	**D1**	**D2[d]**	**D15**	**D1**	**D15**		**FU1**	**Survival FU (Q3M)**
Visit Window (Days)	**(-28 to -1)**				**± 2**		**± 2**	**±3**	**± 3**	**± 2**	**(± 7)**	**(± 15)**
Study Intervention (Section 7.1)												
Contact IRT (Randomization for Parts 2A and 2B only)	X	X										
Dispense BMS-986466		X			X			X				
Dispense Adagrasib 600 mg[j]		X			X			X				
Dispense Adagrasib 400 mg[k]		X					X[k]					
Cetuximab (Parts 1B and 2B only)[l]		X		X	X		X	X	X			
Study Intervention Compliance				X	X		X	X	X	X		

Abbreviations: AE, adverse event; ALK, anaplastic lymphoma kinase; BMI, body mass index; BRAF, proto-oncogene B-Raf; BTC, biliary tract cancer; C, cycle; CE, conformité européenne; CRC, colorectal cancer; CT, computed tomography; D, day; ECG, electrocardiogram; DDI, drug-drug interaction; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic Case Report Form; EGFR, epidermal growth factor receptor (her-1); EOT, end of treatment; FDA, Food and Drug Administration; FGFR2, fibroblast growth factor receptor 2; FSH, follicle-stimulating hormone; FU, follow-up; HBV, hepatitis B virus; hCG, human chorionic gonadotrophin; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDH1, isocitrate dehydrogenase 1; IRT, Interactive Response Technology; KRAS, Kirsten rat sarcoma viral oncogene; M, month; MET, mesenchymal to epithelial transition; MMR, mismatch repair; MRI, magnetic resonance imaging; MSI, microsatellite instability; MUGA, multigated acquisition; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tyrosine receptor kinase; NYS, New York State; PDAC, pancreatic duct adenocarcinoma; PD-L1, programed death ligand 1; PE, physical examination; PK, pharmacokinetic; Q3M, every 3 months; RET, rearranged during transfection; ROS1, ROS proto-oncogene 1; TPS, tumor proportion score; WOCBP, women of childbearing potential.

[a] If all components of study intervention are delayed, the procedures scheduled for that same time point should be delayed to coincide with when the time point's dosing actually occurs (except radiographic tumor assessments).

[b] Some of the assessments referred to in this section may not be captured as data in the eCRF. They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.

[c] EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be made prior to study discharge for the participants who are permanently discontinued.

[d] C2D2 visit applicable for Parts 1A and 1B only.

[e] In Part 1: Single 12-lead ECG not required if triplicate ECG obtained (eg, Part 1 C1D1 and C2D1). See Table 2-4 for triplicate ECG time points on assigned day. Part 2: 12-lead ECGs as clinically indicated.

[f] For Part 2, 2-D echocardiogram or MUGA every odd cycle if clinically indicated.

[g] Serum or urine pregnancy test (minimum sensitivity equivalent units 25 IU/L or equivalent units of hCG) to be done at screening visit and repeated within 24 hours prior to first dose of study intervention. WOCBP must have a negative pregnancy test within 24 hours prior to the start of study intervention and results also must be evaluated prior to study intervention administration. If pregnancy test is taken within 24 hours of dosing (C1D1), a further pregnancy test is not required. An extension up to 72 hours prior to the start of study intervention is permissible in situations where results cannot be obtained within standard 24-hour window.

[h] NSCLC and CRC: Participants must have a documented KRAS G12C mutation from an NYS-approved, FDA-approved/cleared, or CE-marked test or, when such result is not available, positive KRAS G12C mutation status should be confirmed by a central laboratory (Guardant360 CDx) in liquid biopsy samples collected at the time of screening (for parts 1A and 1B) and in liquid biopsy and/or tumor samples (only for parts 2A and 2B) collected at the time of the screening or from archival biopsies (less than 1 year old). PDAC and BTC: Participants must have a documented KRAS G12C mutation from NYS-approved, FDA-approved/cleared or CE-marked test and liquid biopsy samples collected only for retrospective testing.

[i] Other targetable mutations, including EGFR, ALK, ROS1, RET, NTRK, MET amplification, MET exon 14 skipping mutations, FGFR2, IDH1, BRAF including BRAF non-V600X and other non-KRAS G12C mutations, should be documented if available.

[j] Dispense adagrasib 600 mg every 28 days (± 2 days).

[k] Dispense adagrasib 400 mg every 42 days (± 3 days).

[l] Given intravenous biweekly. If weekly cetuximab dosing is implemented, additional visits on Days 8 and 22 will be required. In addition to cetuximab administration, relevant targeted PE, vital signs, and oxygen saturation should be done.

Table 2-3: Pharmacokinetic Sampling Schedule for BMS-986466 (Part 1 DDI Cohort; CA1260015)

Study Day of Sample Collection (1 Cycle = 28 Days)	Event	Time Relative to BMS-986466 Dose and/or Adagrasib Dose (hr:min)	BMS-986466 PK Plasma Sample	Adagrasib PK Plasma Sample	Triplicate ECGs[a]
Cycle 1 Day 1	Predose[b]	0:00	X		X
Cycle 1 Day 1		[redacted]	X		
Cycle 1 Day 1			X		
Cycle 1 Day 1			X		
Cycle 1 Day 2		24:00	X		
Cycle 1 Day 3		48:00	X		
[redacted]	Predose[b]	0:00	X	X	X
		[redacted]		X	
				X	
				X	
	Predose[b]	0:00	X	X	X
		[redacted]	X	X	X
			X	X	X
			X	X	
Cycle 1 Day 10[c]	Predose[b]	0:00	X	X	
Cycle 1 Day 12[c]	Predose[b]	0:00	X		
Cycle 1 Day 18[c]	Predose[b]	0:00	X		
Cycle 2 Day 1[c]	Predose[b]	0:00	X		
Cycle 3 Day 1[c]	Predose[b]	0:00	X		

Abbreviations: DDI, drug-drug interaction; ECG, electrocardiogram; hr, hour(s); min, minutes; PK, pharmacokinetic.

Note: For more information, see Section 9.5.1. [redacted]

[redacted]

[a] All triplicate ECGs should be recorded 5 minutes apart on the Sponsor-provided ECG machine and results should be transmitted electronically to the central laboratory.

[b] [redacted] If it is known that a dose is going to be delayed, then collect the pre-dose sample just prior to delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, do not collect additional pre-dose sample.

[c] [redacted] onward sample collections are relative to the adagrasib dose.

Table 2-4: Pharmacokinetic Sampling Schedule for BMS-986466, Adagrasib along with Triplicate ECG (Dose Escalation Parts 1A and 1B; CA1260015)

Study Day of Sample Collection (1 Cycle = 28 Days)	Event	Time Relative to BMS-986466 Dose (hr:min)	BMS-986466 PK Plasma Sample	Adagrasib PK Plasma Sample	Triplicate ECGs[a]
Cycle 1 Day 1	Predose[b]	0:00	X	X	X
Cycle 1 Day 1		[redacted]	X	X	X
Cycle 1 Day 1			X	X	X
Cycle 1 Day 1			X	X	
Cycle 1 Day 2	Predose[b]	0:00	X	X	
Cycle 1 Day 15	Predose[b]	0:00	X	X	
Cycle 2 Day 1	Predose[b]	0:00	X	X	X
Cycle 2 Day 1		[redacted]	X	X	X
Cycle 2 Day 1			X	X	X
Cycle 2 Day 1			X	X	
Cycle 2 Day 2	Predose[b]	0:00	X	X	
Cycle 2 Day 15	Predose[b]	0:00	X	X	
Cycle 3 Day 1	Predose[b]	0:00	X	X	

Abbreviations: ECG, electrocardiogram; hr, hour(s); min, minutes; PK, pharmacokinetic.

Note: For more information regarding PK collection sample windows, see Section 9.5.1. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[a] All triplicate ECGs should be recorded 5 minutes apart on the Sponsor-provided ECG machine and results should be transmitted electronically to the central laboratory.

[b] [redacted] If it is known that a dose is going to be delayed, then collect the pre-dose sample just prior to delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, do not collect additional pre-dose sample.

Table 2-5: Pharmacokinetic Sampling Schedule for BMS-986466, Adagrasib (Dose Expansion Parts 2A and 2B; CA1260015)

Study Day of Sample Collection (1 Cycle = 28 Days)	Event	Time Relative to BMS-986466 Dose (hr:min)	BMS-986466 PK Plasma Sample	Adagrasib PK Plasma Sample
Cycle 1 Day 1	Predose[a]	0:00	X	X
Cycle 1 Day 1		[redacted]	X	X
Cycle 2 Day 1	Predose[a]	0:00	X	X
Cycle 2 Day 1		[redacted]	X	X
Cycle 3 Day 1	Predose[a]	0:00	X	X

Abbreviations: hr, hour(s); min, minutes; PK, pharmacokinetic.

Note: For more information, see Section 9.5.1. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

a [redacted] If it is known that a dose is going to be delayed, then collect the pre-dose sample just prior to delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, do not collect additional pre-dose sample.

Table 2-6: Biomarker Sampling Schedule (Part 1 DDI Cohort Only; CA1260015)

Study Day of Sample Collection (1 Cycle = 28 Days)	Event	Time Relative to BMS-986466 Dose (hr:min)	Tumor for IHC, RNA Seq	Whole Blood for pERK[a]	Whole Blood for Myeloid/ Immune Panel	Whole Blood for ctDNA NGS	Plasma for Soluble PD Markers	Whole Blood for DNA Sequencing
Screening (Day -28 to -1)	Baseline		X[b]			X		X
Cycle 1 Day 1	Predose[c]	0:00			X		X	
[redacted]	Predose[c]	0:00		X[redacted]				
		[redacted]		X[redacted]				
				X[redacted]				
				X[redacted]				
	Predose[c]	0:00		X				
Cycle 2 Day 1	Predose[c]	0:00			X	X	X	
Cycle 2 Day 1			X[b]					
Cycle 3 Day 1	Predose[c]	0:00			X	X	X	
Cycle 4 Day 1	Predose[c]	0:00			X		X	
Cycle 5 Day 1	Predose[c]	0:00			X		X	
Cycle 6 Day 1	Predose[c]	0:00			X		X	
EOT			X[b]		X	X	X	

Abbreviations: ctDNA, circulating tumor deoxyribonucleic acid; DDI, drug-drug interaction; DNA, deoxyribonucleic acid; EOT, end of treatment; hr, hour(s); IHC, immunohistochemistry; min, minutes; NGS, next-generation sequencing; PD, pharmacodynamic; pERK, phosphorylation of extracellular signal-regulated kinase; RNA, ribonucleic acid; Seq, sequencing.

[a] Whole blood pERK assay for Part 1 dose-escalation only (including DDI and non-DDI).

[b] Optional (tumor biopsies can be collected irrespective of study intervention administration). Visit window (± 7 days).

[c] Collect predose applicable for blood samples (within 2 hours prior to dosing of BMS-986466).

[redacted]

Table 2-7: Biomarker Sampling Schedule (All Parts Excluding Part 1 DDI Cohort; CA1260015)

Study Day of Sample Collection (1 Cycle = 28 Days)	Event	Time Relative to BMS-986466 Dose (hr:min)	Tumor for IHC, RNA Seq	Whole Blood for pERK[a]	Whole Blood for Myeloid/ Immune Panel	Whole Blood for ctDNA NGS	Plasma for Soluble PD Markers	Whole Blood for DNA Seq
Screening (Day -28 to -1)	Baseline		X[b]			X		X
Cycle 1 Day 1	Predose[c]	0:00		X	X		X	
Cycle 1 Day 1		[redacted]		X[a]				
Cycle 1 Day 1				X[a]				
Cycle 1 Day 1				X[a]				
Cycle 1 Day 2	Predose[c]	0:00		X				
Cycle 2 Day 1	Predose[c]	0:00		X	X[c]	X[c]	X[c]	
Cycle 2 Day 1			X[b]					
Cycle 2 Day 1		[redacted]		X[a]				
Cycle 2 Day 1				X[a]				
Cycle 2 Day 1				X[a]				
Cycle 2 Day 2	Predose[c]	0:00		X[a]				
Cycle 3 Day 1	Predose[c]	0:00			X	X	X	
Cycle 4 Day 1	Predose[c]	0:00			X		X	
Cycle 5 Day 1	Predose[c]	0:00			X		X	
Cycle 6 Day 1	Predose[c]	0:00			X		X	
EOT upon Progression			X[e]		X	X	X	

Abbreviations: ctDNA, circulating tumor deoxyribonucleic acid; DDI; drug-drug-interaction; DNA, deoxyribonucleic acid; EOT, end of treatment; hr, hour(s); IHC, immunohistochemistry; min, minutes; NGS, next-generation sequencing; PD, pharmacodynamic; pERK, phosphorylation of extracellular signal-regulated kinase; RNA, ribonucleic acid; Seq, sequencing.

[a] Whole blood pERK assay for Parts 1A and 1B (dose escalation).

[b] Optional (tumor biopsies can be collected irrespective of study intervention administration for Parts 1A and 1B). Visit window (± 7 days).

[c] Collect predose (within 2 hours prior to dosing of BMS-986466).

[redacted]

[e] Optional.

3 INTRODUCTION

CA1260015 is a Phase 1/2 study of BMS-986466 in combination with adagrasib in participants with Kirsten rat sarcoma virus glycine 12 to cysteine (KRAS G12C)-mutated non-small cell lung cancer (NSCLC), pancreatic duct adenocarcinoma (PDAC), and biliary tract cancer (BTC) and BMS-986466 in combination with adagrasib with or without cetuximab in participants with KRAS G12C-mutant colorectal cancer (CRC). Adagrasib (MRTX849) is an oral inhibitor of RAS GTPase family indicated for treatment of adult patients with KRAS G12C-mutant locally advanced or metastatic NSCLC and is also being tested for KRAS G12C-mutant CRC. BMS-986466 (also known as BBP-398; IACS-15509) is an oral, allosteric inhibitor of Src homology-2 phosphatase (SHP2), a tyrosine phosphatase that plays a key role in the receptor tyrosine kinase (RTK)-mediated mitogen-activated protein kinase (MAPK) signal transduction pathway.[1] In preclinical models, SHP2 inhibition potentiates the activity of KRAS inhibitors and suppresses RTK-driven resistance observed with KRAS G12C inhibitors. This study will evaluate the safety and tolerability; establish the maximum tolerated dose (MTD) if reached; identify dose level(s) for expansion; and evaluate the preliminary efficacy of BMS-986466 in combination with adagrasib in participants with 2L+ KRAS G12C-mutant NSCLC and BMS-986466 in combination with adagrasib with or without cetuximab in participants with 2L+ KRAS G12C-mutant CRC.

3.1 Study Rationale

KRAS is one of the most commonly mutated oncogenes with KRAS G12C mutations comprising approximately 14% of NSCLC, 3% of CRC, 1.5% in PDAC[2], with a lower prevalence in other cancers.[3] Targeted therapies to KRAS G12C mutations have successfully been developed and 2 inhibitors of RAS GTPase family, sotorasib and adagrasib, were granted accelerated approval by the United States (US) Food and Drug Administration (FDA) in adult patients with KRAS G12C-mutant NSCLC who have received at least 1 prior systemic therapy. Additionally, both sotorasib and adagrasib have demonstrated clinical benefit in KRAS G12C-mutant CRC with objective response rate (ORR) of 9.7% and 19%, respectively.[4,5] Despite this transformational breakthrough, a considerable proportion of patients do not respond or do not have durable responses with KRAS G12C monotherapy; thus, an unmet need remains in patients with KRAS G12C-mutant tumors.

Resistance to KRAS inhibitors has been demonstrated in both nonclinical and clinical studies and is frequently driven by compensatory activation or upregulation of other components of the pathway, including RTKs.[6,7] Recent studies have shown that inhibition of SHP2 suppresses MAPK pathway activation and inhibits the growth of tumors that harbor oncogenic KRAS mutations. In addition, SHP2 inhibition can potentiate the activity of KRAS inhibitors in nonclinical tumor models.[8,9] These data suggest that inhibition of SHP2 has the potential to inhibit the growth of tumors that harbor certain oncogenic RAS mutations (eg, KRAS G12C), including tumors in which adaptive resistance to therapeutic inhibitors of these pathways has developed. Importantly, the observation that epidermal growth factor receptor (EGFR) blockade in combination with KRAS G12C inhibitors, namely adagrasib and sotorasib, increases the ORR relative to KRAS G12Ci monotherapy in CRC provides clinical validation of RTK-driven resistance.[4,5,10] In addition, preclinical data demonstrate SHP2 inhibition more effectively

suppresses RTK-driven resistance than EGFR blockade, providing further rationale for exploring the combination of KRAS G12C and SHP2 inhibitors in the clinic.[11]

[redacted]

The proposed CA1260015 is a Phase 1/2 open-label study evaluating the combination of BMS-986466 with adagrasib in KRAS G12C-mutant NSCLC and BMS-986466 in combination with adagrasib with or without cetuximab in KRAS G12C-mutant CRC. The objective is to evaluate safety and tolerability, establish the MTD if reached, identify dose level(s) of both combinations for dose expansion.

3.2 Background

3.2.1 BMS-986466 Mechanism of Action

BMS-986466 is a potent, selective, orally active allosteric inhibitor of SHP2, a ubiquitously expressed scaffolding protein and tyrosine phosphatase that plays a key regulatory role in both tumor and immune cell signaling. SHP2 transduces signaling from multiple RTKs to activate the small guanosine triphosphatase (GTPase), RAS, and MAPK signaling pathway and can dephosphorylate and deactivate several negative regulators of the RAS/MAPK pathway.

A detailed description of the chemistry, pharmacology, and safety of BMS-986466 is provided in the Investigator's Brochure (IB).[12]

3.2.1.1 BMS-986466 Nonclinical Pharmacology

[redacted] Furthermore, the combination of KRAS G12C and SHP2 inhibitors demonstrated superior efficacy than the combination of KRAS G12C inhibitor and EGFR blockade in CRC xenograft models.[11]

[redacted]

3.2.1.2 BMS-986466 Nonclinical Pharmacokinetics

In pre-clinical studies, BMS-986466 exhibited low plasma clearance, moderate to high volume of distribution at steady-state (Vss) and moderate terminal half-lives across species, and it was well absorbed with time to maximum plasma drug concentration (Tmax) of [redacted] post dose.

The results of a cytochrome P450 (CYP) reaction phenotyping study suggest that in vitro metabolism of BMS-986466 is mainly mediated by [redacted]. In vitro studies suggest BMS-986466 did not notably inhibit the major human CYP isoforms nor did it induce [redacted], [redacted], or [redacted] in human hepatocytes; it is a substrate of [redacted], and an inhibitor of [redacted].

3.2.1.3 BMS-986466 Nonclinical Toxicology

Although single and repeat-dose nonclinical toxicology studies with BMS-986466 in rats and dogs were overall well tolerated at doses equivalent to the lower doses proposed for this study, the studies suggest potential toxicities that may be observed with oral administration of BMS-986466 to humans, including diarrhea, vomiting, lymphopenia, and liver toxicity with increased transaminases. The inhibitory concentration 50 (IC50; > 100 µM) in the in vitro hERG assay and no test article-related effects in the cardiovascular and central nervous system (CNS) parameters in the in vivo studies indicate low risk for adverse pharmacological effects on the CNS and cardiovascular systems. In rats, increased thickness of the physis and increased trabecular bone in

the metaphyseal region of tibia and femur, mineralization in several organs correlating with changes in serum calcium and phosphorus, as well as degenerative changes in the ovaries (corpus lutea) were observed. In dogs, reductions in circulating red cell and leukocyte parameters, bone marrow atrophy, depletion of splenic white pulp, and thymic atrophy (reflected by the hematologic changes) were observed.[12]

3.2.1.4 BMS-986466 Clinical Pharmacology

Based on BMS-986466 monotherapy data from Study NAV-1001, BMS-986466 exposure increases dose proportionally over the range of 80 to 550 mg once daily (QD) with low inter-participant variability. BMS-986466 is rapidly absorbed, with time to maximum plasma drug concentration (Tmax) values in the range of [redacted] post oral dose. The estimated half-life is determined to be approximately [redacted]. Accumulation ratio of AUC is approximately [redacted] over the dose range of 80 to [redacted] mg QD.

To further assess clinical drug-drug interaction (DDI) potential of BMS-986466, a physiologically based pharmacokinetic (PBPK) model was developed based on BMS-986466 in vitro metabolism/transporter data and preliminary clinical PK data from the dose escalation phase of NAV-1001. [redacted]

3.2.1.5 BMS-986466 Clinical Safety

In NAV-1001, as of 13-Aug-2022, a total of 31 participants have been treated with monotherapy of BMS-986466 at 6 dose levels: 80 mg (n = 1), 150 mg (n = 3), [redacted] mg (n = 3), 400 mg (n = 5), 550 mg (n = 13), and [redacted] mg (n = 6). Nineteen participants across all dose levels completed the dose-limiting toxicity (DLT) assessment period of at least 21 days, and 16 participants discontinued treatment early due to disease progression. No DLTs were reported.[12]

Twenty-eight (90.3%) participants reported adverse events (AEs). Four (12.9%) participants reported Grade 3 treatment-related AEs (TRAEs): diarrhea, platelet count decreased, and aspartate aminotransferase (AST) increased (n = 1 each, possibly related) and edema peripheral (n = 1, related). All TRAEs occurred in the 550 mg dose level, except AST increased that occurred at the 150 mg dose level. No Grade 4 or 5 AEs were considered related to treatment. Eleven (35.5%) participants reported SAEs, and none were deemed related to treatment.

Five participants reported AEs that led to study drug discontinuation: Grade 3 edema peripheral (n = 1, related); Grade 2 ejection fraction decreased (n = 1, possibly related); Grade 1 temperature intolerance (n = 1, possibly related); Grade 4 acute respiratory failure (n = 1, unlikely related); and Grade 3 deep vein thrombosis (n = 1, not related). Excluding the Grade 2 ejection fraction

decreased at BMS-986466 [redacted] mg daily, all other AEs leading to discontinuation occurred at the BMS-986466 550 mg QD dose. Overall, no relevant safety findings impacting the benefit/risk of BMS-986466 have been reported. For detailed safety listings by dose level in Study NAV-1001, refer to Tables 8 and 9 in Section 5.3.1 of the BMS-986466 IB.[12]

3.2.1.6 BMS-986466 Clinical Efficacy

Based on preliminary observations and pharmacodynamic (PD) data from Study NAV-1001, [redacted], there has been no evidence of clinical response as of Apr-2023. The best overall response reported is stable disease.

3.2.2 Adagrasib

Adagrasib is a potent, orally available, small molecule, covalent inhibitor of KRAS G12C that irreversibly and selectively binds KRAS G12C in its inactive, GDP-bound state. Adagrasib has favorable pharmacokinetic (PK) properties, including a long half-life (23 hours), dose dependence, and CNS penetration. Adagrasib acts as a strong CYP3A4 inhibitor when dosed at 400 mg twice daily (BID) and at 600 mg BID and increases midazolam's (a sensitive CYP3A substrate) AUC by 20- and 30-fold, respectively.[14]

In clinical trials, adagrasib has demonstrated clinical benefit in participants with KRAS G12C-mutant NSCLC, CRC, PDAC, and BTC treated with adagrasib 600 mg BID (ORR 43%, 19%, 33%, and 42%[15] respectively) and participants with KRAS G12C-mutant CRC treated with adagrasib 600 mg BID plus cetuximab (ORR 46%). Overall, adagrasib has demonstrated to be safe and tolerable as monotherapy[14] and in combination with cetuximab.[5, 16] The most common (≥ 25%) adverse reactions for adagrasib monotherapy were nausea, diarrhea, vomiting, fatigue, musculoskeletal pain, hepatotoxicity, renal impairment, edema, dyspnea, and decreased appetite. The most common Grade 3 or 4 (≥ 2%) laboratory abnormalities were decreased lymphocytes, decreased hemoglobin, increased alanine aminotransferase (ALT), increased AST, hypokalemia, hyponatremia, increased lipase, decreased leukocytes, decreased neutrophils, and increased alkaline phosphatase (ALP). Adagrasib was granted accelerated approval for the treatment of adult patients with KRAS G12C-mutant, locally advanced or metastatic NSCLC, who have received at least 1 prior systemic therapy. See Section 5.4.4 and the adagrasib United States Prescribing Information (USPI)[14] for additional information.

3.2.3 Cetuximab

Cetuximab is an EGFR antagonist indicated for treatment of KRAS wild-type, EGFR-expressing, metastatic CRC.[17] It is not indicated for the treatment of RAS-mutant CRC or when the results of the RAS mutation tests are unknown.[18]

Refer to the USPI/SmPC for additional information.[17,19]

3.3 Benefit/Risk Assessment

Since SHP2 is a central node in downstream RTK activation, SHP2 inhibitors may be beneficial as a component of combination therapy in cancers driven by constitutive MAPK pathway

mutations to maximize the therapeutic potential of RTK, RAS, and other MAPK pathway inhibitors, which often have limited efficacy as single agents due to activation of feedback loops that enhance upstream signaling and lead to extracellular signal-regulated kinase (ERK) reactivation. Hence it is hypothesized that addition of BMS-986466 to KRAS G12C targeted therapy may improve efficacy. This hypothesis is supported by data demonstrating that compensatory bypass signaling feedback activation of either upstream or downstream mediators of the RTK/MAPK pathway reduce effectiveness of KRAS G12Ci both preclinically and clinically.[9,20,21,22,23,24,25] BMS-986466 has not been administered in combination with adagrasib or cetuximab to humans. Therefore, nonclinical toxicology, in vitro and in vivo safety pharmacology, and in vitro genotoxicity studies with the individual components alone (not combination toxicology studies) will be utilized to guide the initial benefit/risk assessment for this clinical trial.

More detailed information about the known and expected benefits and risks and reasonably anticipated AEs of BMS-986466 may be found in the IB.[12] Additional information regarding adagrasib and cetuximab are presented in their product labels, including results from other clinical studies and, hence, is not being reported here.

The study has been designed with study visits that allow for close monitoring of participants' safety throughout the clinical trial (see Section 2), and participants are encouraged to contact the investigator if an intercurrent illness develops between study visits. Testing for coronavirus disease 2019 (COVID-19) to inform decisions about clinical care during the study should follow local standard practice. Non-live COVID-19 vaccination is considered a simple concomitant medication within the study. However, the efficacy and safety of non-live vaccines (including non-live COVID-19 vaccines) in participants receiving BMS-986466 with adagrasib with or without cetuximab is unknown.

3.3.1 Risk Assessment

Although the study may not provide clinical benefit to the enrolled participants, BMS-986466 is a novel therapeutic agent that has the potential to significantly improve outcomes in a similar population of patients once an optimal human dose and schedule is identified, supporting its evaluation in clinical studies. Other notable risks include AEs and the potential for DDIs since BMS-986466 is a substrate of CYP3A4 while adagrasib is a strong CYP3A4 inhibitor. Dosing modifications for AEs are outlined in Section 7.4.

An assessment of potential risks associated with study interventions and trial procedures is presented in Table 3.3.1-1.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s)		
Drug-drug Interaction	Adagrasib USPI[14] and BMS-986466 IB[12]	• Start with a DDI cohort to validate predicted clinical drug interaction prior to the combination escalation. • Exclude participants that require medications that will change the exposure of adagrasib or BMS-986466, including [redacted] modulators. • Intensive PK sampling during Part 1 DDI cohort and dose escalation to allow adequate DDI assessment. • Inclusion of comprehensive list of strong and moderate [redacted] inhibitors, CYP2C8, [redacted], [redacted] inhibitors that must be avoided or taken with caution (see Section 7.7.1). • Inclusion of list of substrates of [redacted], [redacted], 2C9, 2D6, [redacted], and [redacted] that must be taken with caution.
GI Toxicities: • Nausea/Vomiting • Diarrhea	Adagrasib USPI[14], BMS-986466 IB[12], and Cetuximab SmPc[19]	• A sentinel participant approach with a 7-day observation period for each new dose level (see Section 5.1.1). • Routine scheduled clinical laboratory monitoring throughout treatment of hematologic, hepatic, and metabolic parameters for early detection of abnormalities. • Dose modification per Section 7.4 and Table 7.4-3.
LVEF Reduction	Adagrasib USPI[14] and BMS-986466 IB[12]	• Routine scheduled 2-D ECHO/MUGA throughout treatment for early detection of abnormalities. • BNP and troponin included in routine safety laboratory evaluations.
QTc Prolongation	Adagrasib USPI[14]	• A sentinel participant approach with a 7-day observation period for each new dose level. • Triplicate and 12-lead ECGs performed at selected times throughout the study. • Avoid drugs with a known potential to prolong the QTc. • Inclusion of list of drugs known to prolong QTc (refer to Appendix 8). • Dose modification per Section 7.4 and Table 7.4-3.
Liver Toxicity	Adagrasib USPI[14] and BMS-986466 IB[12]	• Routine scheduled clinical laboratory monitoring throughout treatment of hepatic, and metabolic parameters for early detection of abnormalities.

Table 3.3.1-1: Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		• Close monitoring during the study for mitigation of drug-induced liver injury. • Dose modification per Section 7.4 and Table 7.4-3.
Interstitial Lung Disease/Pneumonitis	Adagrasib USPI[14], cetuximab USPI[17]/SmPC[19], and BMS-986466 IB[12]	• Vital signs and oxygen saturation at each visit. • Exclude participants with previous interstitial lung disease or pneumonitis (previous Grade 1 or 2 immuno-mediated pneumonitis is permitted if completely resolved) (see Section 6.2). • Dose modification per Section 7.4 and Table 7.4-3.
Renal Impairment	Adagrasib USPI[14]	• Routine scheduled clinical laboratory monitoring throughout treatment of renal function and urinalysis.
Hematologic Effects	Adagrasib USPI[14] and BMS-986466 IB[12]	• Routine scheduled clinical laboratory monitoring throughout treatment. • Dose modification per Section 7.4 and Table 7.4-3.
Hypomagnesemia	Cetuximab USPI[17]	• Routine scheduled clinical chemistry laboratory monitoring throughout treatment. • Dose modification per Section 7.4 and Table 7.4-3.
Infertility	Adagrasib USPI[14] and BMS-986466 IB[12]	• Pregnancy and family planning counselling.
Study Procedures		
Tumor Biopsy (eg, pain, infection)	Not applicable	• Per institutional protocol/investigator's discretion.
Phlebotomy (eg, pain, ecchymosis, bleeding, syncope)	Not applicable	• Per institutional protocol/investigator's discretion.
Other		
Allergy to Contrast Agent (eg, hives, anaphylaxis)	Not applicable	• Prophylaxis and/or treatment per institutional protocol/investigator's discretion.

Abbreviations: [redacted]; BNP, b-type natriuretic protein; CYP, cytochrome P450; DDI, drug-to-drug interaction; ECG, electrocardiogram; ECHO, echocardiogram; GI, gastrointestinal; IB, Investigator's Brochure; LVEF, left ventricle ejection fraction; MUGA, multigated acquisition; [redacted]; PK, pharmacokinetic; SmPC, summary of product characteristics; USPI, United States Prescribing Information.

3.3.2 Benefit Assessment

This is a clinical trial evaluating the safety and efficacy of BMS-986466 in combination with adagrasib with or without cetuximab in human participants with advanced KRAS G12C-mutant NSCLC and CRC. Although benefits might be hypothesized based on mechanism of action and/or preclinical observations, actual clinical benefits to patients with advanced cancer have not been established.

3.3.3 Overall Benefit/Risk Conclusion

Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with BMS-986466 in combination with adagrasib with or without cetuximab are justified by the anticipated benefits that may be afforded to participants with advanced KRAS G12C-mutant NSCLC and CRC.

The Sponsor will evaluate the benefit/risk profile of the study on an ongoing basis. This evaluation will be based on all available data, with particular attention to (i) AEs or other safety trends in this or any other clinical study of BMS-986466 whose character, severity, and/or frequency suggest that participants would be exposed to an unreasonable and significant risk of illness or injury; (ii) new non-clinical data suggesting unreasonable and significant risk of illness or injury.

If an important and urgent safety concern is identified, enrollment may be halted and appropriate measures will be taken, including interactions with appropriate Health Authorities.

4 OBJECTIVES AND ENDPOINTS

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Primary	
• To characterize the safety and tolerability; to establish the MTD, if reached; to evaluate the MAD if MTD is not reached; and to identify dose level(s) for expansion of: – Part 1A: BMS-986466 administered in combination with adagrasib to participants with KRAS G12C-mutant NSCLC, CRC, PDAC, and BTC – Part 1B: BMS-986466 administered in combination with adagrasib with cetuximab to participants with KRAS G12C-mutant CRC	• Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and deaths
• To evaluate anti-tumor activity: – Part 2A: BMS-986466 in combination with adagrasib vs adagrasib in participants with KRAS G12C-mutant (G12Ci treatment-naïve) NSCLC – Part 2B: BMS-986466 in combination with adagrasib with or without cetuximab vs adagrasib with cetuximab in participants with KRAS G12C-mutant (G12Ci treatment-naïve) CRC	• ORR per RECIST v1.1 by BICR

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
Secondary	
• Parts 1 and 2: To characterize the PK profile of BMS-986466 following first dose and at steady state in combination with adagrasib with or without cetuximab	• Summary measures of BMS-986466 PK parameters in plasma including Cmax, Tmax, and AUC(0-T), from concentration-time data
• To evaluate the preliminary efficacy of: – Part 2A: BMS-986466 in combination with adagrasib vs adagrasib in participants with KRAS G12C-mutant (G12Ci treatment-naïve) NSCLC – Part 2B: BMS-986466 in combination with adagrasib with or without cetuximab vs adagrasib with cetuximab in participants with KRAS G12C-mutant (G12Ci treatment-naïve) CRC	• PFS, DCR, DOR, and TTR per RECIST v1.1 by BICR
• To assess the safety and tolerability of: – Part 2A: BMS-986446 in combination with adagrasib in participants with KRAS G12C-mutant (G12Ci treatment-naïve) NSCLC – Part 2B: BMS-986446 in combination with adagrasib with or without cetuximab in participants with KRAS G12C-mutant (G12Ci treatment-naïve) CRC	• Incidence of AEs, SAEs, AEs leading to discontinuation, and deaths
• To assess the PD profile of BMS-986466	• Summary measures of target engagement such as, but not limited to, pERK.
Exploratory	
• Part 1 DDI : To determine the magnitude of drug interaction between BMS-986466 (victim) and adagrasib	• Geometric mean ratio of BMS-986466 AUC(0-T) and Cmax in the presence and absence of adagrasib
• Part 2A: To assess the OS in KRAS G12C-mutant (G12Ci treatment-naïve) NSCLC participants treated with BMS-986466 in combination with adagrasib • Part 2B: To assess the OS in KRAS G12C-mutant (G12Ci treatment-naïve) CRC participants treated with BMS-986466 in combination with adagrasib with or without cetuximab	• OS
• To explore the associations between BMS-986466 PK, safety, efficacy, and clinical biomarkers	• Association measures between BMS-986466 PK levels and select outcomes and biomarkers of interest
• To explore the pharmacodynamic activity of BMS-986466 administered in combination with adagrasib with or without cetuximab via assessment of translational biomarkers	• Summary measures of change (or percentage change) from baseline in intratumoral and peripheral biomarkers of immune activation and their association with anti-tumor activity
• To explore potential associations between antitumor activity and select biomarker measures in the tumor and peripheral blood prior to treatment	• Summary measures of anti-tumor activity by pretreatment level of biomarkers of interest
• To characterize adagrasib PK when co-administered with cetuximab	• Summary measures of adagrasib PK parameters in plasma.

Table 4-1: Objectives and Endpoints

Objectives	Endpoints
• To explore the dose and exposure-related effects of BMS-986466 in combination with adagrasib with or without cetuximab on QTc interval.	• Concentration QTc analysis
• To explore potential associations between image-based features and antitumor activity	• Summary of measures of image-based feature changes, including but not limited to heterogeneity, shape and/or volume

Abbreviations: AE, adverse event; AUC(0-T), area under the concentration-time curve from time zero to time of last quantifiable concentration; BICR, Blinded Independent Central Review; Cmax, maximum observed concentration; CRC, colorectal cancer; DLT, dose-limiting toxicity; DCR, disease control rate; DOR, duration of response; G12Ci, G12C inhibitor; KRAS, Kirsten rat sarcoma viral oncogene; MAD, maximum administered dose; MTD, maximum tolerated dose; NSCL, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, pharmacodynamic; pERK, phosphorylation of extracellular signal-regulated kinase; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; Tmax, time of maximum observed plasma concentration; TTR, time to response.

5 STUDY DESIGN

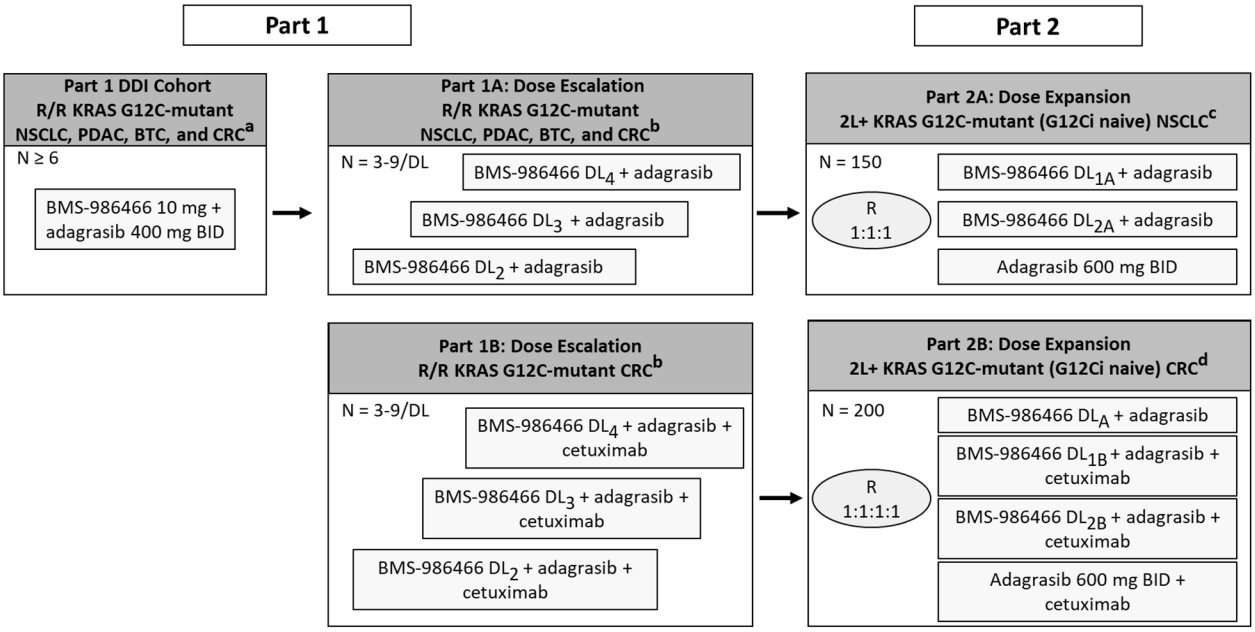
5.1 Overall Design

This is a Phase 1/2 multi-center, open-label study of BMS-986466 in combination with adagrasib in participants with KRAS G12C-mutant NSCLC, PDAC, and BTC and BMS-986466 in combination with adagrasib with or without cetuximab in KRAS G12C-mutant CRC.

The study is composed of 2 parts: the first part, Part 1 (Phase 1) includes DDI cohort and dose escalation (Parts 1A and 1B); whereas the second part, Part 2 (Phase 2) includes randomized dose expansion with comparator cohort (Parts 2A and 2B).

The study design schema is presented in Figure 5.1-1.

Figure 5.1-1: Study Design Schema



Abbreviations: 2L+, second-line therapy or later; BID, twice daily; BTC, biliary tract cancer; C, cycle; CRC, colorectal cancer; D, day; DDI, drug-drug interaction; DL, dose level; G12Ci, G12C inhibitor; IV, intravenous; KRAS, Kirsten rat sarcoma viral oncogene; MTD, maximum tolerated dose; N/n, number of participants; NSCLC, non-small cell lung cancer; PDAC, pancreatic duct adenocarcinoma; Q2W, every 2 weeks; QD, once daily; R, randomization; R/R, relapsed and refractory to all available therapies.

[a] Part 1 DDI cohort: BMS-986466 10 mg single dose on C1D1 [redacted] and adagrasib 400 mg BID starting on [redacted]. Combination BMS-986466 10 mg QD and adagrasib 400 mg BID starting C3D1.

[b] BMS-986466 dosing is dependent on DDI cohort to achieve exposures comparable to BMS-986466 [redacted], and [redacted] mg QD monotherapy from Study NAV-1001. BMS-986466 will be given in combination with adagrasib 400 mg BID with or without cetuximab 500 mg/m^2 IV Q2W. Alternate dose levels and/or schedules of BMS-986466 (not to exceed exposures of the MTD), adagrasib (not to exceed 600 mg BID) with or without cetuximab (not to exceed 500 mg/m^2 Q2W) may be modified, or intermediate dose levels may be added.

[c] Approximately 3 dose levels of BMS-986466 in combination with adagrasib will be evaluated not to exceed exposures of the maximum tolerable dose level evaluated in Part 1A.

[d] Approximately 3 dose levels of BMS-986466 will be evaluated in combination with adagrasib 400 mg BID with cetuximab 500 mg/m^2 Q2W not to exceed exposures of the MTD evaluated in Part 1B.

[redacted]

[redacted]

5.1.1 Part 1: DDI Cohort and Dose Escalation

- Part 1 will begin with evaluation of the DDI followed by Part 1A, dose escalation of BMS-986466 in combination with adagrasib in KRAS G12C-mutant NSCLC, PDAC, BTC, and CRC.
- Part 1B will evaluate the dose escalation of BMS-986466 in combination with adagrasib plus cetuximab in KRAS G12C-mutant CRC.

In the first part (DDI cohort), the potential DDI between BMS-986466 and adagrasib will be evaluated. A minimum of 6 PK-evaluable participants will be treated with a single dose of BMS-986466 10 mg PO on C1D1 followed by continuous dosing of adagrasib 400 mg BID starting on [redacted] and another single dose of BMS-986466 10 mg on [redacted]. Starting on C3D1, participants will be treated daily with the combination of BMS-986466 10 mg QD and adagrasib 400 mg BID. PK samples will be collected as per Table 2-3. Based on the data from this DDI cohort, dose levels will be evaluated to achieve exposures approximately comparable to or less than BMS-986466 [redacted] mg QD monotherapy from Study NAV-1001 in combination with adagrasib (Part 1A) or adagrasib plus cetuximab (Part 1B). The PK evaluation from the DDI cohort will assess the geometric mean ratio between AUC(INF), AUC(0-T), and Cmax of BMS-986466 with and without adagrasib and the results will inform the subsequent dose levels of BMS-986466 in combination with adagrasib 400 mg.

Decisions to dose escalate or de-escalate in the dose escalation Parts 1A and 1B will be guided by the time-to-event Bayesian optimal interval (TITE-BOIN) method,[26] where [redacted] (refer to Appendix 7 TITE-BOIN design). [redacted] Excluding the DDI cohort, after the first participant per dose level is treated, there will be a 7-day observation

period before treating additional participants at the same dose level. Part 1A will identify a safe dose range of BMS-986466, based on which DL_{1A} and DL_{2A} to be tested further in Part 2A. Part 1B will begin in parallel once the first dose level for BMS-986466 plus adagrasib combination is declared safe in Part 1A. The dose of BMS-986466 tested in Part 1B will not exceed the MTD explored in Part 1A.

In Parts 1A and 1B, decisions for dose escalation and to continue enrollment according to the outlined study protocol will be made by the Sponsor in collaboration with the investigators, and take into consideration all available safety, PK, and pharmacodynamic (PD) data. Based on the safety data, planned dose levels and/or schedules of BMS-986466 (not to exceed the MTD), adagrasib (not to exceed the approved dose of 600 mg BID) and/or cetuximab (not to exceed the approved dose of 500 mg/m^2 every 2 weeks [Q2W]) may be modified, or intermediate dose levels may be added after discussion and agreement between the Sponsor and the investigators. The Sponsor has the option to expand the DDI cohort and/or any dose level previously established to be tolerable to obtain additional data. The implementation of various dose levels and/or schedules based on evolving PBPK data in the dose escalation and dose expansion may be done using dose clarification memo/protocol clarification letters as appropriate as per local regulations.

All participating sites may not be able to enroll in DDI and/or dose escalation cohorts in Part 1 due to their time of onboarding/activation, challenges around PK samples stability and sample management logistics.

5.1.2 Part 2: Randomized Dose Expansion

Part 2 is a randomized, open-label dose expansion with comparator cohorts to assess preliminary efficacy, safety, and tolerability of optimal dose level(s) of BMS-986466 in combination with adagrasib with or without cetuximab. The doses to be administered in Parts 2A and 2B will not exceed doses determined to be tolerable from Parts 1A and 1B of the study, respectively.

- Part 2A will evaluate BMS-986466 in combination with adagrasib in KRAS G12C-mutant (G12C inhibitor treatment-naïve) NSCLC participants.
- Part 2B will evaluate BMS-986466 in combination with adagrasib with or without cetuximab in KRAS G12C-mutant (G12C inhibitor treatment-naïve) CRC participants.

5.1.2.1 Part 2A: 2L KRAS G12C-mutant (G12C Inhibitor-treatment Naïve) NSCLC

Part 2A will begin after Part 1A identifies up to 2 safe dose levels, DL_{1A} and DL_{2A}, of BMS-986466 to be tested in combination with adagrasib. The doses of BMS-986466 and adagrasib will not exceed the MTD in Part 1A. Participants with 2L+ KRAS G12C-mutant (G12C inhibitor-treatment naïve) NSCLC will be randomized (1:1:1) to receive either:

- BMS-986466 DL_{1A} with adagrasib
- BMS-986466 DL_{2A} with adagrasib
- Adagrasib 600 mg BID

5.1.2.2 Part 2B: 2L KRAS G12C-mutant (G12C Inhibitor-treatment Naïve) CRC

Part 2B will begin after Part 1B identifies up to 2 safe dose levels, DL_{1B} and DL_{2B}, of BMS-986466 to be tested in combination with adagrasib plus cetuximab. The dose selected for BMS-986466 in combination with adagrasib without cetuximab, herein referred to as DL_A, will be based on the totality of the available data from Parts 1A and 2A (not to exceed the MTD from Part 1A). Up to 2 dose levels of BMS-986466 may be tested in combination with adagrasib with cetuximab (not to exceed the MTD in Part 1B.) A comparator cohort of adagrasib plus cetuximab will also be tested. Participants with 2L+ KRAS G12C-mutant (G12C inhibitor-treatment naïve) CRC will be randomized (1:1:1:1) to receive either:

- BMS-986466 DL_A with adagrasib
- BMS-986466 DL_{1B} with adagrasib plus cetuximab
- BMS-986466 DL_{2B} with adagrasib plus cetuximab
- Adagrasib 600 mg BID with cetuximab

5.1.3 Screening

The screening period will be up to 28 days and begins by establishing the participant's initial eligibility after signing the informed consent form. Participants will be enrolled using Interactive Response Technology (IRT). Participants must start treatment within 3 days of treatment assignment (Part 1) or randomization (Part 2). The screening assessments are shown in Table 2-1 and Table 2-2.

If a participant exceeds the 28-day screening period due to a study-related procedure (eg, scheduling of a tumor biopsy or waiting for a study-related laboratory value), the participant must be reconsented, but does not require a new participant identification number. In this situation, the Medical Monitor should be notified, and the fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility.

See Section 6.4.1 for re-screening procedures and requirements.

5.1.4 Treatment Period

The treatment period will last approximately 2 years or until confirmed disease progression, unacceptable AE, withdrawal by participant, or death. Participants with clinical benefit after 2 years of treatment are eligible to continue treatment after discussion with the Medical Monitor. See Section 7.8 for continued access to study intervention after the end of study. Cycles are 28 days and the DLT evaluation period is 1 cycle (28 days).

On-treatment monitoring will include planned clinic visits with standard safety monitoring including cardiovascular monitoring, blood draws for laboratory testing, PK, and biomarkers (Part 1: Table 2-1, Part 2: Table 2-2). Imaging for tumor assessment will occur every 8 weeks (Q8W) during the first 48 weeks of treatment followed by every 12 weeks (Q12W) until disease progression or study discontinuation, whichever occurs later. All participants will be supplied with

a mechanism to capture daily symptoms, if any, and the intake of BMS-986466 and adagrasib (with or without food).

5.1.5 Follow-up Period

The follow-up period includes a safety follow-up and a survival follow-up, which occur in parallel after the end of treatment (EOT) visit. EOT is defined as the visit where the decision is made to discontinue the participant from treatment. Evaluations will be made prior to study discharge for the participants who are permanently discontinued. For participants who complete all scheduled cycles of therapy, the EOT visit will be the same as the last scheduled and completed on-treatment visit (eg, C26D1) and the start of the safety follow-up period. For participants who do not complete all scheduled cycles of therapy, the EOT visit will be the most recent on treatment visit (with all available safety and response data); it does not need to be repeated and will be considered as the start of the safety follow-up period.

In the follow-up period, safety and survival follow-up will occur concurrently. The safety follow-up period is 30 days (± 7 days) after the EOT visit. Survival follow-up every 3 months (± 15 days) for all parts will begin at EOT and last for a period of 2 years, or until death, lost to follow-up, withdrawal of consent, conclusion of the study, or study termination, whichever comes first. The survival follow-up visits can be conducted in person or via telephone.

5.1.6 Data Monitoring Committee and Other Committees

Bristol-Myers Squibb Company (BMS) has developed a multi-layered process to ensure safety monitoring through close collaboration of study site investigators, the BMS study team, and the BMS Worldwide Patient Safety (WWPS)-led Safety Management Team (SMT), and this will be employed in this study. BMS WWPS is an internal group that operates independently from the clinical team to monitor safety across all BMS protocols and analyze all data in an unblinded fashion. Within BMS, an SMT is established for investigational therapies under clinical development, and a member of WWPS chairs this team. In addition, signal detection is performed at least quarterly and ad hoc throughout the study by the SMT composed, at a minimum, of the WWPS Medical Safety Assessment Physician (Chair of the SMT), the Medical Monitor, Global Regulatory Lead, and Pharmacovigilance Scientist, all of whom analyze the data in an unblinded fashion. A Data Monitoring Committee will not be used in the study.

Since this is an open-label study, WWPS, the Medical Monitor, and the investigators will have access to all data necessary for safety evaluation and continuous safety monitoring as described in Section 10.4.1.

Dose escalation decisions and decisions to continue enrollment according to the outlined study protocol will be made by the Sponsor in collaboration with the investigators, Medical Monitor, medical safety physician, and other appropriate members and take into consideration all available safety, PK, and PD data at convened Scientific Review Committee (SRC).

5.2 Number of Participants

A total of approximately 410 evaluable participants will be treated in this study as described below.

- A minimum of 6 PK-evaluable participants will be treated in Part 1 DDI cohort.

- In Parts 1A and 1B (excluding the DDI cohort), approximately 3 to 9 DLT-evaluable participants will be treated per dose level up to approximately 54 participants.
- In Parts 2A and 2B, approximately 150 and 200 response-evaluable participants will be treated, respectively.

5.3 End of Study Definition

The start of the study is defined as the first participant's first visit.

The primary completion date is defined as the date on which the last data point is collected for the study's last primary endpoint (outcome). For this study, the last primary outcome for the primary endpoints, defined as follows:

For Part 1: When the dose level(s) for expansion for Part 2 have been selected.

For Part 2: The primary completion date will be the date when the data of the last participant for primary analysis has been collected.

End of study is defined as the last participant's last visit.

Participants are considered to have completed the study if they have completed all periods of the study, including last visit.

5.4 Scientific Rationale for Study Design

BMS-986466 is a potent, selective, orally active allosteric inhibitor of SHP2 that plays a key regulatory role in both tumor and immune cell signaling. [redacted] SHP2 being a central node in the MAPK pathway, adding a SHP2 inhibitor with KRAS G12C inhibitor may help to overcome the resistance to KRAS inhibitors by inhibiting the feedback activity, potentially improving antitumor activity and overall response in participants with KRAS G12C-mutant solid tumors who fail to respond to KRAS inhibitors or in participants naïve to KRAS inhibitors, as explained in Section 5.4.3. [redacted]. This combination study is designed to thoroughly evaluate safety, PK, and peripheral blood and tumor PD of BMS-986466 in combination with adagrasib, with or without cetuximab in KRAS G12C-mutant solid tumors.

In Part 1, the DDI evaluation will guide the dosing and schedule selection for combination testing in dose escalation with the objective of identifying dose(s) and schedule(s) that provide maximal target engagement in the peripheral blood/tumor, while remaining safe and well tolerable.

Part 2 is focused on evaluating safety and efficacy of BMS-986466 in combination with adagrasib and with or without cetuximab in randomized dose expansion with comparators. Given the

growing knowledge about KRAS inhibitors and the evolving landscape of KRAS G12C inhibitor monotherapy versus combination efficacy[4] evaluation of these regimens in this study will provide important safety and PD insights on 2 targeted, rational combination approaches that can be employed within a variety of tumor indications.

5.4.1 Rationale for DDI Cohort

Adagrasib is a strong, time dependent CYP3A4 inhibitor, and BMS-986466 is a CYP3A4 substrate. In Part 1, the DDI cohort will identify a safe starting dose for BMS-986466 in combination with adagrasib by measuring the magnitude of potential DDI between BMS-986466 and adagrasib. This cohort is designed to compare single dose BMS-986466 PK with and without concomitant administration of adagrasib (see Section 5.5.2). Based on the magnitude of observed DDI, the starting dose of BMS-986466 in the dose escalation in combination with adagrasib 400 mg BID (Part 1A) will be adjusted to match the approximate exposure comparable to or less than the exposure of BMS-986466 achieved at [redacted] mg QD when administrated as a single agent (see Section 5.5).

5.4.2 Rationale for Dose Escalation Design

The TITE-BOIN design is used to guide escalation decisions and the MTD selection in Part 1. Unlike many existing Phase 1 designs, which require suspending the accrual after treating each cohort of participants, the TITE-BOIN design allows the option for real-time dose assignment decisions for new participants while some enrolled participants' toxicities data are still pending. This may shorten the trial duration and reduce the logistic difficulties caused by repeatedly suspending accrual. The TITE-BOIN works by predicting the DLT outcome for participants whose DLT data are pending based on their follow-up time. It is implemented in a simple way similar to the traditional 3+3 design but is more flexible and possesses superior operating characteristics that are comparable to those more complex model-based designs, such as the time-to-event continual reassessment method (TITE-CRM). Parts 1A and 1B will evaluate the primary study objective (see Table 4-1).

5.4.3 Rationale for SHP2 and EGFR Inhibitors in Combination with KRAS G12C Inhibitors

RAS pathway inhibitors often have limited efficacy as single agents due to the activation of feedback loops that enhance upstream signaling and lead to ERK reactivation. Since SHP2 is a central node in downstream RTK activation, SHP2 inhibitors may also be beneficial as a component of combination therapy to maximize the therapeutic potential of RAS pathway inhibitors. Recent preclinical studies, including those with BMS-986466, have shown that SHP2 inhibition can potentiate the activity of approved KRAS G12C inhibitors in nonclinical cell line and tumor models by inhibiting feedback activation.[7,8,27] Additionally, SHP2 inhibition also decreases RTK-driven SOS1-dependent GTP loading of RAS, which leads to elevated RAS-GDP levels and therefore, may enhance the efficacy of adagrasib, as it binds irreversibly to the inactive guanosine diphosphate (GDP)-bound form of mutant KRAS G12C but not to the active GTP-bound form.[11]

Using EGFR inhibitors to improve efficacy with KRAS G12C inhibitors has been demonstrated in preclinical models and in clinical studies. In Study KRYSTAL-1 (NCT03785249), adagrasib in combination with cetuximab had an ORR of 46% compared to 19% with adagrasib monotherapy.[5] This was recapitulated in a pre-clinical model of KRAS G12C-mutant CRC in which the addition of a SHP2 inhibitor to a KRAS G12C inhibitor was superior to the combination of an EGFR inhibitor plus KRAS G12C inhibitor and both combinations were superior to KRAS G12C inhibitor monotherapy.[22] Thus, preclinical and clinical data provide the rationale for SHP2 and EGFR inhibitors to be used in combination with KRAS G12C inhibitors.

5.4.4 Rationale for Adagrasib and Adagrasib Plus Cetuximab as Comparator

KRYSTAL-1 is a registrational Phase 2 study evaluating adagrasib 600 mg BID in participants with 2L+ KRAS G12C-mutant NSCLC.[10] Of 112 response-evaluable participants, 48 (43%) participants had an objective response with 1 participant having a complete response and the remaining 47 participants having a partial response. The mPFS is 6.5 months (95% confidence interval [CI] 4.7-8.4) and OS is 12.6 months (95% CI 9.2-19.2).

Also in KRYSTAL-1, participants with 2L+ KRAS G12C-mutant CRC were treated with adagrasib 600 mg BID (n = 45) or adagrasib 600 mg BID plus cetuximab (n = 28).[5] The ORR for adagrasib monotherapy was 19% and there was additional benefit in the combination with cetuximab (ORR = 46%). KRYSTAL-10 (NCT04793958) is an ongoing Phase 3 study investigating adagrasib 600 mg BID with cetuximab 500 mg/m^2 versus chemotherapy in participants with 2L KRAS G12C-mutant CRC.[28] In the same Phase 2 KRYSTAL-1 study, 21 PDAC and 12 BTC participants treated with adagrasib monotherapy with two median prior lines of therapy showed an ORR of 33% and 42%, respectively.[29]

These results have led to the recent accelerated FDA approval of adagrasib for the treatment of 2L+ KRAS G12C-mutant NSCLC[14] and breakthrough therapy designation for adagrasib plus cetuximab for the treatment of 2L+ KRAS G12C-mutant CRC.[4]

Based on the above data, adagrasib with or without cetuximab is considered to be a safe and efficacious comparator that will permit evaluation of the contribution of BMS-986466.

5.5 Justification for Dose

5.5.1 Choice of Target Exposures for BMS-986466 Based on Study NAV-1001

Based on the FIH NAV-1001 study results, in which participants received oral BMS-986466 monotherapy from 80 to 550 mg QD, BMS-986466 [redacted] mg QD was considered to be a safe and well tolerated dose [redacted].

Following oral QD dosing, BMS-986466 exhibited dose-proportional exposure increases up to 550 mg QD with low interparticipant variability based on 358 PK samples available from 32 participants from Study NAV-1001. [redacted]

[redacted]. Although no DLTs were observed at the 550 mg QD dose level, given the observed AEs, including a Grade 3 thrombocytopenia, (leading to 2 dose reductions out of 4 DLT-evaluable participants; refer to the IB for additional information[12]), the 550 mg QD dose level is not considered to be well tolerated [redacted] observed at this dose level. In comparison, BMS-986466 [redacted] mg QD is considered to be safe and well tolerated with predicted exposure to be 79% above the biologically effective AUCss, as compared to 19% above the biological effective AUCss (derived from mice xenograft tumor growth inhibition) at 400 mg QD and 119% at 550 mg QD, respectively.

[redacted]

5.5.2 Justification for the Choice of BMS-986466 10 mg Single Dose in Combination with Adagrasib 400 mg BID in Part 1A DDI Cohort

BMS-986466 metabolism is primarily mediated by CYP3A4. Also, notably it does not inhibit the major human CYP isoforms, nor does it induce CYP1A2, 2B6, or 3A4 in human hepatocytes. Thus, the main drug interaction risk for BMS-986466 is being a victim and can have its clearance modified by inhibitors or inducers of CYP3A4. On the other hand, adagrasib is a strong, time dependent CYP3A4 inhibitor; at 400 and 600 mg BID dose, it increases midazolam AUC by 20- and 30-fold, respectively.[14] As a result, the dose of BMS-986466 may need to be adjusted carefully when used in combination with adagrasib to adequately address the drug interaction potential.

To evaluate the potential DDI between adagrasib and BMS-986466, in Part 1A the first cohort (DDI cohort) is planned. This cohort will evaluate BMS-986466 10 mg single dose (considered as DL_1 for study) on C1D1, followed by continuous dosing of adagrasib 400 mg BID starting [redacted] and another single dose of BMS-986466 10 mg on [redacted]. Participants will not start continuous dosing of BMS-986466 in combination with adagrasib 400 mg BID until C3D1, assuming the DDI evaluation is supportive of acceptable safety exposure.

Despite PBPK modeling predictions suggesting that adagrasib 400 mg BID is expected to increase BMS-986466 exposure by [redacted], for participant safety, the proposed strategy is more conservative. The selected single dose of 10 mg of BMS-986466 in the DDI cohort is 20-fold lower (suggested by USPI for the adagrasib-midazolam DDI) than the dose of [redacted] mg QD (2 dose levels lower than the dose of [redacted] mg QD, [redacted] is approximately 10 mg). Therefore, BMS-986466 10 mg single dose in combination with adagrasib is expected to achieve an exposure of less than BMS-986466 [redacted] mg QD monotherapy. Based on the acceptable safety observations at BMS-986466 [redacted] mg QD, and at [redacted] mg QD, a single dose of 10 mg BMS-986466 is not expected to increase the toxicity of adagrasib.

Given the preliminary observed half-life of approximately [redacted] for BMS-986466 and the drug interaction with adagrasib, which prolongs the BMS-986466 half-life, PK samples will be collected [redacted]-BMS-986466 dose when administered as a single agent and up to [redacted] when a single dose of BMS-986466 is administered with continuous dose of adagrasib in order to adequately capture the terminal phase of the PK profile.

5.5.3 Dose Selection Strategy for BMS-986466 in Parts 1A and 1B

For Parts 1A and 1B, the dosing regimen for BMS-986466 will be adjusted based on the results of DDI evaluation from the DDI cohort, in order to match the exposure achieved in BMS-986466 monotherapy at [redacted] mg QD dose. To address the potential overlapping toxicity between BMS-986466 and adagrasib, the starting dose for the combination will be selected to match the approximate exposure comparable to or less than the exposure of [redacted] mg QD, rather than [redacted] mg QD, even though BMS-986466 at the dose of [redacted] mg QD was considered to be safe and well tolerated, and [redacted] in the monotherapy setting.

Further, to optimize the BMS-986466 dosing regimen in the combination setting, dose-escalation will be performed to escalate the dose up to the level achieving approximate exposure comparable to or less than the exposure of [redacted] mg QD. The dose-escalation decision will be based on the safety observation at the previous dose level, PBPK, and population PK modeling, and simulation will be adopted to support dose selection and optimization.

5.5.4 Justification for the Choice of Adagrasib 400 mg BID in Combination with BMS-986466

Although the USPI recommended dose for adagrasib is 600 mg BID, due to the safety observations, including 79% Grade 3 or greater treatment-emergent adverse events (TEAEs), 82% of TEAEs leading to dose reduction or interruption, and 13% TEAEs leading to dose discontinuation, a Post Marketing Requirement was issued to "compare the safety of adagrasib 600 mg BID versus an alternative daily dosage."[14,30] Based on the safety profile of adagrasib and potential overlapping toxicities for adagrasib and BMS-986466, adagrasib 400 mg BID will be used in combination with BMS-986466.

Adagrasib 400 mg BID is expected to be a biologically active dose. Based on nonclinical human xenograft models, anti-tumor efficacy is expected at human exposure over the range of 596 to 1,544 ng/mL C_{avg} (derived most sensitive and least sensitive cell lines). Adagrasib 400 mg BID is expected to achieve $C_{avg,ss}$ of 1,764 ng/mL and $C_{min,ss}$ of 1,804 ng/mL (versus $C_{avg,ss}$ of 2,633 ng/mL and $C_{min,ss}$ of 2,693 at 600 mg BID, given the observed dose proportionality),[31] which is roughly beyond the upper bound threshold (1,544 ng/mL) identified from the nonclinical model. Also, efficacy has been observed in participants who received 400 mg BID (preliminary ORR rate = 67% [4/6, all PRs] versus overall ORR [42.9%] at 600 mg BID).[31]

In concordance with the selection of adagrasib 400 mg BID dose for combination escalation, the 400 mg BID dose will also be selected for DDI cohort in order to provide direct evidence supporting DDI evaluation at adagrasib 400 mg BID.

In the event that BMS-986466 at the tested dose levels in combination with adagrasib 400 mg BID has manageable safety profile, the Sponsor may test BMS-986466 in combination with alternative doses of adagrasib not to exceed the approved dose of 600 mg BID.

5.5.5 Justification for the Choice of Adagrasib 600 mg BID with or without Cetuximab as a Comparator

When used as a comparator, either as monotherapy or in combination with cetuximab, adagrasib 600 mg BID will be administered. Adagrasib 600 mg BID is an approved monotherapy dose that was granted accelerated approval by the FDA in 2L+ KRAS G12C-mutant NSCLC. The FDA granted Breakthrough Therapy Designation to adagrasib in combination with cetuximab for KRAS G12C-mutant CRC, and the registrational Phase 3 study KRYSTAL-10 includes a combination of adagrasib (600 mg BID) with cetuximab (500 mg/m^2 Q2W) as an investigational arm.[28] Hence, the comparator cohorts will use these regimens in Part 2 (see Section 5.4.4 for additional information).

5.6 Rationale for Exploratory Biomarker Research

Biomarker samples may also be used for research to develop methods, assays, prognostics, and/or diagnostics and to explore relationships between participant molecular and cellular data versus participant clinical response and/or resistance to therapy.

Genetic variation may affect a participant's response to study intervention, susceptibility to disease, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that affect intervention absorption, distribution, metabolism, and excretion; mechanism of action of the intervention; disease etiology; and/or molecular subtype of the disease being treated.

DNA samples will be used for research related to the study intervention(s) and/or disease/condition under study and related conditions. The samples may also be used to develop tests/assays, including diagnostic tests related to the study intervention(s) and/or the disease/condition under study and related conditions. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome.

5.7 Rationale for Optional Future Research

Future research may be performed using residual samples originally collected for another test required in this study from consented participants only. Future research is intended to allow for research aimed at emergent or future questions that are not addressed elsewhere in the protocol and may include research that is unrelated to the study intervention(s) and/or disease under study. The research may involve genetic tests using deoxyribonucleic acid (DNA) or ribonucleic acid (RNA); this may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome. Analysis of samples for future research may also involve the use of other clinical data collected as part of this study. Such future research may also lead to the development of new diagnostic tests. The participant's decision to consent to this optional future research will not affect his/her ability to participate in the main study.

6 STUDY POPULATION

The target study population consists of participants with KRAS G12C-mutant advanced solid tumors, including NSCLC, PDAC, BTC, and CRC, who have met the following inclusion criteria and no exclusion criteria. Approximately 410 participants will be enrolled across various parts of the study.

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

6.1 Inclusion Criteria

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

1) Signed Written Informed Consent

a) Participants 18 years and above must have signed and dated an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved written informed consent form (ICF) in accordance with regulatory, local, and institutional guidelines. This ICF must be obtained before performing any protocol-related procedures that are not part of normal patient care. Participants under legal protection who require a legally authorized representative (LAR) are prohibited from consenting.

b) Participants must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing, and other requirements of the study.

2) Type of Participant and Target Disease Characteristics

a) Measurable disease per RECIST v1.1.

b) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at screening and confirmed prior to randomization.

c) Participants must have a life expectancy of at least 3 months at the time of first dose according to the investigator's judgement.

d) All participants with KRAS G12C-mutant NSCLC:

i) Should have documented status for PD-L1 (tumor proportion score [TPS]), serine/threonine kinase 11 [STK11], KRAS non-G12C mutations, epidermal growth factor receptor (EGFR) including exon 20 insertion mutations, anaplastic lymphoma kinase (ALK) rearrangements, ROS proto-oncogene 1 (ROS1) rearrangements, rearranged during transfection (RET) rearrangements, neurotrophic tropomyosin-receptor kinase (NTRK) gene fusions, mesenchymal to epithelial transition (MET) amplification, MET exon 14 skipping, or proto-oncogene B-Raf (BRAF) non-V600X mutations, if known.

ii) Should have received prior treatment with platinum-based doublet chemotherapy and anti PD-(L)1.

iii) Harboring other known actionable mutations (eg, EGFR, ALK, and ROS1) should have received prior treatment with an approved targeted therapy (as available per country/region standard-of-care practices).

e) All participants with KRAS G12C-mutant CRC:

i) Should have documented status for microsatellite instability (MSI), mismatch repair (MMR), and tumor mutational burden (TMB), if known.

ii) Should have received prior systemic therapy, including prior treatment with fluoropyrimidine, oxaliplatin and/or irinotecan-based chemotherapy, and vascular endothelial growth factor (VEGF)-targeted antibodies. Participants with microsatellite instability (MSI)-high CRC should have received approved immune checkpoint inhibitor therapy.

f) All participants with KRAS G12C-mutant PDAC or BTC:

i) Should have documented status for EGFR, fibroblast growth factor receptor 2 (FGFR2), isocitrate dehydrogenase 1 (IDH1), BRAF non-V600X, and other mutations, if available.

g) *For Participants in Part 1*:

i) Participants in Part 1 DDI and 1A: must have histologically documented, locally advanced and unresectable, or metastatic NSCLC, PDAC, BTC, or CRC with KRAS G12C mutation, whether naïve to KRAS G12C inhibitor treatment or not.

ii) Participants in Part 1B must have histologically documented, locally advanced and unresectable, or metastatic CRC with KRAS G12C mutation, whether naïve to KRAS G12C inhibitor treatment or not.

iii) For NSCLC and CRC: Participants must have a documented KRAS G12C mutation from an New York State (NYS)-approved, FDA-approved/cleared, or conformité européenne (CE)-marked test or, when such result is not available, positive KRAS G12C mutation status should be confirmed by a central laboratory (Guardant360 CDx) in liquid biopsy samples collected at the time of screening.

iv) For PDAC and BTC: Participants must have a documented KRAS G12C mutation from an NYS-approved, FDA-approved/cleared or CE-marked test and liquid biopsy samples collected only for retrospective testing.

v) Have progression or are intolerant or have disease recurrence on or after available standard of care treatments

h) *For Participants in Part 2 Dose Expansion:*

i) Participants must have a documented KRAS G12C mutation from an NYS-approved, FDA-approved/cleared or CE-marked test or, when such result is not available, positive KRAS G12C mutation status should be confirmed by a central laboratory (Guardant360 CDx) in liquid biopsy and/or tumor samples collected at the time of screening or from archival biopsies (less than 1 year old).

ii) Have tumor lesions that can be biopsied at acceptable risk and must consent to undergo pre-treatment and on treatment biopsy collection. See Section 9.7 for additional information.

i) *Participants in Part 2A:*

i) Must have histologically documented, locally advanced and unresectable or metastatic KRAS G12C-mutant NSCLC, naïve to treatment with KRAS G12C inhibitor.

ii) Must have progression or disease recurrence or are intolerant after at least 1 prior line of systemic therapy, which must include platinum-based doublet chemotherapy and anti-PD-(L)1 therapy.

j) *Participants in Part 2B*:

i) Must have histologically documented, locally advanced and unresectable, or metastatic KRAS G12C-mutant CRC, naïve to treatment with KRAS G12C inhibitor.

ii) Must have progression or disease recurrence or are intolerant after at least 1 prior line of systemic therapy.

3) Age of Participant

a) Participant must be age ≥ 18 years or local age of majority at the time of consent.

4) Reproductive Status

- Investigators shall counsel women of childbearing potential (WOCBP) participants (as defined in Appendix 4), and male participants who are sexually active with WOCBP, on the importance of pregnancy prevention, the implications of an unexpected pregnancy, and the potential of infertility or fetal toxicity occurring due to transmission of study intervention, present in seminal fluid, to a developing fetus, even if the participant has undergone a successful vasectomy or if the partner is pregnant.
- The investigator shall evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
- Local laws and regulations may require the use of alternative and/or additional contraceptive methods.

a) Female Participants:

i) Female participants, who are not of childbearing potential, must have documented proof. Note: Documentation can be obtained from the site personnel's review of the participant's medical records or medical examination of medical history interview.

(1) Women who are not of childbearing potential (as defined in Appendix 4) are exempt from contraceptive requirements.

ii) WOCBP must have a negative highly sensitive urine or serum human chorionic gonadotropin (serum HCG) pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin) within 24 hours prior to the start of study intervention.

(1) 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.

(2) Additional requirements for pregnancy testing during and after study intervention are in Section 2 Schedule of Activities.

(3) The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to potentially decrease the risk for inclusion of a woman with an undetected pregnancy.

iii) WOCBP and male participants who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception as described below and included in the ICF.

(1) Hormonal contraceptive agents are **prohibited** during this study because of an anticipated drug-drug interaction which could cause unintended high concentrations of hormonal contraception drugs and possibly lead to adverse effects (see Section 7.7.1). WOCBP are not permitted to use hormonal contraceptives as a method of contraception (as described in Appendix 4).

iv) A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

(1) Is not a WOCBP

OR

(2) Is a WOCBP and using a non-hormonal contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably, with user independent methods, as described in Appendix 4, during the intervention period and for at least 2 months after the last dose of BMS-986466, 1 week after the last dose of adagrasib and 2 months after the last dose of cetuximab, whichever is longest and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction for the same period.

b) Male Participants:

– Males who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception as described below and included in the ICF.

i) Azoospermic males are not exempt from contraceptive requirements and will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant.

ii) Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participant has undergone a successful vasectomy or if the partner is pregnant or breastfeeding. Male participants should continue to use a condom during the intervention period and for at least 2 months after the last dose of BMS-986466, 1 week after the last dose of adagrasib and 2 months after the last dose of cetuximab, whichever is longest.

iii) Female partners of male participants should be advised to use a highly effective method of contraception during the intervention period and for at least 2 months after the last dose of BMS-986466, 1 week after the last dose of adagrasib and 2 months after the last dose of cetuximab, whichever is longest, after the last dose of study intervention for the male participant.

iv) Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from sexual activity or use a male condom during any sexual activity (eg, vaginal, anal, oral), even if the participant has undergone a successful vasectomy, during the intervention period and for at least 2 months after the last dose of BMS-986466, 1 week after the last dose of adagrasib and 2 months after the last dose of cetuximab, whichever is longest.

v) Male participants must refrain from donating sperm during the intervention period and for at least 2 months after the last dose of BMS-986466, 1 week after the last dose of adagrasib and 2 months after the last dose of cetuximab, whichever is longest.

vi) Breastfeeding partners of male participants should be advised to consult their health care provider about using appropriate highly effective contraception during the time the male participant is required to use condoms. Female partners of male participants are permitted to use hormonal contraception.

6.2 Exclusion Criteria

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

1) Medical Conditions

a) Have tumors harboring known activating mutations in BRAF V600X, protein tyrosine phosphatase non-receptor type 1 (PTPN11 [SHP2]), or KRAS Q61X.

b) Any major surgery within 4 weeks of first dose of study intervention. Participants must have recovered from the effects of major surgery or significant traumatic injury at least 14 days before the first dose of study intervention.

c) Any gastrointestinal disease or surgery that could impact the absorption of the study intervention.

d) Inability to administer and/or tolerate oral medication.

e) Have untreated brain metastases. Participants who have had brain metastases resected or have received radiation therapy ending at least 4 weeks prior to C1D1 are eligible if they meet all of the following criteria prior to first dose of study medication:

   i) Residual neurological symptoms related to the CNS treatment Grade ≤ 2;

   ii) On a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent) for at least 2 weeks prior to C1D1; and

   iii) Follow-up contrast-enhanced magnetic resonance imaging (MRI) within 4 weeks prior to C1D1 shows no new lesions appearing.

f) Participants with leptomeningeal metastases (carcinomatous meningitis).

g) Concurrent malignancy (present during screening) requiring treatment or history of prior malignancy active within 2 years prior to treatment (ie, participants with a history of prior malignancy are eligible if treatment was completed at least 2 years before randomization and the participant has no evidence of disease). Participants with history of prior early stage basal/squamous cell skin cancer or non-invasive or in situ cancers that have undergone definitive treatment at any time are also eligible.

h) Uncontrolled or significant cardiovascular disease including, but not limited to, any of the following:

   i) Myocardial infarction or stroke/transient ischemic attack within the past 12 months.

   ii) Unstable or poorly controlled angina pectoris or symptomatic peripheral vascular disease including Prinzmetal variant of angina pectoris.

   iii) History of aortic aneurysm.

   iv) Any history of clinically significant arrhythmias (such as sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes), individual or family history of long QT syndrome.

   v) History of other clinically significant heart disease (eg, cardiomyopathy, congestive heart failure with New York Heart Association functional classification III to IV, pericarditis, or significant pericardial effusion).

   vi) History of left ventricular ejection fraction (LVEF) < 50% within the previous 12 months before starting the study intervention.

vii) QT interval corrected for heart rate using Fridericia's formula (QTcF) prolongation > 470 msec (for women) and > 450 msec (for men), except for right bundle branch block.

viii) Complete left bundle branch block, bifascicular block, or other clinically significant abnormal ECG finding at screening.

ix) Clinically symptomatic bradycardia or sick sinus syndrome.

i) Interstitial lung disease or pneumonitis (previous Grade 1 or 2 immuno-mediated pneumonitis is permitted if completely resolved)

j) History of allogenic bone marrow transplant.

k) On dialysis.

l) Any significant acute or chronic medical illness, active uncontrolled infection, or organ system dysfunction, such as ascites, coagulopathy, or encephalopathy or other reasons that, in the investigator's opinion, could compromise the participants' safety or interfere with or compromise the integrity of study outcomes.

m) Any other sound medical, psychiatric, and/or social reason as determined by the investigator.

2) Reproductive Status

a) Women who are breastfeeding or pregnant.

3) Prior/Concomitant Therapy

a) Inability to comply with restrictions and prohibited treatments as listed in Section 7.7: Concomitant Therapy.

b) Have previously received a SHP2 inhibitor (eg, TNO-155, RMC-4630, RLY-1971, JAB-3068, JAB-3312, or PF-07284892).

c) For Part 2 only: Have previously received a KRAS G12C inhibitor (eg, sotorasib, adagrasib, or other investigational agents).

d) Systemic anticancer therapies or biological therapies (including programmed cell death protein 1 [PD-1], PD-L1, or CTLA-4 antibodies) within 4 weeks or 5 half-lives (whichever is shorter) prior to the first administration of study intervention.

e) Have participated in an interventional clinical study within last 4 weeks OR, if applicable, be within 5 times the half-life period of the investigational study intervention, whichever is lesser, prior to the first administration of the study intervention.

f) Participants with unresectable locally advanced NSCLC who are eligible for curative intent therapy with chemoradiation.

g) Prior focal palliative radiotherapy must have been completed at least 2 weeks before the first dose of study intervention. Participants must have recovered (ie, Grade ≤ 1 or at baseline) from radiation-related toxicities prior to first study intervention.

h) Use of known strong or moderate inducers or inhibitors of CYP3A4, CYP2C8 (including herbal supplements or food products containing grapefruit juice, star fruit, or Seville oranges) within 14 days or 5 half-lives (whichever is longer) of start of treatment or expected to require such medicines during the study.

i) Use of known P-gp and BCRP inhibitors within 14 days or 5 half-lives (whichever is longer) of start of treatment or expected to require such medicines during the study.

j) Use of known CYP3A4 sensitive substrates within 14 days or 5 half-lives of the drug or its major active metabolite(s), whichever is longer, prior to start of treatment or expected to require chronic use of such medicines during the study.

k) Use of known CYP2C9, CYP2D6, CYP2B6, MATE-1/-2K, and P-gp sensitive substrates, where minimal concentration changes may lead to serious adverse reactions, within 14 days or 5 half-lives of the drug or its major active metabolite(s), whichever is longer, prior to the start of the treatment, or if expected to require chronic use of such medicines during the study.

l) Acid-reducing agents, such as proton pump inhibitors (PPIs) or H2 receptor antagonists, within 14 days or 5 half-lives, whichever is longer, prior to the first administration of the study intervention.

m) Medications that prolong QT interval.

4) Physical and Laboratory Test Findings

a) White blood cells < 2,000/μL

b) Absolute neutrophil count < 1,500/μL

c) Platelets < 100,000/μL

d) Hemoglobin < 9 g/dL

e) Creatinine clearance < 60 mL/min (measured using Cockcroft-Gault formula).

f) Total bilirubin > 1.5× ULN (except participants with Gilbert syndrome who must have a total bilirubin level of < 3.0× ULN).

g) AST/ALT: > 2.5× ULN.

h) Electrolyte abnormalities must be corrected prior to study intervention (calcium, potassium, sodium, magnesium, phosphate).

i) Any positive test result for hepatitis B virus (HBV) indicating presence of virus, eg, hepatitis B surface antigen (HBsAg, Australia antigen) positive. Note: Participants with positive HBV antibody and an undetectable viral load are eligible to enroll.

j) Any positive test result for hepatitis C virus (HCV) indicating presence of active viral replication (detectable HCV RNA). Note: Participants with positive HCV antibody and an undetectable HCV RNA are eligible to enroll.

k) Any positive test result for HIV indicating presence of active viral replication and/or receiving treatment for HIV. Note: Participants with positive HIV antibody and an undetectable viral load that do not require treatment are eligible to enroll.

5) Allergies and Adverse Drug Reactions

a) History of allergy to adagrasib, and/or BMS-986466 active or inactive ingredients of drug or related compounds.

b) For Parts 1B and 2B: History of allergy to cetuximab active or inactive ingredients of drug or related compounds.

c) History of any significant drug allergy (such as anaphylaxis or hepatotoxicity).

6) Other Exclusion Criteria

a) Prisoners or participants who are involuntarily incarcerated. (Note: Under certain specific circumstances and only in countries where local regulations permit, a person who has been

imprisoned may be included or permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)

b) Participation in another interventional clinical trial concurrent with this study.

6.3 Lifestyle Restrictions

6.3.1 Meals and Dietary Restrictions

Refrain from consumption of Seville oranges, grapefruit, or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices from 7 days before the start of study intervention until after the final dose.

6.3.2 Caffeine, Alcohol, and Tobacco

In general, participants should avoid use of alcohol and tobacco while on treatment.

6.3.3 Activity

Not applicable.

6.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but who are not subsequently entered in the study/included in the analysis population.

A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, as applicable, and to respond to queries from regulatory authorities. Minimal information includes date of consent, demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs) that occurred following consent.

6.4.1 Re-testing During Screening

This study permits the re-enrollment of a participant who has discontinued the study as a screen failure (ie, participant has not been randomized/has not been treated). If re-enrolled, the participant must be re-consented.

Re-testing of laboratory parameters and/or other assessments in any single screening period will be permitted (in addition to any parameters that require a confirmatory value).

The most current result prior to randomization is the value by which study inclusion will be assessed because it represents the participant's most current clinical state.

Re-testing is limited to these specific laboratory parameters and/or assessments:

- The fewest number of procedures from the initial screening should be repeated to qualify the participant, while maintaining participant safety and eligibility

7 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

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

Study intervention includes both Investigational [Medicinal] Product (IP/IMP) and Non-investigational/Auxiliary [Medicinal] Product (Non-IP/Non-IMP/AxMP) as indicated in Table 7.1-1.

An Investigational Product (IP), also known as an Investigational Medicinal Product (IMP) in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) differently from the authorized form, used for an unauthorized indication, or when used to gain further information about the authorized form.

Other medications used as support or escape medication for preventative, diagnostic, or therapeutic reasons, as components of the standard of care for a given diagnosis, may be considered Non-IMPs/AxMPs.

7.1 Study Interventions Administered

The time of dose administration will be called "0" hour.

Restrictions related to food and fluid intake are described in Section 6.3.1. See Section 5.1.4 for the treatment period duration.

Table 7.1-1: Study Intervention(s) Administered

Type/ Intervention Name/Dose Formulation	Unit Dose Strength(s)	IMP/Non-IMP/AxMP Blinded or Open-label	Sourcing[a]	Packaging and Labeling	Current/ Former Name(s) or Alias(es)
Drug/ BMS-986466/ Capsules	10 mg/[redacted] mg/ [redacted] mg	IMP, Open-label	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.	BBP-398/ IACS-15509

Table 7.1-1: Study Intervention(s) Administered

Type/ Intervention Name/Dose Formulation	Unit Dose Strength(s)	IMP/Non-IMP/AxMP Blinded or Open-label	Sourcing[a]	Packaging and Labeling	Current/ Former Name(s) or Alias(es)
Drug/Adagrasib/ Tablets	200 mg per tablet	IMP, Open-label	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee	Study intervention will be provided in bottles. Each bottle will be labeled as required per country requirement.	MRTX849, KRAZATI®
Drug/Cetuximab/ Vials	5 mg/mL (100-mL vial)	IMP, Open-label	Provided centrally by the Sponsor or locally by the study site, subsidiary, or designee	Study intervention will be provided in vials. Each vial will be labeled as required per country requirement.	Erbitux®

Abbreviations: AxMP, Auxiliary Medicinal Product; IMP, Investigational Medicinal Product; SmPC, summary of product characteristics.

[a] These products may be obtained by investigational sites as local commercial product in certain countries if allowed by local regulations. In these cases, products may be a different pack size/potency than listed in the table. These products should be prepared/stored/administered in accordance with the package insert or SmPC.

Table 7.1-2: Study Arm(s)

Arm Title/ Arm Type	Intervention Description/ Dosage Levels	Route of Administration
BMS-986466	DDI cohort: single dose of 10 mg on C1D1 [redacted]. Regular administration starting C3D1. All other cohorts: starting on Day 1 of each cycle, dose TBD	Oral
Adagrasib	DDI cohort: 400 mg BID starting [redacted] Other cohorts: starting on Day 1 of each cycle, 400 mg BID or 600 mg BID	Oral
Cetuximab (Parts 1B and 2B only)	Initial and subsequent doses: 500 mg/m^2 infused over 120 minutes once every 2 weeks.	IV

Abbreviations: BID, twice a day; C, cycle; D, day; DDI, drug-drug interaction; IV, intravenously; TBD, to be determined.

7.1.1 BMS-986466 and Adagrasib Administration

Participants will take BMS-986466 and adagrasib orally. When given together, the morning doses of BMS-986466 and adagrasib should be taken together regardless of food intake at approximately the same time each day with a cup of water. Participants should swallow the BMS-986466 and/or adagrasib whole and not chew them. If vomiting occurs after dosing, the doses should not be replaced.[14]

For scheduled clinic visit days for PK assessments, BMS-986466 and/or adagrasib will be administered to the participant in the clinical facility, regardless of food intake. Water is allowed ad libitum.

If a dose of BMS-986466 is missed, the participant will take the next regular dose at the scheduled time. If a dose of adagrasib is inadvertently missed, the dose should be skipped if > 4 hours have elapsed since the expected dosing time.[14]

Intra-participant dose reductions of BMS-986466 and adagrasib will be permitted under circumstances as described in Table 7.4-1. Doses of BMS-986466 and/or adagrasib may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment.

7.1.2 Cetuximab Administration

Cetuximab will be given as per package insert (500 mg/m^2 intravenously [IV] infused over 120 minutes once every 2 weeks [Q2W]). Participants will be premedicated with a histamine (H) 1 antagonist IV 30 to 60 minutes prior to the initial dose, and premedication for subsequent doses may be necessary if clinically indicated. Participants should be monitored for at least 1 hour following infusion. Intra-participant dose reductions of cetuximab will be permitted under circumstances as described in Table 7.4-4. Doses of cetuximab may be interrupted, delayed, or discontinued depending on how well the participant tolerates the treatment. See Table 7.4-4 for additional information. [redacted]

7.2 Assignment to Study Intervention

All participants will be centrally assigned to treatment using IRT. Before the study is initiated, each user will receive log-in information and directions on how to access the IRT. Study intervention will be dispensed at the study visits listed in the Schedule of Activities (Section 2).

Enrolled participants, including those not dosed, will be assigned sequential participant numbers starting with [redacted]. Those enrolled participants meeting inclusion and exclusion criteria will be eligible to be dosed. The investigative site will utilize the Interactive Response Technology (IRT) to centrally assign (Parts 1, 1A, 1B) or randomize (Parts 2A, 2B) the participant within 3 days of Cycle 1 Day 1.

7.3 Blinding

This is an open-label study with randomization in Part 2. Blinding procedures are not applicable and access to treatment assignment information is unrestricted to any Sponsor team, site, or

participant. The specific treatment to be taken by a participant will be assigned using IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the treatment assignment on the applicable Case Report Form (CRF), if required.

7.4 Dosage Modification

Participants will be monitored for AEs during all phases of the study. Participants experiencing Grade ≥ 3 TRAEs that do not qualify as DLT events will hold study intervention until symptoms improve to Grade ≤ 1 or return to baseline. The decision to proceed to the next dose level of BMS-986466 (either an increase or a decrease) will be made by the investigators and the Sponsor based on safety, tolerability, and preliminary PK and PD data obtained in at least 3 participants at the prior dose level. The dosing schedule may also be adjusted to expand a dosing cohort to further evaluate safety, PK, and/or PD findings at a given dose level or to add cohorts. This protocol allows some alteration from the currently outlined dosing schedule, but the dose will not exceed the maximum exposure of BMS-986466 comparable to the AUC/Cmax from the dose deemed acceptable from Study NAV-1001, or the approved dose for adagrasib or cetuximab. The study procedures for these additional participant(s)/cohort(s) will be the same as those described for other study participants/cohorts.

Dose delays/omissions/interruptions may occur for a single agent or multiple agents, depending on the assessment by the investigator. If it is unclear if a single agent is causing the toxicity or reason for delays/omissions/interruption, all agents should be withheld until resolution of toxicity to baseline or Grade ≤ 1.

In case of an AE relationship assignment to 1 study intervention, dose modifications for that intervention alone are allowed. For AEs attributable to both adagrasib and BMS-986466 requiring a dose modification, the dose of adagrasib may be reduced without the dose reduction of BMS-986466, as reduced adagrasib exposure will also decrease BMS-986466 exposure. For each participant, a maximum of 2 dose reductions of BMS-986466 will be allowed. Dose reduction for BMS-986466 means treatment at the next lower, previously tested dose level. If a dose reduction is required below the lowest BMS-986466 dose that was previously tested, the dose should be selected after the discussion with the Medical Monitor.

Adagrasib 600 mg BID starting dose (approved dose) may be reduced 2 dose levels to a minimum of 600 mg QD for AEs or laboratory abnormalities, as per the package insert.[14] Adagrasib at 400 mg BID starting dose may be reduced only 1 dose level, as summarized in Table 7.4-1.

Cetuximab may be reduced 2 dose levels to a minimum of [redacted] mg/m^2 for AEs or laboratory abnormalities. Dose reductions beyond the second dose reduction are not allowed for cetuximab. Recommended dose modifications for cetuximab based on the occurrence of cetuximab TRAEs are summarized in Table 7.4-2.

- If criteria for discontinuation of the cetuximab are met, adagrasib and BMS-986466 may continue until the criteria for treatment discontinuation are met.
- If criteria for discontinuation of the BMS-986466 are met, adagrasib and cetuximab (if applicable) may continue until the criteria for treatment discontinuation are met.

- If criteria for discontinuation of the adagrasib are met, all study interventions should be discontinued.

All dose modifications and missed doses/dosing holidays due to AE will be captured in the electronic data capture (EDC) and also in participant-supplied pill diaries/mechanism used to track the compliance with the dosing regimen.

In case a dose reduction/modification is necessary, the study intervention will be administered as follows in Table 7.4-3 and Table 7.4-4.

Table 7.4-1: Recommended Adagrasib Dose Reductions

Starting Adagrasib Dose	First Dose Reduction	Second Dose Reduction
600 mg BID (approved dose)	400 mg BID	600 mg QD
400 mg BID	600 mg QD	Not applicable

Abbreviations: BID, twice daily; QD, once daily.

Table 7.4-2: Recommended Cetuximab Dose Reductions

Starting Cetuximab Dose	First Dose Reduction	Second Dose Reduction
500 mg/m^2 Q2W	[redacted] mg/m^2 [redacted]	[redacted] mg/m^2 [redacted]

Abbreviation: Q2W, every 2 weeks.

Table 7.4-3: BMS-986466 and Adagrasib Dose Modifications

Adverse Reaction	Severity	Dosage Modification
Nausea or Vomiting, Despite Appropriate Supportive Care (Including Anti-emetic Therapy)	Grade 3 or 4	• Withhold adagrasib and BMS-986466 until recovery to Grade ≤ 1 or return to baseline. • Resume adagrasib at the next lower dose level and BMS-986466 at pre-interruption dose.
Diarrhea, Despite Appropriate Supportive Care (Including Anti-diarrheal Therapy)	Grade 3 or 4	• Withhold adagrasib and BMS-986466 until recovery to Grade ≤ 1 or return to baseline. • Resume adagrasib at the next lower dose level and BMS-986466 at pre-interruption dose.
Hepatotoxicity	Grade 2 AST or ALT	• Decrease adagrasib to next lower dose level.
	Grade 3 or 4 AST or ALT	• Withhold adagrasib and BMS-986466 until recovery to Grade ≤ 1 or return to baseline. • Resume adagrasib at the next lower dose level. • If first Grade 3 occurrence, resume BMS-986466 at pre interruption dose if recovery to Grade ≤ 1 or baseline occurs within 14 days. Otherwise, resume BMS-986466 at next lower dose level.
	AST or ALT > 3× ULN with total bilirubin > 2× ULN in the absence of alternative causes	• Permanently discontinue from study intervention.
QTc Interval Prolongation	QTc absolute value greater than 500 ms or with an increase greater than 60 ms from baseline	• Withhold adagrasib and BMS-986466 until QTc interval resolves to less than 481 ms or returns to baseline. • Resume adagrasib at the next lower dose level and BMS-986466 at pre-interruption dose.
Torsade de Pointes	Torsade de Pointes, polymorphic ventricular tachycardia, or signs or symptoms of serious or life-threatening arrhythmia	• Permanently discontinue from study intervention.
Interstitial Lung Disease/ Pneumonitis	Any grade	• Withhold adagrasib and BMS-986466 if ILD/pneumonitis is suspected. • Permanently discontinue study intervention if ILD/pneumonitis is confirmed.

Table 7.4-3: BMS-986466 and Adagrasib Dose Modifications

Adverse Reaction	Severity	Dosage Modification
Other Adverse Reactions	Grade 3 or 4	• Withhold adagrasib and BMS-986466 until recovery to Grade ≤ 1 or return to baseline. • Resume adagrasib at the next lower dose level. • If first Grade 3 occurrence, resume BMS-986466 at pre-interruption dose if recovery to Grade ≤ 1 or baseline occurs within 14 days. Otherwise, resume BMS-986466 at next lower dose level.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; ULN, upper limit of normal.

Table 7.4-4: Cetuximab Recommended Dosage Modifications

Adverse Reaction	Severity	Dosage Modification
Rash	Grade 1 or 2	Maintain dose level; consider initiating appropriate therapy (such as antihistamines, topical corticosteroids, and low-dose systemic corticosteroids).
	Grade 3, despite therapy	Hold cetuximab until resolved to Grade ≤ 2, then: • If resolved in ≤ 7 days (or ≤ 14 days for acneiform rash), then maintain dose level. • If not resolved in ≤ 7 days despite appropriate skin toxicity therapy (or ≤ 14 days for acneiform rash), then permanently discontinue cetuximab.
	Grade 3 recurrent	Hold cetuximab until resolved to Grade ≤ 2, then: • If resolved in ≤ 7 days (or ≤ 14 days for acneiform rash), then decrease 1 dose level. • If not resolved in ≤ 7 days despite appropriate skin toxicity therapy (or ≤ 14 days for acneiform rash), then permanently discontinue cetuximab. • Permanently discontinue cetuximab after the third recurrence (upon the fourth occurrence).
	Grade 4, despite skin toxicity therapy	Permanently discontinue cetuximab.
Hypomagnesemia		Hypomagnesemia has been seen with cetuximab. Should hypomagnesemia occur, magnesium supplementation should be provided. No dose adjustment is required; however, continue careful monitoring.

Table 7.4-4: Cetuximab Recommended Dosage Modifications

Adverse Reaction	Severity	Dosage Modification
Infusion Reaction (If an infusion reaction occurs while cetuximab is being infused, the infusion should be stopped immediately, and the participant should be evaluated)	Grade 1 or 2	Restart and complete the disrupted infusion at the discretion of the investigator. The infusion must be restarted at a reduced rate. Additional pre-medications such as antihistamines or low-dose systemic corticosteroids may be administered when the infusion is restarted per institutional standards. All subsequent infusions must also be administered at the reduced rate.
	Grade 3 or 4	Permanently discontinue cetuximab.
Pulmonary Toxicity	Grade 2 or worsening pulmonary symptoms	Cetuximab therapy should be stopped, and symptoms investigated. Cetuximab therapy may resume when symptoms resolve to Grade ≤ 1.
	Grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates	Hold cetuximab until interstitial lung disease is ruled out. Permanently discontinue cetuximab if interstitial lung disease is confirmed.

7.4.1 Dose-limiting Toxicities

The DLT evaluation period is 1 cycle (28 days) for Part 1 dose escalation. All participants who receive at least 1 dose of BMS-986466 will be evaluable for safety. Participants in Part 1A will be considered DLT evaluable if they complete ≥ 75% of all planned doses of BMS-986466 and adagrasib without experiencing a DLT or experience a DLT after receiving at least 1 dose of BMS-986466 and adagrasib. Participants in Part 1B must complete ≥ 75% of all planned doses of BMS-986466 and adagrasib and have received at least 2 doses of cetuximab without experiencing a DLT or experience a DLT after receiving at least 1 dose of BMS-986466, adagrasib, and cetuximab. Participants with suspected DLTs may have study intervention delayed (at the treating investigator's discretion) until the relatedness is defined. Participants who do not meet the DLT evaluation criteria may be replaced during the dose escalation part.

AEs that meet the following criteria will be DLTs, except for those that are clearly and incontrovertibly due to disease progression or extraneous causes (see Sections 7.4.1.1 and 7.4.1.2).

7.4.1.1 Non-hematological Toxicity

- Any Grade ≥ 3 non-hematological toxicity. Exceptions will be made for the following:
  - Grade 3 nausea, diarrhea, or vomiting that resolves to baseline or Grade 1 within 72 hours after holding study intervention and implementing optimal medical management.
  - Grade 3 fatigue lasting for less than 7 days.
  - Grade 3 increases in amylase or lipase that are not associated with clinical symptoms or radiographic manifestations of pancreatitis.
  - Grade 3 rash that reduces to Grade ≤ 1 within 14 days.
  - Grade 3 or higher electrolyte imbalances/abnormalities that are not associated with clinical sequelae and resolve spontaneously or are responding to supplementation/appropriate management within 72 hours.
- AST/ALT > 3× and ≤ 5× ULN or total bilirubin > 1.5× and ≤ 3× ULN if the baseline was normal; AST/ALT > 3× and ≤ 5× baseline or total bilirubin > 1.5× and ≤ 3× baseline if the baseline was abnormal.
- Any AST/ALT > 5× ULN or total bilirubin > 3× ULN irrespective of baseline values; any case that meets Hy's Law criteria (either ALT or AST > 3× ULN AND total bilirubin > 2× ULN).

7.4.1.2 Hematological Toxicity

- Grade 4 anemia
- Grade 4 neutropenia of > 7 days duration
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with clinically significant bleeding
- Febrile neutropenia

7.5 Preparation/Handling/Storage/Accountability

The IP/IMP/Non-IMP/AxMP must be stored in a secure area according to local regulations. It is the responsibility of the investigator, or designee where permitted, to ensure that IP/IMP/Non-IMP/AxMP is only dispensed to study participants. The IP/IMP/Non-IMP/AxMP must be dispensed only from official study sites by authorized personnel according to local regulations.

The product storage manager should ensure that the study intervention is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by the Sponsor. If concerns regarding the quality or appearance of the study intervention arise, the study intervention should not be dispensed, and the Sponsor should be contacted immediately.

Study intervention not supplied by the Sponsor will be stored in accordance with the package insert.

IP/IMP/Non-IMP/AxMP documentation (whether supplied by the Sponsor or not) must be maintained and must include all processes required to ensure the drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

- The investigator or designee must confirm that 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, prepare, or administer study intervention.
- All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, head of the medical institution (where applicable), or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition of records).
- Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

For study interventions not provided by the Sponsor and obtained commercially by the site, storage should be in accordance with the product label.

7.6 Study Intervention Compliance

Study intervention compliance will be monitored periodically by drug accountability (review of dosing diary). Drug accountability should be reviewed by the study site staff at each visit to confirm treatment compliance. Study site staff should discuss discrepancies with the participant at each on-treatment study visit.

- When participants are dosed 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.
- When participants self-administer BMS-986466 and adagrasib at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed (by review of dosing diaries, direct questioning, counting returned tablets/capsules, etc) during the site visits and documented in the source documents and relevant dosing diaries. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.
- A record of the quantity of BMS-986466 and adagrasib dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions, will also be recorded in the CRF.
- For Parts 1B and 2B:
  - For cetuximab compliance: IV cetuximab will be administered in the outpatient setting during biweekly visits, the compliance with study intervention will be assessed by source documentation and relevant forms. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

7.7 Concomitant Therapy

7.7.1 Prohibited and/or Restricted Treatments

The following medications and treatments are prohibited during the study (unless used to treat a drug-related AE). For a comprehensive and up to date list of substrates, inhibitors, and inducers, refer to the FDA website.[32]

- Concomitant use of strong/moderate inhibitors of CYP3A4 or strong/moderate inducers of CYP3A4 is prohibited. Concurrent use of strong/moderate inhibitors or inducers of CYP3A4 may affect the systemic exposure of BMS-986466.
- Seville oranges, grapefruit, or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices, cannabinoid (CBD) can inhibit CYP3A4 and should not be consumed while on study.
- Concomitant use of BCRP inhibitors should be avoided. Participants that receive them should be closely monitored for safety events.
- Avoid concomitant use with sensitive CYP3A4 substrates.
- Avoid concomitant use with sensitive CYP2C9, CYP2D6, CYP2B6, P-gp, and MATE-1/-2K substrates where minimal concentration change may lead to serious adverse reactions.
- Participants who require concomitant use of QT modulating drugs for pre-existing conditions will be excluded. Adagrasib treatment should be held for participants who require a QT modulatory drug during the treatment period for the management of AEs.
- Any concurrent systemic anti-neoplastic therapy (ie, chemotherapy, hormonal therapy, immunotherapy, or standard or investigational agents for treatment of malignancy).
- Avoid acid-reducing agents, such as proton pump inhibitors (PPIs) or H2 receptor antagonists.

- Any non-palliative radiation therapy. Radiation therapy administered with palliative intent (ie, for pain, bleeding, spinal cord compression, brain metastasis, new or impending pathologic fracture, superior vena-cava syndrome, or obstruction) is permitted.
- Any complementary medications (eg, herbal supplements such as St. John's wort or traditional Chinese medicines) intended to treat the disease under study. Such medications are permitted if they are used as supportive care and are not known modulators of CYP3A4.

7.7.2 Imaging Restrictions and Precautions

It is the local imaging facility's responsibility to determine, based on participant attributes (eg, allergy history, diabetic history, renal status), the appropriate imaging modality and contrast regimen per imaging study. Imaging contraindications and contrast risks are to be considered in this assessment. Participants with renal insufficiency are to be assessed as to whether they should receive contrast and if so, which contrast agent and dose are appropriate. Specific to magnetic resonance imaging (MRI), participants with severe renal insufficiency (ie, estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) are at increased risk of nephrogenic systemic fibrosis; therefore, MRI contrast is contraindicated. In addition, participants may be excluded from MRI if they have tattoos, metallic implants, pacemakers, etc. These restrictions will be outlined in the Imaging Manual.

Gentle hydration before and after IV contrast should follow local standard of care. The ultimate decision to perform MRI in an individual participant enrolled in this study rests with the site radiologist, the investigator, and standards set by the local Ethics Committee.

7.8 Continued Access to Study Intervention After the End of the Study

At the conclusion of the study, if the study intervention is not available as an approved treatment in the local country, participants who continue to demonstrate clinical benefit will be eligible to receive Sponsor-supplied study intervention for a maximum treatment duration as specified in Section 7.1. If the study intervention is not available as an approved and available treatment, study intervention will be provided via an extension of the study, a rollover study requiring approval by the responsible Health Authority and Ethics Committee, or through another mechanism at the discretion of the Sponsor.

The Sponsor reserves the right to terminate access to Sponsor-supplied study intervention if any of the following occur: a) the study is terminated due to safety concerns; b) the development of BMS-986466 is terminated for other reasons, including, but not limited to, lack of efficacy and/or not meeting the study objectives; or c) the participant can obtain medication from a government-sponsored or other health program. In all cases, the Sponsor will follow local regulations.

8 DISCONTINUATION CRITERIA

Discontinuation of the study at specific sites or of the entire study is detailed in Appendix 2.

8.1 Discontinuation of Study Intervention

Participants MUST discontinue IP/IMP (and Non-IMP/AxMP at the discretion of the investigator) for any of the following reasons:

- Participant's request to stop study intervention. Participants who request to discontinue study intervention will remain in the study and should continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact with him/her or persons previously authorized by the participant to provide this information.
- Any clinical AE, laboratory test result abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Termination of the study by the Sponsor.
- Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment of either a psychiatric or physical illness (eg, infectious disease). (Note: Under specific circumstances and only in countries where local regulations permit, a participant who has been imprisoned may be permitted to continue as a participant. Strict conditions apply, and Sponsor approval is required.)
- Start of anticancer therapy other than as outlined in this protocol (palliative radiation is allowed after discussion with the Medical Monitor).
- Documented and confirmed disease progression as defined by RECIST v1.1 (refer to Appendix 6 and Section 8.1.1).
- Clinical deterioration while receiving active study therapy that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the participant.
- Any TRAE that meets the criteria for permanent discontinuation of all study intervention, as outlined in Table 7.4-1.
- Inability to comply with protocol.
- Discretion of the investigator.
- Pregnancy

Study intervention must be permanently discontinued per criteria in Section 7.4. Discontinue BMS-986466 and/or adagrasib and/or cetuximab for any AE, laboratory abnormality, or intercurrent illness that, in the judgment of the investigator, presents a substantial clinical risk to the participant with continued dosing of study intervention.

Any event that leads to delay in BMS-986466 dosing lasting > 4 weeks from the previous dose requires discontinuation of study drug, with the following exceptions:

- Dosing delays lasting > 4 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Medical Monitor.

Refer to Section 2: Schedule of Activities for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that can be completed.

All participants who discontinue study intervention should comply with protocol-specified follow-up procedures as outlined in Section 2: Schedule of Activities. The only exception to this

requirement is when a participant withdraws consent for all study procedures, including post-treatment study follow-up, or loses the ability to consent freely (eg, is imprisoned or involuntarily incarcerated for the treatment of either a psychiatric or physical illness).

If study intervention is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records per local regulatory requirements in each region/country and entered on the appropriate CRF page.

8.1.1 Post-study Intervention Study Follow-up

In this study, safety and efficacy are key endpoints. Post-study follow-up is of critical importance and is essential to preserving participant safety and the integrity of the study. Participants who discontinue study intervention must continue to be followed (in this study or a rollover study) for collection of outcome and/or survival follow-up data as required and in line with Section 5: Study Design until death or the conclusion of the study.

8.2 Discontinuation From the Study

- Participants should notify the investigator of the decision to withdraw consent from future follow-up.
- The withdrawal of consent should be explained in detail in the medical records by the investigator as to whether the withdrawal is from further treatment with study intervention only or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page.
- In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.2.1 Individual Discontinuation Criteria

- A participant may withdraw completely from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon. Stopping study intervention is not considered withdrawal from the study.
- At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in Section 2 Schedule of Activities. See the Schedule of Activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued from both the study intervention and the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

8.3 Lost to Follow-up

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

- All reasonable efforts must be made to locate participants to determine and report their ongoing status. This includes follow-up with persons authorized by the participant.
- Lost to follow-up is defined by the inability to reach the participant after a minimum of **3** documented phone calls, faxes, or emails, as well as lack of response by participant to **1** registered mail letter. All attempts should be documented in the participant's medical records.
- If the investigator's use of a third-party representative to assist in the follow-up portion of the study has been included in the participant's informed consent, then the investigator may use a Sponsor-retained third-party representative to assist site staff with obtaining the participant's contact information or other public vital status data, such as public health registries and databases, necessary to complete the follow-up portion of the study.
- The site staff and representative will consult publicly available sources, such as public health registries and databases, to obtain updated contact information.
- If, after all attempts, the participant remains lost to follow-up, then the last known alive date as determined by the investigator should be reported and documented in the participant's medical records.
- If it is determined that the participant has died, the site will use permissible local methods to obtain date and cause of death.

8.4 Study Stopping Criteria

- Systematic review of SAEs experienced through the duration of therapy will serve as a key basis for pausing or prematurely stopping the study. Review of these SAEs, and any decision to stop enrollment or terminate the study, will be determined by the Sponsor in collaboration with the investigators regarding possible study continuation, adjustment of the dose/schedule, health authority consultation, and study termination.
- During Part 1, stopping rules based on TITE-BOIN will be used to continuously monitor for excess toxicity, defined as the occurrence of AEs during any cycle that would fulfill the DLT criteria (refer to Appendix 7).
- During Part 2, continuous safety monitoring will be applied, based on the Bayesian framework. If at any time during the treatment and safety follow-up periods, it reaches the pre-specified threshold of toxicity, then, taking into account all available safety information, additional evaluation will be conducted to allow a complete by treatment arm safety assessment and benefit/risk evaluation. [redacted] (see Section 10.4.5 for additional information).
- The Sponsor and investigators will convene regularly to review all the available safety, PK, PD, and efficacy data and in the event of any of the following occurrences:
  - Unanticipated SAEs that are related to study intervention are reported.
  - Death attributable to study intervention is reported.

  - The Sponsor or IRB/IEC decides that participant safety may be compromised by continuing the study.
- Decisions to stop the enrollment or terminate the study will be communicated promptly to investigators, to the IRBs/IECs, Institutional Biosafety Committees, if applicable, and to the appropriate regulatory authorities.

9 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and timing are summarized in Section 2: Schedule of Activities.
- Protocol waivers or exemptions are not allowed.
- All immediate safety concerns must be discussed with the Sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue treatment.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before initiation of study intervention/randomization. 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, complete blood count) and obtained before signing of informed consent may be utilized for screening or baseline purposes provided the procedure meets the protocol-defined criteria and has been performed within the time frame defined in the Schedule of Activities.
- Evaluate participants immediately to rule out cardiac toxicity if the participants show signs of QTc prolongation (eg, palpitations, dizziness).
- Some of the assessments referred to in this section may not be captured as data in the electronic CRF (eCRF). They are intended to be used as safety monitoring by the treating physician. Additional testing or assessments may be performed as clinically necessary or where required by institutional or local regulations.
- Perform additional measures, including non-study required laboratory tests, as clinically indicated or to comply with local regulations. Laboratory toxicities (eg, suspected drug induced liver enzyme evaluations) will be monitored during the follow-up phase via on-site/local labs until all study drug-related toxicities resolve, return to baseline, or are deemed irreversible.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

9.1 Efficacy Assessments

9.1.1 Efficacy Assessment for the Study

Screening, on treatment and follow-up images should be acquired as outlined in Table 2-1 and Table 2-2 and as defined in Section 8.1. For participants continuing past that period, imaging will continue as defined in Table 2-2. Any additional imaging that may demonstrate tumor response or

progression (including scans performed at unscheduled time points and/or at an outside institution) should be collected for tumor assessment and be submitted to the central imaging vendor (for Part 2 only). Imaging should continue until disease progression or discontinuation of all study intervention, whichever occurs later.

Efficacy assessments for the anti-tumor activity of BMS-986466 in combination with adagrasib and with or without cetuximab will be based on tumor measurements using RECIST v1.1 with computed tomography (CT) and/or MRI, as appropriate, at baseline, and during the treatment period.

Only data for the procedures and assessments specified in this protocol should be submitted to the Sponsor or designee on a CRF. Additional procedures and assessments may be performed as part of standard of care. However, data for these assessments should remain in the participant's medical record and should not be provided to the Sponsor or designee, unless specifically requested from the Sponsor or designee.

9.1.2 Imaging Assessment for the Study

All images will be submitted to a central imaging vendor and recorded in the EDC. For Part 2, the images will also be read by a blinded independent central review (BICR). Prior to scanning the first participant, sites should be qualified and understand the image acquisition guidelines and submission process as outlined in the Imaging Manual provided by the central imaging vendor.

Any additional CT/MR images performed either at unscheduled time points and/or at an outside institution that may demonstrate tumor response or progression per RECIST v1.1 should be recorded in the EDC and submitted to the central imaging vendor. X-rays and bone scans that clearly demonstrate interval progression of disease, for example most commonly as unequivocal lesions that are unmistakably new since the prior CT/MRI, should also be submitted to central imaging vendor.

Tumor assessments should continue on the protocol-defined imaging schedule regardless of dosing delays or discontinuation. Changes in tumor measurements and responses will be assessed by the same investigator or designee using RECIST v1.1 criteria. Investigators will report the number and size of new lesions that appear while on the study. The time point of tumor assessments will be reported on the eCRF based on the investigator's assessment using RECIST v1.1 criteria (refer to Appendix 6 for specifics of RECIST v1.1 criteria to be used in this study). Assessments of partial response and complete response must be confirmed at least 4 weeks (28 days) after the initial response. A best overall response (BOR) of stable disease (SD) requires a minimum of 49 days on study from date of first dose to the date of the first imaging assessment.

Refer to Section 2.3.3 in Appendix 6 for determination of BOR.

9.1.2.1 Imaging Schedule

Screening Procedural Outline

Body Imaging: Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, within 28 days prior to date of first dose.

Brain Imaging: MRI of the brain (without and with contrast) is mandatory for all NSCLC participants. MRI of the brain is required for CRC participants with known or suspected brain metastases at the time of screening, within 28 days prior to date of first dose. CT of the brain (without and with contrast) can be performed if MRI is contraindicated.

On-treatment Procedural Outline

Body Imaging: Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease, should occur Q8W (± 7 days) starting from date of first dose for the first 48 weeks, then Q12W (± 7 days) until disease progression or discontinuation of all study intervention, whichever occurs later. If pregnancy is the reason for study intervention discontinuation, no imaging is performed.

Brain Imaging: Participants with a brain metastasis at baseline should have surveillance MRIs (without and with contrast) per standard of care (approximately Q12W [± 7days]) or sooner if clinically indicated. CT of the brain without and with contrast can be performed if MRI is contraindicated.

Long-term Follow-up Procedural Outline

Body Imaging: Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should occur Q8W starting from date of first dose (± 7 days) for the first 48 weeks, then Q12W (± 7 days) until disease progression or discontinuation of all study intervention, whichever occurs later, for up to 2 years from the date of EOT.

Brain Imaging: Participants with a history of brain metastasis should have surveillance MRIs (without and with contrast) per standard of care (approximately Q12W) or sooner if clinically indicated. Participants without a history of brain metastasis should undergo brain MRI when clinically indicated CT of the brain without and with contrast can be performed if MRI is contraindicated.

9.1.2.2 Methods of Measurement

Contrast-enhanced CT of the chest, CT/MRI of the abdomen, pelvis, and all other known and/or suspected sites of disease should be performed for tumor assessments. Images should be acquired with slice thickness of 5 mm or less with no intervening gap (contiguous). Every attempt should be made to image each participant using an identical acquisition protocol on the same scanner for all imaging time points. In case of a contraindication for either contrast agent or MRI (eg, incompatible pacemaker), it is strongly recommended to use the following guidance:

If a participant has a contraindication for CT IV contrast, then a non-contrast CT of the chest and a contrast-enhanced MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for both MRI and CT IV contrasts, then a non-contrast CT of the chest and a non-contrast MRI of the abdomen, pelvis, and other known/suspected sites of disease should be obtained.

If a participant has a contraindication for MRI in addition to contraindication to CT IV contrast, then a non-contrast CT of the chest, abdomen, pelvis, and other known/suspected sites of disease is acceptable.

Use of CT component of a positron emission tomography (PET)-CT scanner: Combined modality scanning such as with PET-CT is increasingly used in clinical care and is a modality/technology that is in rapid evolution; therefore, the recommendations outlined here may change rather quickly with time. At present, low dose or attenuation correction CT portions of a combined PET-CT are of limited use in anatomy-based efficacy assessments and it is therefore suggested that they should not be substituted for dedicated diagnostic contrast-enhanced CT scans for anatomy-based RECIST v1.1 measurements. However, if a site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements. Note, however, that the PET portion of the CT introduces additional data that may bias an investigator if it is not routinely or serially performed.

Bone scan or PET scan are not adequate for assessment of RECIST v1.1 response in target lesions. In selected circumstances where such modalities are the sole modality used to assess certain non-target organs, those non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

Bone scans may be collected per local standards, as clinically indicated.

9.2 Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, or a surrogate (or the participant's legally acceptable representative).

The investigator and any qualified designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study intervention or the study, or that caused the participant to discontinue before completing the study.

Use CTCAE v5.0 definitions and grading for safety reporting of all AEs and SAEs on the CRF.

Refer to Appendix 3 for SAE reporting.

All AEs and SAEs (including associated with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] infection) are collected from time of consent until 30 days post discontinuation of study intervention, except in cases where a study participant has started a new anti-neoplastic therapy. However, any AE occurring after the start of a new treatment that is suspected to be related to study intervention by the investigator will be reported. Beyond 30 days from the last dose of study intervention, participants will be followed for drug-related AEs/SAEs until resolution, returns to baseline, or is deemed irreversible, or until the participant is lost to follow-up or withdraws study consent.

Participants will be followed for all SAEs and all AEs (SAEs and non-serious AEs) associated with confirmed or suspected SARS-CoV-2 infection until resolution, the condition stabilizes, the event is otherwise explained, the event is deemed irreversible, the participant is lost to follow-up, or for suspected cases, until SARS-CoV-2 infection is ruled-out.

9.2.1 Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs must be collected from the time of signing the informed consent form, including those thought to be associated with protocol-specified procedures and until 30 days following discontinuation of dosing or the last scheduled visit as noted in the Schedule of Activities (Section 2). However, SAEs that are considered to be related to study drug have an indefinite timeframe during which they must be reported.

The investigator must report any SAE that occurs after these periods and that is believed to be related to a study intervention or protocol-specified procedure (eg, a follow-up skin biopsy).

- All SAEs will be recorded and reported to the Sponsor or designee, promptly and not to exceed 24 hours of awareness of the event , as indicated in Appendix 3.
- The investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of updated information being available.

Investigators are not obligated to actively seek AEs or SAEs 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 he/she considers the event reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

The method of evaluating and assessing causality of AEs and SAEs and the procedures for completing and reporting/transmitting SAE reports are provided in Appendix 3.

9.2.2 Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care should be taken not to introduce bias when collecting AEs and/or SAEs. Inquiry about specific AEs should be guided by clinical judgment in the context of known AEs, when appropriate for the program or protocol.

9.2.3 Follow-up of AEs and SAEs

- Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Appendix 3).
- Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study intervention and for those present at the end of study intervention as appropriate.
- All identified non-serious AEs must be recorded and described on the non-serious AE page of the CRF (paper or electronic). Completion of supplemental CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported/identified during the study.

All SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up (as defined in Section 8.3: Lost to Follow-up).

Further information on follow-up procedures is given in Appendix 3.

9.2.4 Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of SAEs is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a product under clinical investigation are met.
- An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate, according to local requirements.

The Sponsor or designee must report AEs to regulatory authorities and ethics committees according to local applicable laws and regulations. A suspected, unexpected serious adverse reaction (SUSAR) is a subset of SAEs and must be reported to the appropriate regulatory authorities and investigators following local and global guidelines and requirements.

9.2.5 Pregnancy

If, following initiation of the study intervention, it is discovered that a participant is pregnant or may have been pregnant at the time of study intervention exposure, including at least 2 months after the last dose of BMS-986466, 1 week after the last dose of adagrasib, and 2 months after the last dose of cetuximab, whichever is longest after study intervention administration, the investigator must immediately notify the Sponsor Medical Monitor/designee of this event and complete and forward a Pregnancy Surveillance Form to the Sponsor designee within 24 hours of awareness of the event. Pregnancy reporting must follow the same transmission timing and processes to BMS as those used for SAEs, in accordance with reporting procedures described in Appendix 3.

In all cases, the study intervention will be discontinued in an appropriate manner (eg, dose tapering if necessary for participant safety).

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information, must be reported on the Pregnancy Surveillance Form. Protocol-required procedures for study discontinuation and follow-up must be performed.

Any pregnancy that occurs in a female partner of a male participant at the time of study intervention exposure, including at least 2 months after the last dose of BMS-986466, 1 week after the last dose of adagrasib, and 2 months after the last dose of cetuximab, whichever is longest after study intervention administration, should be reported to the Sponsor or designee. For the Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female

partner must sign an ICF for disclosure of this information. Information on this pregnancy will be collected and recorded on the Pregnancy Surveillance Form.

If any sexual activity involving penile intercourse (eg, vaginal, anal, oral) has occurred between a male participant and a pregnant partner(s) without the use of a condom during and for at least 2 months after the last dose of BMS-986466, 1 week after the last dose of adagrasib, and 2 months after the last dose of cetuximab, whichever is longest after study intervention administration, the information should be reported to the Sponsor or designee, even if the male participant has undergone a successful vasectomy.

9.2.6 Laboratory Test Result Abnormalities

The following laboratory test result abnormalities should be captured on the Adverse Events – Non-serious and Serious Events CRF page. Paper forms are only intended as a back-up option when the electronic system is not functioning.

- Any laboratory test result that is clinically significant or meets the definition of an SAE
- Any laboratory test result abnormality that requires the participant to have study intervention discontinued or interrupted
- Any laboratory test result abnormality that requires the participant to receive specific corrective therapy

It is expected that, wherever possible, the clinical rather than the laboratory term will be used by the reporting investigator (eg, anemia versus low hemoglobin value).

9.2.7 Potential Drug-induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory test result abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs (see Section 9.2: Adverse Events and Appendix 3 for reporting details).

A potential DILI is defined as follows:

- Aminotransferase (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]) elevation > 3× upper limit of normal (ULN)

  AND

- Total bilirubin > 2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

  AND

- No other immediately apparent possible causes of aminotransferase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

The key responsibilities for investigators during potential drug-induced liver injury (p-DILI) assessment include (i) early detection, medical evaluation (including the exclusion of other potential causes), and rapid laboratory confirmation of liver-related abnormalities; and (ii) Sponsor notification of p-DILI cases via SAE forms. Following the gathering and assessment of relevant clinical information, Sponsor is responsible for (i) timely evaluation and triaging of p-DILI cases; (ii) expedited reporting of p-DILI cases; and (iii) expanded review of p-DILI cases including a detailed assessment of all available clinical information, investigations, and biochemical data.

Investigators are expected to monitor ongoing routine and ad hoc hepatic laboratory test results to rapidly determine whether a participant meets p-DILI criteria. They are expected to promptly notify the Sponsor of all p-DILI cases. p-DILI cases may be identified by abnormal liver biochemistry values, whether or not they are accompanied by liver-related signs and/or symptoms. In both cases, expedited confirmation with repeat laboratory testing should occur within 3 business days using a hepatic laboratory panel (ALT, AST, total bilirubin, ALP). Any participant with an abnormal hepatic laboratory panel that meets p-DILI criteria is a candidate for study intervention discontinuation. Any confirmed p-DILI events must be reported (along with a description of the clinical findings) to the Sponsor as an SAE within 24 hours of confirmation.

An extensive clinical history, examination, and appropriate investigations should be obtained to exclude cholestatic and other apparent causes that may explain the observed abnormalities in liver function and/or hepatic signs and symptoms. Other apparent causes include, non-exhaustively and by way of example only, the following: infectious diseases (such as active hepatitis A, B, and C), congenital diseases (such as Gilbert's syndrome), neoplastic diseases, autoimmune diseases (such as primary biliary cirrhosis), and the use of concomitant hepatotoxic medications (such as antibiotics, the oral contraceptive pill, and herbal medicines). All investigations to exclude potential causes of liver function abnormalities or hepatic signs and/or symptoms should be guided by relevant factors such as the participant's age, gender, clinical history, and signs and symptoms.

9.2.8 Other Safety Considerations

Any significant worsening of conditions noted during interim or final physical examinations, ECG, radiographic imaging, or any other potential safety assessment required or not required by the protocol should also be recorded as a non-serious AE or SAE, as appropriate, and reported accordingly.

9.3 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. Overdoses that meet the regulatory definition of an SAE will be reported as SAEs (see Appendix 3).

In the event of an overdose, the investigator should:

- Contact the Medical Monitor immediately.
- Closely monitor the participant for AEs/SAEs and laboratory test result abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

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

9.4 Safety

Planned time points for all safety assessments are listed in Section 2: Schedule of Activities.

Safety assessments will be based on reported AEs and the measurement results of vital signs, ECGs, physical examinations, and clinical laboratory tests. AEs will be coded using the most current version of Medical Dictionary for Regulatory Activities and the incidence of observed AEs will be tabulated and reviewed for potential significance and clinical importance. AEs will be tabulated by system organ class, preferred term, and treatment and reviewed for potential significance and clinical importance. Clinical laboratory results will also be listed and tabulated.

AEs will be assessed continuously during the study and for a minimum of 30 days after the last dose of study intervention including BMS-986466, adagrasib, and/or cetuximab. Local laboratory will perform the clinical laboratory tests and will provide reference ranges for these tests. Both AEs and laboratory tests will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0.

9.4.1 Physical Examinations and Measurements

Refer to Section 2: Schedule of Activities. If the screening physical examination is performed within 72 hours prior to dosing on Day 1, then a single examination may count as both the screening and pre-dose evaluation. If there are any new or worsening clinically significant changes since the last examination, report changes on the appropriate non-serious or serious AE CRF page.

At screening, Day 1 of each cycle, EOT, and Follow-up Visit 1, the physical examination should be comprehensive. For subsequent visits, the targeted physical examinations should be symptom directed as clinically indicated. Investigators should pay special attention to clinical signs related to previous serious illnesses. Any treatment-emergent abnormal findings will be recorded as AEs.

9.4.2 Vital Signs and Oxygen Saturation

Refer to Section 2: Schedule of Activities. Includes body temperature, respiratory rate, seated blood pressure, and seated heart rate. Blood pressure and heart rate should be measured after the participant has been resting quietly for at least 5 minutes. Obtain oxygen saturation by pulse oximetry at rest in room air.

9.4.3 Electrocardiograms

Refer to Section 2: Schedule of Activities for timing of ECG assessments for safety in Table 2-1 and Table 2-2. The investigators will review the 12-lead ECGs throughout the study. The corrected QTc will be applied to each ECG reading.

Refer to the schedule of specific ECG collections to analyze the effect of BMS-986466 on the QTc interval in Table 2-1 and Table 2-2 in Parts 1 and 2.

In Part 1, triplicate ECGs collected 5 minutes apart (using the ECG machine supplied by the Sponsor and results should be transmitted electronically to the central laboratory) as follows:

- Part 1 DDI cohort: On C1D1 [redacted] at approximately 30 min before BMS-986466 dosing, and [redacted] at approximately 30 minutes before BMS-986466 dosing, and after the [redacted] post-dose PK sample
- Parts 1A (excluding DDI Cohort) and 1B: On C1D1 at approximately 30 minutes before BMS-986466 dosing and C1D1 and C2D1 after the [redacted] post-dose PK sample

For all of Part 2, a single 12-lead ECG will be collected as outlined in Table 2-4 and Table 2-5. On C2D1 a single 12-lead ECG (using site ECG machine or supplied by the Sponsor, if requested) will be performed at approximately 30 minutes before BMS-986466 dosing and after the [redacted] post-dose PK sample.

All ECGs should be recorded after the participant has been supine for at least 5 minutes. All other time points require a single 12-lead ECG reading collected for safety purposes, and site ECG machines should be used. Additional ECG monitoring as clinically indicated.

9.4.4 2-D Echocardiogram/MUGA

In Parts 1 DDI, 1A, and 1B, 2-D echocardiograms or MUGA are required at screening, C2D1, C3D1 then every odd cycle (eg, C5D1, C7D1, etc), and at EOT. In Parts 2A and 2B, 2-D echocardiograms or MUGA are required at screening, C2D1, and every odd cycle (C3, C5, C7, etc) if clinically indicated.

9.4.5 Clinical Safety Laboratory Assessments

- Investigators must document their review of each laboratory safety report.
- A local laboratory will perform the analyses and will provide reference ranges for these tests.
- Results of clinical laboratory tests performed on Day -1 must be available prior to dosing.
- The laboratory tests that will be performed for study participants are shown in Section 2 and Table 9.4.5-1.
- Results of all laboratory tests required by this protocol must be provided to the Sponsor, recorded either on the laboratory pages of the CRF or by another mechanism as agreed upon between the investigator and the Sponsor (eg, provided electronically). If the units of a test result differ from those printed on the CRF, the recorded laboratory values must specify the correct units.
- Any abnormal laboratory test result considered clinically significant by the investigator must be recorded on the appropriate AE page of the CRF.

Table 9.4.5-1: Clinical Laboratory Assessments

Hematology	
Hemoglobin	
Hematocrit	
Total leukocyte count, including differential	
Platelet count	
Screening only: Prothrombin time, activated partial thromboplastin time, and international normalized ratio	
Chemistry	
Aspartate aminotransferase (AST/SGOT) Alanine aminotransferase (ALT/SGPT) Total bilirubin Direct bilirubin (reflex, if total bilirubin is abnormal) Alkaline phosphatase Lactate dehydrogenase Creatinine Blood urea nitrogen Uric acid Gamma-glutamyl transferase (reflex, if liver function is abnormal) BNP Troponin Blood glucose (fasting at screening only)	Total protein Albumin Sodium Potassium Chloride Calcium Phosphorus Magnesium Creatine kinase Creatinine clearance (at screening) Amylase Lipase Screening only: TSH, free T3, free T4
Urinalysis	
Protein	
Glucose	
Blood	
Leukocyte esterase	
Specific gravity	
pH	
Microscopic examination of the sediment if blood, protein, or leukocytes esterase are positive on the dipstick	
Serology (Screening only)	
Hepatitis B/C, HIV-1, and HIV-2 antibodies. Measure viral load for participants with positive serology for either of the virus.	
Other Analyses	
Pregnancy test (WOCBP only: screening, predose, EOT).	
Follicle-stimulating hormone (screening only; for post-menopausal women only) use as applicable	

Abbreviations: ALT, alanine aminotransaminase; AST, aspartate transaminase; BNP, b-type natriuretic protein; EOT, end of treatment; HIV, human immunodeficiency virus; SGOT, serum glutamic-oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; WOCBP, women of childbearing potential.

9.4.6 Suicidal Risk Monitoring

Not applicable.

9.5 Pharmacokinetics

PK of BMS-986466 will be derived from plasma concentration versus time. The PK of adagrasib may be assessed if data permits. The PK parameters to be assessed, if feasible, include the following:

Cmax	Maximum observed plasma concentration
Tmax	Time of maximum observed plasma concentration
AUC(0-T)	Area under the plasma concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	Area under the plasma concentration-time curve from time zero extrapolated to infinite time (single dosing only)
Ctrough	Trough-observed plasma concentration (multiple dosing only)
AUC(TAU)	Area under the concentration-time curve in 1 dosing interval (multiple dosing only)
Cavg	Average plasma concentration derived by AUC(0-t) being divided by time t
AI_Cmax	Cmax accumulation index (multiple dosing only)
AI_AUC	AUC accumulation index (multiple dosing only)

Individual participant PK parameter values will be derived by non-compartmental methods by a validated PK analysis program. Actual times will be used for the analyses. See Table 2-3, Table 2-4, and Table 2-5 in Section 2: Schedule of Activities for the PK sampling schedule.

PK data from this study may be combined with PK data from other studies to characterize the PK using population PK and PBPK analysis and to assess exposure-response relationships for efficacy and safety. Results of this analysis will be reported separately (see Section 10.4 Statistical Analyses for additional details).

9.5.1 Pharmacokinetic Sampling Instructions and Collection Windows

Refer to Table 2-3, Table 2-4, and Table 2-5 in Section 2: Schedule of Activities for the PK sampling schedule.

All on-treatment time points are intended to align with days on which study intervention is administered. If it is known that a dose will be delayed, then the pre-dose sample, if appropriate, should be collected just prior to the delayed dose. However, if a pre-dose sample is collected but the dose is subsequently delayed, an additional pre-dose sample should not be collected. For participants receiving cetuximab in Parts 1B and 2B, blood samples should be drawn from a site other than the infusion site (ie, contralateral arm) on days of infusion. If the infusion was interrupted, the interruption details will also be documented on the CRF. Further details of sample collection, processing, and shipment will be provided in the laboratory/procedure manual.

Detailed instructions for PK blood collection, labeling, processing, storage, and shipping will be provided to the site in the laboratory/procedure manual.

9.5.1.1 Pharmacokinetic Sample Collection Windows

It is expected that every effort will be made to collect PK samples at the times indicated in the protocol. The following time windows serve as a guideline for PK sample collections:

- [redacted]

- [redacted]

9.5.2 Pharmacokinetic Sample Analyses

Treatment assignments will be released to the bioanalytical laboratory to minimize unnecessary analysis and/or re-analysis of PK/anti-drug antibody (ADA) study samples.

Concentration analyses for BMS-986466 and adagrasib will be performed by validated bioanalytical method(s).

Bioanalytical samples designated for assessments (eg, immunogenicity, PK, or biomarker) from the same collection time point may be used interchangeably for analyses, if required (including, but not limited to, insufficient volume for complement assessment to follow-up on suspected immunogenicity-related AEs, etc).

Additionally, residual bioanalytical samples will be archived for up to 20 years after the end of the study or the maximum period allowed by applicable law and may be used for potential exploratory bioanalysis (including, but not limited to, analysis of drug-ADA immune complexes, metabolite analyses, etc) and/or for additional method purposes (including, but not limited to, cross-validation, ADA/PK selectivity, cut point, etc).

9.6 Immunogenicity Assessments

No immunogenicity will be assessed in this study. Based on cetuximab USPI,[17] the incidence of anti-cetuximab binding antibodies in 105 participants (from Studies I4E-MC-JXBA, I4E-MC-JXBB, and I4E-MC-JXBD) with at least 1 post-baseline blood sample (≥ 4 weeks post first cetuximab administration) was < 5%. Small molecule drugs such as BMS-986466 and adagrasib are not expected to change the immunogenicity profile of cetuximab.

9.7 Biomarkers

Peripheral blood and tumor tissue samples will be collected in this study at baseline and several on-treatment time points to identify PD markers associated with response and/or resistance to therapy. Additional biomarkers related to mechanism of action of BMS-986466 will be explored. The PD changes between baseline and on-treatment measures will also be monitored and evaluated for associations with PK data and select AEs. Peripheral blood and tumor samples will be collected at the times indicated in Table 2-6 and Table 2-7 for biomarker assessments. If biomarker samples are collected but study intervention is not administered, samples will be retained. Further details of blood and tumor tissue collection and processing will be provided to the site in the laboratory manual.

Other samples may be used for research to develop methods, assays, prognostics, and/or companion diagnostics related to BMS-986466 treatment.

9.7.1 Germline Genetics

For the purpose of normal germline reference comparison for tumor DNA sequencing, blood samples for DNA isolation and sequencing will be collected from all participants unless prohibited by local law/regulation or if not approved by the IRB/IEC. In these cases, the DNA collection may be presented to participants as an optional collection. See Table 2-6 and Table 2-7 in Section 2: Schedule of Activities for the biomarker sampling schedule.

Collection and shipment information for these samples is in the laboratory/procedure manual. The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained for up to 20 years beyond the end of the study, unless prohibited by local law/regulation or IRB/IEC, to understand genetic mechanisms of response and/or the disease/condition under study and related conditions.

9.7.2 Participant Selection Biomarkers

For NSCLC and CRC enrollment: Participants must have a documented KRAS G12C mutation from an NYS-approved, FDA-approved/cleared, or CE-marked test or, when such result is not available, positive KRAS G12C mutation status should be confirmed by a central laboratory (Guardant360 CDx) in liquid biopsy samples collected at the time of screening (for parts 1 DDI, 1A and 1B) and in liquid biopsy and/or tumor samples (only for parts 2A and 2B) collected at the time of the screening or from archival biopsies (less than 1 year old).

For PDAC and BTC enrollment: Participants must have a documented KRAS G12C mutation from an NYS approved, FDA approved/cleared or CE-marked test and liquid biopsy samples collected only for retrospective testing. Participants must have no other activating mutations in BRAF V600X, PTPN11 (SHP2), or KRAS Q61X.

9.7.3 Blood Samples for Exploratory Biomarkers

Whole blood will be collected during dose escalation prior to treatment and at various time points on treatment in order to evaluate PD of pathway modulation. [redacted] The pre-dose sample [redacted] levels are compared to the on-treatment sample [redacted] levels to determine [redacted] in normal blood cells. Both pre-treatment and on-treatment whole blood, plasma, and/or serum sample collections will also be utilized for [redacted] to evaluate various surrogate tumor and/or immune PD effects. Finally, blood samples will be collected at screening and on-treatment time points (see Table 2-6 and Table 2-7) for circulating tumor DNA sequencing in order to follow various DNA mutations (ie), as they relate to clinical response and resistance.

9.7.4 Tumor Samples for Exploratory Biomarkers

Mandatory fresh tumor biopsies will be collected during Part 2 dose expansion (optional for Part 1), at screening and C2D1 (± 7 days), in order to evaluate PD of pathway modulation, immune response, and other changes in tumor cells. See Table 2-6 and Table 2-7 regarding the requirements for mandatory versus optional biopsy collections. A formalin-fixed, paraffin-embedded (FFPE) tissue block of tumor tissue from a core biopsy, punch biopsy, excisional or incisional biopsy, or

surgical specimen obtained during screening or within 3 months before the start of the screening period, with no intervening systemic anti-cancer treatment between time of acquisition and enrollment, must be sent to the central laboratory prior to randomization, except if the biopsy was attempted but was not completed due to safety concerns. Fine needle aspirates or other cytology samples are not acceptable. A repeat biopsy at screening from the same or an alternative site will be required if clinically feasible (at the discretion of the investigator), and the initial attempt was unsuccessful in obtaining adequate tissue for biomarker analysis. Only 1 repeat attempt may be performed at each time point, if clinically feasible. An unsuccessful fresh tumor biopsy at screening will not exclude participants from receiving or continuing the study intervention. Bone lesions are unacceptable sites for biopsy. Tumor biopsy material will be utilized for immunohistochemical analysis as well as DNA and/or RNA sequencing to determine the PD effects of drug on tumor cells and to determine potential resistance biomarkers. Please notify the Medical Monitor if on-treatment biopsy may pose unacceptable clinical risk or if tumor at the time of on-treatment biopsy is not accessible for sampling. Institutional guidelines for the safe performance of biopsies should be followed. The screening and on-treatment biopsies will follow the same guidance methodology for sample collections, processing, and submission provided in the laboratory manual.

Archived tumor specimens in the form of blocks or sectioned slides obtained within 1 year of screening should be submitted prior to study intervention, if available.

Based on the data and upon discussion with the investigator and Sponsor, biopsies may become optional for all parts of the study.

This protocol will involve storage of residual samples including blood and tissue for up to 20 years for additional research.

9.7.5 Other Biomarkers

Not applicable.

9.8 Optional Future Research

This protocol will include both additional sample collection and residual sample storage for optional future research. The following additional samples will be collected from participants for this research as specified in Section 2: Schedule of Activities:

- Blood/tumor for DNA

Samples kept for future research will be stored at the Sponsor-designated storage facility.

The manager of these samples will ensure that they are properly used throughout their usable life and will destroy the samples at the end of the scheduled storage period, no longer than 25 years after the end of the study or the maximum period allowed by applicable law.

Samples will be stored in a coded fashion, and no researcher will have access to the key. The key will be securely held by the investigator at the clinical site, so there is no direct ability for a researcher to connect a sample to a specific individual.

Further details of sample collection and processing will be provided to the site in the laboratory/procedure manual.

9.9 Other Assessments

Not applicable.

9.10 Healthcare Resource Utilization

Health economics/medical resource utilization and health economics parameters will not be evaluated in this study.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

It is expected that the ORR of participants with KRAS G12C mutation randomized to BMS-986466 plus adagrasib will be improved as compared to the ORR in participants receiving adagrasib monotherapy in NSCLC, while the ORR of BMS-986466 plus adagrasib and cetuximab will be improved as compared to the ORR in participants receiving adagrasib with cetuximab in CRC.

10.2 Sample Size Determination

Part 1 (DDI cohort): A minimum of 6 PK-evaluable participants in the DDI cohort.

Part 1A (Dose Escalation): A total of up to approximately 27 DLT-evaluable participants will be enrolled. At least 3 participants will be accrued in each dose.

Part 1B (Dose Escalation): A total of up to approximately 27 DLT-evaluable participants will be enrolled. At least 3 participants will be accrued in each dose.

Part 2A (Dose Expansion): A sample size of approximately 150 response-evaluable participants will be randomized to 3 treatment arms in the ratio of 1:1:1, which allows for 80% power [redacted]

Part 2B (Dose Expansion): A sample size of approximately 200 response-evaluable participants will be randomized to 4 treatment arms in the ratio of 1:1:1:1, which allows for 80% power to [redacted]

10.3 Analysis Sets

For the purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who signed the informed consent form and obtained a participant number.
Treated	All participants who received at least 1 dose of study intervention.
Randomized	All participants who were randomized using IRT.

Population	Description
Response-evaluable	All participants who received at least 1 dose of study intervention, have a baseline tumor assessment with measurable disease, and 1 of the following: 1) At least 1 evaluable on-treatment tumor assessment 2) Clinical progression 3) Death prior to the first on-treatment tumor evaluation
DLT-evaluable	Participants in Part 1A will be considered DLT evaluable if they complete ≥ 75% of all planned doses of BMS-986466 and adagrasib without experiencing a DLT or experience a DLT after receiving at least 1 dose of BMS-986466 and adagrasib. Participants in Part 1B must complete ≥ 75% of all planned doses of BMS-986466 and adagrasib and have received at least 2 doses of cetuximab without experiencing a DLT or experience a DLT after receiving at least 1 dose of BMS-986466, adagrasib, and cetuximab.
PK	All participants who received at least 1 dose of BMS-986466 and/or adagrasib and had any available concentration-time data.
PK-evaluable	Subset of the PK population. All participants in the PK population with adequate PK profiles.
Biomarker	All treated participants with available biomarker data.

Abbreviation: AUC(0-T), area under the concentration-time curve from time zero to time of last quantifiable concentration; Cmax, maximum observed concentration; DDI, drug-drug interaction; DLT, dose-limiting toxicity; IRT, Interactive Response Technology; PK, pharmacokinetic.

10.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

A description of the participant population will be included in the Clinical Study Report, including subgroups of age, gender, race, and other study-specific populations and demographic characteristics.

Unless otherwise specified, all analyses will be performed separately by study part.

10.4.1 General Considerations

The analysis of safety will be based on all treated population. The efficacy analysis (Parts 2A and 2B) will be based on all randomized population. Further details will be provided in the SAP.

10.4.2 Primary Endpoint(s)

The primary endpoint for Part 1 is to assess safety based on incidence of AEs, SAEs, AEs leading to discontinuation, and deaths. In addition, the selected tolerable dose levels of BMS-986466 in combination with adagrasib (Part 1A) and BMS-986466 in combination with adagrasib and cetuximab (Part 1B) will be determined using the DLT rate within the 28-day window among DLT-evaluable participants in Parts 1A and 1B. The incidence of DLTs will be calculated and

compared to the actions recommended by the TITE-BOIN design to guide the dose escalation/stay/de-escalation decision for the BMS-986466 plus adagrasib treatment and for the BMS-986466 plus adagrasib plus cetuximab treatment (refer to Appendix 7).

The primary endpoint for Part 2 is ORR of BMS-986466 plus adagrasib compared to adagrasib control (Part 2A), and ORR of BMS-986466 in combination with adagrasib plus cetuximab compared to adagrasib plus cetuximab control (Part 2B), in the randomized population. Bayesian continuous safety monitoring framework will be utilized to monitor toxicity and detect safety signals affecting conduct of the study. ORR is defined as the proportion of participants who achieve a best response of CR or PR using the RECIST v1.1 criteria.

The primary endpoints and analyses are shown in Table 10.4.2-1.

Table 10.4.2-1: Primary Endpoints

Primary Endpoint	Description of Analysis	Time Frame
Incidence of DLTs, AEs, SAEs, AEs leading to discontinuation, and deaths	DLT rate by dose level, frequency distribution of treated participants with AE using the worst CTCAE v5.0 grade. Participants will only be counted (1) once at the preferred term level; (2) once at the system organ class level; and (3) once in the "total participant" row at their worst CTCAE grade, regardless of system organ class or PT.	• For DLTs, up to 28 days • For AEs, up to approximately 2 years
ORR assessed by BICR is defined as the proportion of participants who achieve a best response of CR or PR using the RECIST v1.1 criteria	The ORR and its corresponding 95% exact CI will be calculated by Clopper-Pearson method for each arm, based on BICR by RECIST v1.1. The ORR difference will also be estimated by 95% CI, and p-value.	Up to approximately 4 years

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; ORR, overall response rate; PR, partial response; PT, preferred term; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event.

Efficacy analysis will be performed with one-sided alpha level of 0.1 to evaluate if the ORR of BMS-986466 plus adagrasib is superior to that of adagrasib (Part 2A), and if the ORR of BMS-986466 plus adagrasib plus cetuximab is superior to that of adagrasib plus cetuximab (Part 2B).

Table 10.4.2-2: Summary of the Attributes of the Main Estimand for the Primary Objective

Estimand Attribute	Definition		
Treatment	• Part 1A: BMS-986466 and adagrasib • Part 1B: BMS-986466, adagrasib and cetuximab		
Population	DLT evaluable		
Variable	DLT		
Intercurrent Events	**Event**	**Strategy**	**Description (or Rationale)**
	Discontinuation from study without DLT prior to end of DLT assessment period	Principal stratum strategy	DLT will only be reported among DLT evaluable participants during the DLT evaluable period
Population-level Summary	Proportion of participants with DLTs per dose level per part		
Treatment	• Part 1A: BMS-986466 and adagrasib • Part 1B: BMS-986466, adagrasib, and cetuximab		
Population	Eligible participants who receive at least 1 dose of study medication		
Variable	Incidence of AEs, SAEs, AEs leading to discontinuation, and death		
Intercurrent Events	**Event**	**Strategy**	**Description (or Rationale)**
	All intercurrent events, eg, discontinuation of treatment	Treatment policy strategy	AEs, SAEs, AEs leading to discontinuation, and death will be reported regardless of the intercurrent events
Population-level Summary	Proportion of participants with events per dose level per part		
Treatment	• Part 2A: BMS-986466 and adagrasib • Part 2B: BMS-986466, adagrasib, and cetuximab		
Population	All randomized participants		
Variable	BOR per RECIST v1.1 by BICR		
Intercurrent Events	**Event**	**Strategy**	**Description (or Rationale)**
	New anticancer therapy prior to any progression	While on treatment policy strategy	BOR will be analyzed before the start of the new anticancer therapy.
	Dropout or death without disease assessment	Composite strategy	Dropout or death without disease assessment will be considered as non-responder
Population-level Summary	Proportion of participants with best overall response of any CR or PR per BICR for ORR (with 2-sided 95% Clopper-Pearson CI)		

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review; BOR, best overall response; CI, confidence interval; CR, complete response; DLT, dose-limiting toxicity; ORR, overall response rate; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event.

10.4.3 Secondary Endpoint(s)

The secondary endpoints (Parts 1 and 2) and statistical analysis methods are described in Table 10.4.3-1.

The effect of each treatment will be estimated based on the additional efficacy endpoints using point estimates and 95% CI. Details of censoring rules for the time-to-event endpoints will be provided in the study SAP.

Table 10.4.3-1: Secondary Endpoints

Secondary Endpoint	Description	Time Frame
BMS-986466 Geometric Mean Ratio of AUC(0-T) and Cmax	To determine the magnitude of drug interaction between BMS-986466 (victim) and adagrasib	Up to approximately 60 days
BMS-986466 PK parameters in plasma: Cmax, Tmax, AUC(0-T), AUC(INF), AUC(TAU), Cavg, Ctrough, AI_Cmax, AI_AUC, as appropriate, from concentration-time data	Summary measures will be tabulated for BMS-986466 PK parameters, if feasible, and wherever applicable, by treatment and dosing regimen. Summary statistics for plasma BMS-986466 Ctrough will also be tabulated by treatment, study day, and time.	Up to approximately 60 days
PFS is defined as the time between the first dose of treatment/randomization and the date of first documented tumor progression, based on BICR (per RECIST v1.1) or death due to any cause, whichever occurs first.	The PFS curve will be estimated using the Kaplan-Meier product-limit method. A 2-sided 95% CI for median PFS in each treatment group will be computed via the log-log transformation method. PFS rates at fixed time points will be presented along with their associated 95% CIs.	Up to approximately 4 years
Incidence of AEs, SAEs, AEs leading to discontinuation, and deaths	Frequency distribution of treated participants with AE using the worst CTCAE v5.0 grade. Participants will only be counted (1) once at the preferred term level; (2) once at the system organ class level; and (3) once in the 'total participant' row at their worst CTCAE grade, regardless of system organ class or PT.	Up to approximately 2 years
DOR assessed by BICR is defined as the time between the date of first documented response (CR or PR) to the date of the first documented progression as determined by RECIST v1.1 criteria or death due to any cause, whichever occurs first.	Median DOR and its corresponding 95% CI will be estimated using Kaplan-Meier method.	Up to approximately 4 years

Table 10.4.3-1: Secondary Endpoints

Secondary Endpoint	Description	Time Frame
DCR is defined as the number of treated/randomized participants who achieve a primary BOR of confirmed CR, confirmed PR, or SD (and/or SD > 6 months), based on BICR assessments (using RECIST v1.1) divided by the number of all treated/randomized participants.	The DCR and its corresponding 95% exact CI will be calculated by Clopper-Pearson method for each arm, based on BICR by RECIST v1.1.	Up to approximately 4 years
TTR assessed by BICR is defined as the time between the first dose of treatment/randomization to the date of the first confirmed documented response (CR or PR) per RECIST v1.1 criteria.	Descriptive statistics and summaries will be presented for TTR.	Up to approximately 4 years
Summary measures of target engagement, such as, but not limited to, pERK.	Descriptive statistics of pERK	• Up to approximately 10 days in the DDI cohort • Up to approximately 30 days in the non-DDI cohort

Abbreviations: AE, adverse event; AI_AUC; area under the plasma concentration-time curve accumulation index; AI_Cmax, Cmax accumulation index; AUC(0-T), area under the concentration-time curve from time zero to time of last quantifiable concentration; AUC(INF), area under the plasma concentration-time curve from time zero extrapolated to the infinite time; AUC(TAU), area under the concentration-time curve within a dosing interval; BICR, Blinded Independent Central Review; BOR, best overall response; CI, confidence interval; Cmax, maximum observed concentration; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; Ctrough, trough observed plasma or serum concentration; DCR, disease control rate; DOR, duration of response; pERK, phosphorylation of extracellular signal-regulated kinase; PFS, progression-free survival; PK, pharmacokinetic; PR, partial response; PT, preferred term; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; SD, stable disease; Tmax, time of maximum observed plasma concentration; TTR, time to response.

Table 10.4.3-2: Summary of the Attributes of the Main Estimand for the Key Secondary Objective

Estimand Attribute	Definition		
Treatment	• DDI cohort • Part 1A: BMS-986466 and adagrasib • Part 1B: BMS-986466, adagrasib, and cetuximab		
Population	Eligible participants who received at least 1 dose of BMS-986466 and/or adagrasib and had any available concentration-time data and have adequate PK profiles or have at least 1 evaluable PK parameter.		
Variable	BMS-986466 PK parameters		
Intercurrent Events	**Event**	**Strategy**	**Description (or Rationale)**
	All intercurrent events, eg, discontinuation of treatment	Treatment policy strategy	The PK results will be reported regardless of the intercurrent events
Population-level Summary	Summary measures will be tabulated for BMS-986466 PK parameters, if feasible, and wherever applicable, by treatment and dosing regimen. Summary statistics for plasma BMS-986466 Ctrough will also be tabulated by treatment, study day, and time. For the DDI cohort, geometric mean and geometric mean ratio will be reported.		
Treatment	• Part 2A: BMS-986466 and adagrasib • Part 2B: BMS-986466, adagrasib, and cetuximab		
Population	All randomized participants		
Variable	PFS per RECIST v1.1 by BICR		
Intercurrent Events	**Event**	**Strategy**	**Description (or Rationale)**
	New anticancer therapy prior to any progression	Treatment strategy	The endpoints will be analyzed regardless of the start of the new anticancer therapy
Population-level Summary	• Kaplan-Meier estimated HR, median survival time and landmark survival rate of PFS		
Treatment	• Part 2A: BMS-986466 and adagrasib • Part 2B: BMS-986466, adagrasib and cetuximab		
Population	Eligible participants who receive at least 1 dose of study intervention		
Variable	Incidence of AEs, SAEs, AEs leading to discontinuation, and death		
Intercurrent Events	**Event**	**Strategy**	**Description (or Rationale)**
	All intercurrent events, eg, discontinuation of treatment	Treatment policy strategy	AEs, SAEs, AE leading to discontinuation, and death will be reported regardless of the intercurrent events

Table 10.4.3-2: Summary of the Attributes of the Main Estimand for the Key Secondary Objective

Estimand Attribute	Definition
Population-level Summary	Proportion of participants with events per dose level per part

Abbreviations: AE, adverse event; BICR, Blinded Independent Central Review; DDI, drug-drug interaction; HR, hazard ratio; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event.

10.4.4 Exploratory Endpoint(s)

Exploratory PK, biomarker, and efficacy analyses will be described in the SAP, finalized before final database lock. Unless specified otherwise, all safety analyses will be performed on all treated participants.

10.4.5 Other Safety Analyses

10.4.5.1 Continuous Safety Monitoring

A Bayesian continuous monitoring framework will be utilized in the randomized part of the study to monitor for toxicity and detect safety signals that may lead to changes in study conduct. Incidence rates of TRAEs of Grade 3 and above as assessed by the investigator during treatment and safety follow up period will be evaluated in reference to [redacted] of Grade 3 and above, which is close to the incidence rate observed in adagrasib and cetuximab studies.[10]

For safety data for each arm in Part 2A and Part 2B, the Bayesian safety monitoring boundaries are established using a noninformative prior, Beta (0.5, 0.5). The posterior distribution is Beta(0.5+n, 0.5+[m-n]), where n and m are the number of TRAEs observed out of the total number of evaluable participants. [redacted] This criterion is not binding; If anytime during the treatment and safety follow-up period, it reaches the pre-specified threshold of toxicity, then, taking into account all available safety information, additional evaluation will be conducted to allow a complete by treatment arm safety assessment and risk benefit evaluation. [redacted]

[redacted]

10.4.6 Other Analyses

PBPK modeling will be performed by integrating in vitro DDI information for BMS-986466 and adagrasib and PK data obtained from DDI cohorts. PBPK modeling will serve as supportive evidence informing dose selection for dose escalation cohorts.

The BMS-986466 concentration data obtained in this study may be combined with data from other studies in the clinical development program to develop a population PK model. The population PK model will be used to evaluate the impact of intrinsic and extrinsic covariates on the PK of BMS-986466. In addition, exposure-response analyses with selected efficacy and safety endpoints may be conducted. Population PK modeling and simulation and exposure response analysis will be used to support dose selection and optimization. Results of population PK and exposure-response analyses may be reported separately.

10.5 Interim Analyses

In both Parts 2A and 2B, interim analyses (including integrated PK/PD, dose-response, and exposure-response analysis) will be conducted after approximately the first 60 and 80 response-evaluable participants, respectively, to support dose selection for expansion in each indication. The data from interim analysis may be reviewed by the study team, SRC, and SMT to plan for further development of the BMS-986466 program. Based on post-interim analysis of the data, including safety, PK, PD, and efficacy, the Sponsor may stop enrollment in any cohort. Enrollment may continue during the interim analysis. Additional details of the interim analyses will be provided in the SAP.

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12 APPENDICES

APPENDIX 1 ABBREVIATIONS

Term	Definition
2L	second-line therapy
2L+	second-line therapy or later
ADA	anti-drug antibody
AE	adverse event
AI_AUC	area under the plasma concentration-time curve accumulation index
AI_Cmax	Cmax accumulation index
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransaminase
AST	aspartate transaminase
AUC	area under the concentration vs time curve
AUC(0-T)	area under the concentration-time curve from time zero to time of last quantifiable concentration
AUC(INF)	area under the plasma concentration-time curve from time zero extrapolated to the infinite time
AUC(TAU)	area under the concentration-time curve within a dosing interval
AUCss	area under the concentration-time curve at steady-state
AxMP	auxiliary medicinal product
BCRP	breast cancer resistance protein
BICR	Blinded Independent Central Review
BID	twice daily dose
BMI	body mass index
BMS	Bristol-Myers Squibb Company
BNP	b-type natriuretic protein
BOR	best overall response
BRAF	proto-oncogene B-Raf
BTC	biliary tract cancer
C	cycle
Cavg	average concentration
CE	conformité européenne
CI	confidence interval
Cmax	maximum (or peak) concentration

Term	Definition
Cmin	minimum observed concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRC	colorectal carcinoma
CRF	Case Report Form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria Adverse Events
ctDNA	circulating tumor deoxyribonucleic acid
Ctrough	trough observed plasma or serum concentration
CYP	cytochrome P450
D	day
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DL	dose level
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EGFR	epidermal growth factor receptor (her-1)
EOI	end of infusion
EOT	end of treatment
ERK	extracellular signal-regulated kinase
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FDA	Food and Drug Administration
FFPE	formalin-fixed, paraffin-embedded

Term	Definition
FIH	first-in-human
FSH	follicle-stimulating hormone
FU	follow-up
[redacted]	[redacted]
GTP	glutamyl transferase
GTPase	guanosine triphosphatase
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCG	human chorionic gonadotropin
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
IAC	ileocecal/ascending colon
IB	Investigator's Brochure
ICF	informed consent
IDH1	isocitrate dehydrogenase 1
IEC	Independent Ethics Committee
IHC	immunohistochemistry
ILD	interstitial lung disease
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IU	international unit
IV	intravenous(ly)
KRAS	Kirsten rat sarcoma viral oncogene
LDH	lactate dehydrogenase
log	logarithm
LVEF	left ventricular ejection fraction
MAD	maximum administered dose
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion
MATE1	multidrug and toxin extrusion protein 1

Term	Definition
MET	mesenchymal to epithelial transition
MMR	mismatch repair
mPFS	median progression-free survival
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
MUGA	multigated acquisition
N/n	number of participants
NA	not applicable
NSCLC	non-small cell lung cancer
NTRK	neurotrophic tyrosine receptor kinase
NYS	New York State
[redacted]	[redacted]
ORR	objective response rate
OS	overall survival
PDAC	pancreatic duct adenocarcinoma
pERK	phosphorylation of extracellular signal-related kinase
p-DILI	potential drug-induced liver injury
P-gp	p-glycoprotein
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based pharmacokinetics
PD	pharmacodynamics
PD-1	programmed cell death protein 1
PD-L1	programmed death–ligand 1
PE	physical examination
pERK	phosphorylation of extracellular signal-regulated kinase
PET	positron emission tomography
PFS	progression-free survival
PID	patient identification number
PK	pharmacokinetic
PPI	proton pump inhibitor
PR	partial response
PS	performance status

Term	Definition
PT	preferred term
PTPN11	protein tyrosine phosphatase non-receptor type 1
Q3M	every 3 months
QD	once daily
QT	Q and T waves
QT interval	time between the start of the Q wave and the end of the T wave
QTc	QT interval corrected for heath rate
QTcF	QT interval corrected using Fridericia's method
QXW	every X week(s)
R	randomization
R/R	relapsed and refractory
RECIST	Response Evaluation Criteria in Solid Tumors
RET	rearranged during transfection
RNA	ribonucleic acid
ROS1	ROS proto-oncogene 1
RTK	receptor tyrosine kinase
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SHP2	Src homology-2 phosphatase
SmPC	summary of product characteristics
SMT	Safety Management Team
SRC	Scientific Review Committee
STK11	serine/threonine kinase 11
SUSAR	suspected unexpected serious adverse reaction
T3	triiodothyronine
T4	thyroxine
TBD	to be determined
TEAE	treatment-emergent adverse event
TITE-BOIN	time-to-event Bayesian optimal interval

Term	Definition
TITE-CRM	time-to-event continual reassessment method
Tmax	time at which maximum concentration (cmax) occurs
TMB	tumor mutational burden
TPS	tumor proportion score
TRAE	treatment-related adverse event
TSH	thyroid-stimulating hormone
TTR	time to response
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information
VEGF	vascular endothelial growth factor
Vss	volume of distribution at steady state
WOCBP	women of childbearing potential
WWPS	Worldwide Patient Safety

APPENDIX 2 STUDY GOVERNANCE CONSIDERATIONS

REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines
- Applicable laws, regulations, and requirements

The study will be conducted in compliance with the protocol. The protocol, any revisions/amendments, and the participant informed consent form (ICF) will receive approval/favorable opinion by the Institutional Review Board/Independent Ethics Committee (IRB/IEC), and regulatory authorities according to applicable regulations prior to initiation of the study.

All potential serious breaches must be reported to the Sponsor or designee immediately. A potential serious breach is defined as a quality issue (eg, protocol deviation) that is likely to affect, to a significant degree, 1 or more of the following: (1) the rights, physical safety, or mental integrity of 1 or more participants; (2) the scientific value of the clinical trial (eg, reliability and robustness of generated data). Items (1) or (2) can be associated with either GCP regulation(s) or trial protocol(s).

Personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective tasks.

This study will not use the services of study personnel where sanctions have been invoked or where there has been scientific misconduct or fraud (eg, loss of medical licensure, debarment).

INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Before study initiation, the investigator must have written and dated approval/favorable opinion from the IRB/IEC for the protocol, Investigator's Brochure, product labeling information, ICF, participant recruitment materials (eg, advertisements), and any other written information to be provided to participants.

The investigator, Sponsor, or designee should provide the IRB/IEC with reports, updates, and other information (eg, expedited safety reports, amendments, administrative letters) annually, or more frequently, in accordance with regulatory requirements or institution procedures.

The investigator is responsible for providing oversight of the conduct of the study at the site and adherence to requirements of the following where applicable:

- ICH guidelines
- United States (US) Code of Federal Regulations, Title 21, Part 50 (21CFR50)

- European Union (EU) Directive 2001/20/EC
- European Regulation 536/2014 for clinical studies (if applicable)
- European Medical Device Regulation 2017/745 for clinical device research (if applicable)
- the IRB/IEC
- all other applicable local regulations

COMPLIANCE WITH THE PROTOCOL AND PROTOCOL REVISIONS

The investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion of an amendment from the IRB/IEC (and, if applicable, by the local Health Authority), except where necessary to eliminate an immediate hazard(s) to study participants.

If a deviation or change to a protocol is implemented to eliminate an immediate hazard(s) prior to obtaining relevant approval/favorable opinion(s), the deviation or change will be submitted as soon as possible to the following:

- IRB/IEC
- Regulatory authority(ies), if applicable according to local regulations (per national requirements)

Documentation of approval/favorable opinion signed by the chairperson or designee of the IRB(s)/IEC(s) and, if applicable, by the local Health Authority must be sent to Bristol-Myers Squibb Company (BMS).

If an amendment substantially alters the study design or increases the potential risk to the participant: (1) the ICF must be revised and submitted to the IRB(s)/IEC(s) for review and approval/favorable opinion; (2) the revised form must be used to obtain consent from participants currently enrolled in the study if they are affected by the amendment; and (3) the new form must be used to obtain consent from new participants prior to enrollment.

FINANCIAL DISCLOSURE

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information, in accordance with regulations, to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

INFORMED CONSENT PROCESS

Investigators must ensure that participants are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate.

The Sponsor or designee will provide the investigator with an appropriate sample ICF, which will include all elements required by the ICH GCP, and applicable regulatory requirements. The sample ICF will adhere to the ethical principles that have their origin in the Declaration of Helsinki.

The investigator or his/her representative must:

- Obtain IRB/IEC written approval/favorable opinion of the written ICF and any other information to be provided to the participant prior to the beginning of the study and after any revisions are completed for new information.
- Provide a copy of the ICF and written information about the study in the language in which the participant is proficient prior to clinical study participation. The language must be nontechnical and easily understood.
- Explain the nature of the study to the participant and answer all questions regarding the study.
- Inform the participant that his/her participation is voluntary. The participant will be required to sign a statement of informed consent that meets the requirements of 21 CFR Part 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- Allow time necessary for the participant to inquire about the details of the study.
- Obtain an ICF signed and personally dated by the participant and by the person who conducted the informed consent discussion.
- Include a statement in the participant's medical record that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Re-consent the participant to the most current version of the ICF(s) during his/her participation.
- Revise the ICF whenever important new information becomes available that is relevant to the participant's consent. The investigator, or a person designated by the investigator, should fully inform the participant of all pertinent aspects of the study and of any new information relevant to the participant's willingness to continue participation in the study. This communication should be documented.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules applicable to regulatory requirements, the participant's signed ICF, and, in the US, the participant's signed HIPAA authorization.

The ICF must also include a statement that BMS and local and foreign regulatory authorities have direct access to participant records.

The rights, safety, and well-being of the study participants are the most important considerations and should prevail over interests of science and society.

BMS COMMITMENT TO DIVERSITY IN CLINICAL TRIALS

The mission of BMS is to transform patients' lives through science by discovering, developing, and delivering innovative medicines that help them prevail over serious diseases.

BMS is committed to doing its part to ensure that patients have a fair and just opportunity to achieve optimal health outcomes.

BMS is working to improve the recruitment of a diverse participant population with the goal that the clinical trial becomes more reflective of the real-world population and the people impacted by the diseases studied.

RECRUITMENT STRATEGY

A patient engagement and recruitment program will be developed and implemented to assist sites with patient recruitment efforts. Tactics will support patient education and awareness, and HCP outreach. This program will also include solutions to address anticipated recruitment challenges.

DATA PROTECTION, DATA PRIVACY, AND DATA SECURITY

BMS collects and processes personal data of study participants, patients, health care providers, and researchers for biopharmaceutical research and development to advance innovative, high-quality medicines that address the medical needs of patients. BMS ensures the privacy, protection, and confidentiality of such personal data to comply with applicable laws. To achieve these goals, BMS has internal policies that indicate measures and controls for processing personal data. BMS adheres to these standards to ensure that collection and processing of personal data are limited and proportionate to the purpose for which BMS collects such personal data. This purpose is clearly and unambiguously notified to the individual at the time of collection of personal data. In the true spirit of science, BMS is dedicated to sharing clinical trial information and data with participants, medical/research communities, the media, policy makers, and the general public. This is done in a manner that safeguards participant privacy and informed consent while respecting the integrity of national regulatory systems. Clinical trial data, health-related research, and pharmacovigilance activities on key-coded health data transferred by BMS across national borders is done in compliance with the relevant data protection laws in the country and GCP requirements.

BMS protects Personal Information with adequate and appropriate security controls as indicated under the data protection laws. To align with the recommended security standards, BMS has adopted internal security standards and policies to protect personal data at every stage of its processing.

To supplement these standards, BMS enters into Clinical Trial Agreements (CTAgs) with confidentiality obligations to ensure proper handling and protection of personal data by third parties accessing and handling personal data.

BMS takes unauthorized access and disclosure of Personal Information very seriously. BMS has adopted the security standards that include National Institute of Standards and Technology Cybersecurity Framework for studies in the US. BMS aligns with these standards to continuously assess and improve its ability to protect, detect, and respond to cyberattacks and other unauthorized attempts to access personal data. These standards also aid in mitigating possible adverse effects. Furthermore, BMS Information Technology has defined 6 principles to protect our digital resources and information:

1) Responsibilities of IT Personnel

2) Securing the BMS Digital Infrastructure
3) Identity and Access Management
4) External Partner Connections
5) Cyber Threat Detection and Response
6) Internal Cyber Incident Investigation

SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

- The investigator may need to request previous medical records or transfer records depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in the source data location list/map or equivalent document.

The investigator is responsible for ensuring that the source data are accurate, legible, contemporaneous, original, and attributable, whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved, or transmitted electronically via computerized systems (and/or any other kind of electronic devices) as part of regulated clinical trial activities, such systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical records/electronic health records, adverse event (AE) tracking/reporting, protocol-required assessments, and/or drug accountability records.

When paper records from such systems are used in place of an electronic format to perform regulated activities, such paper records should be certified copies. A certified copy consists of a copy of original information that has been verified, as indicated by a dated signature, as an exact copy having all of the same attributes and information as the original.

STUDY INTERVENTION RECORDS

Records for study intervention (whether supplied by BMS, its vendors, or the site) must substantiate study intervention integrity and traceability from receipt, preparation, administration, and through destruction or return. Records must be made available for review at the request of BMS/designee or a Health Authority.

If	Then
Supplied by BMS (or its vendors)	Records or logs must comply with applicable regulations and guidelines and should include the following: • amount received and placed in storage area • amount currently in storage area • label identification number or batch number • amount dispensed to and returned by each participant, including unique participant identifiers • amount transferred to another area/site for dispensing or storage • non-study disposition (eg, lost, wasted) • amount destroyed at study site, if applicable • amount returned to BMS • retain samples for bioavailability/bioequivalence/biocomparability, if applicable • dates and initials of person responsible for Investigational Product dispensing/accountability per the Delegation of Authority Form
Sourced by site and not supplied by BMS or its vendors (examples include Investigational Product sourced from the site's stock or commercial supply or a specialty pharmacy)	The investigator or designee accepts responsibility for documenting traceability and study intervention integrity in accordance with requirements applicable under law and the standard operating procedures/standards of the sourcing pharmacy

BMS or its designee will provide forms to facilitate inventory control if the investigational site does not have an established system that meets these requirements.

CASE REPORT FORMS

The terms "participant" and "subject" refer to a person who has consented to participate in the clinical research study. Typically, the term "participant" is used in the protocol and the term "subject" is used in the Case Report Form (CRF).

An investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated or entered as a control in the investigation. Data that are derived from source documents and reported on the CRF must be consistent with the source documents, or the discrepancies must be explained. Additional clinical information may be collected and analyzed in an effort to enhance understanding of product safety. CRFs may be requested for AEs and/or laboratory test result abnormalities that are reported or identified during the study.

For sites using the Sponsor or designee electronic data capture (EDC) tool, eCRFs will be prepared for all data collection fields except for fields specific to serious adverse events (SAEs) and pregnancy, which will be reported on the electronic SAE form and Pregnancy Surveillance Form, respectively. If the electronic SAE form is not available, a paper SAE form can be used.

The confidentiality of records that could identify participants must be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

The investigator will maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on CRFs.

The completed CRF and SAE/pregnancy CRFs must be promptly reviewed, signed, and dated by the investigator or qualified physician who is a sub-investigator and who is delegated this task on the Delegation of Authority Form. Sub-investigators in Japan may not be delegated the CRF approval task. The investigator must retain a copy of the CRFs, including records of the changes and corrections.

Each individual electronically signing eCRFs must meet Sponsor or designee training requirements and must only access the BMS EDC tool using the unique user account provided by the Sponsor or designee. User accounts are not to be shared or reassigned to other individuals.

MONITORING

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

Representatives of BMS must be allowed to visit all study site locations periodically to assess the data quality and study integrity. On site, they will review study records and directly compare them with source documents, discuss the conduct of the study with the investigator, and verify that the facilities remain acceptable.

Certain CRF pages and/or electronic files may serve as source documents.

In addition, the study may be evaluated by the Sponsor or designee internal auditors and government inspectors who must be allowed access to CRFs, source documents, other study files, and study facilities. BMS audit reports will be kept confidential.

The investigator must notify BMS promptly of any inspections scheduled by regulatory authorities and promptly forward copies of inspection reports to the Sponsor or designee.

RECORDS RETENTION

The investigator (or head of the study site in Japan) must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, or institution procedures, or for the period specified by BMS or its designee, whichever is longer. The investigator (or head of the study site in Japan) must contact BMS prior to destroying any records associated with the study.

BMS or its designee will notify the investigator (or head of the study site in Japan) when the study records are no longer needed.

If the investigator withdraws from the study (eg, relocation, retirement), the records shall be transferred to a mutually agreed-upon designee (eg, another investigator, study site, IRB). Notice of such transfer will be given in writing to BMS or its designee.

Records collected throughout the study will be stored in the BMS clinical data management system for a duration of the life of the product plus 25 years.

RETURN OF STUDY INTERVENTION

For this study, study interventions (those supplied by BMS or a vendor or sourced by the investigator), such as partially used study intervention containers, vials, and syringes, may be destroyed on site.

If	Then
Study interventions supplied by BMS (including its vendors)	Any unused study interventions supplied by BMS can only be destroyed after being inspected and reconciled by the responsible Study Monitor, unless study intervention containers must be immediately destroyed as required for safety or to meet local regulations (eg, cytotoxic or biologic agents). Partially used study interventions and/or empty containers may be destroyed after proper reconciliation and documentation. However, unused Investigational Medicinal Product must be reconciled by the site monitor/clinical research associate prior to destruction. If study interventions will be returned, the return will be arranged by the responsible study monitor.
Study interventions sourced by site, not supplied by BMS (or its vendors; eg, study interventions sourced from the site's stock or commercial supply or a specialty pharmacy)	It is the investigator's or designee's responsibility to dispose of all containers according to the institutional guidelines and procedures.

It is the investigator's or designee's responsibility to arrange for disposal of study interventions, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. The following minimal standards must be met:

- On-site disposal practices must not expose humans to risks from the drug.

- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal (eg, incinerator, licensed sanitary landfill, or licensed waste-disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Study Monitor to review throughout the clinical trial period.

It is the investigator's or designee's responsibility to arrange for disposal of all empty containers.

If conditions for destruction cannot be met, the responsible Study Monitor will make arrangements for return of study interventions provided by BMS (or its vendors). Destruction of non-study interventions sourced by the site, not supplied by BMS, is solely the responsibility of the investigator or designee.

STUDY AND SITE CLOSURE

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

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

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable

regulatory requirements. The investigator shall promptly inform the participant and should ensure appropriate participant therapy and/or follow-up.

DISSEMINATION OF CLINICAL STUDY DATA

To benefit potential study participants, patients, health care providers, and researchers and to help BMS honor its commitments to study participants, BMS will make information about clinical research studies and a summary of their results available to the public per regulatory and BMS requirements. BMS will post study information on local, national, or regional databases in compliance with national and international standards for disclosure. BMS may also voluntarily disclose information to applicable databases.

In the European Union (EU), the summary of results and summary for laypersons will be submitted within 1 year of the end of trial in the EU/European Economic Area and third countries.

CLINICAL STUDY REPORT

A Signatory Investigator must be selected to sign the Clinical Study Report (CSR).

For each CSR related to this protocol, the following criteria will be used to select the Signatory Investigator:

- External Principal Investigator designated at protocol development
- National Coordinating Investigator
- Study Steering Committee chair or designee
- Participant recruitment (eg, among the top quartile of enrollers)
- Involvement in trial design
- Regional representation (eg, among top quartile of enrollers from a specified region or country)

SCIENTIFIC PUBLICATIONS

The data collected during this study are confidential and proprietary to the Sponsor or designee. Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the Clinical Trial Agreement (CTAg) governing [study site or investigator] participation in the study. These requirements include, but are not limited to, submitting proposed publications to the Sponsor or designee at the earliest practicable time prior to submission or presentation and otherwise within the period set forth in the CTAg.

Scientific publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any Principal Investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at the Sponsor is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE; www.icmje.org). Authorship selection is based on

significant contributions to the study (ie, ICMJE criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (ie, evaluable participants with quality data), analysis, or interpretation of data for the work (eg, problem solving, advice, evaluation, insights, and conclusion)
2) Drafting the work or revising it critically for important intellectual content
3) Final approval of the version to be published
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Those who make the most significant contributions, as defined above, will be considered by the Sponsor for authorship of the primary publication. Sub-investigators will generally not be considered for authorship in the primary publication. Geographic representation will also be considered.

Authors will be listed by order of significant contributions (highest to lowest), with the exception of the last author. Authors in first and last position have provided the most significant contributions to the work.

For secondary analyses and related publications, author list and author order may vary from primary to reflect additional contributions.

APPENDIX 3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

ADVERSE EVENTS

Adverse Event Definition:

An adverse event (AE) is defined as any new untoward medical occurrence or worsening of a pre-existing medical condition occurring in a clinical investigation participant after signing of informed consent, whether or not considered related to the study intervention.

An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory test result), symptom, or disease temporally associated with the study intervention.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or results from other safety assessments (eg, electrocardiograms, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Note that abnormal laboratory test results or other safety assessment findings should only be reported as AEs if the final diagnosis is not available. Once the final diagnosis is known, the reported term should be updated to be the diagnosis.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration, even though the condition may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, as a verbatim term (as reported by the investigator), should not be reported as an AE/serious adverse event (SAE) unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae and should specify "intentional overdose" as the verbatim term.

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).

DEFINITION OF SAE

If an event is not an AE per the definition above, then it cannot be an SAE, even if serious conditions are met.

SERIOUS ADVERSE EVENTS

A serious adverse event (SAE) is defined as any untoward medical occurrence that, at any dose:
Results in death.
Is life threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
Requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below). NOTE: The following hospitalizations are not considered SAEs in BMS clinical studies: • A visit to the emergency department or other hospital department < 24 hours that does not result in admission (unless considered an important medical or life-threatening event). • Elective surgery that was planned prior to signing consent. • Admissions per protocol for a planned medical/surgical procedure. • Routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy). • Medical/surgical admission other than to remedy ill health and planned prior to enrollment in the study. Appropriate documentation is required in these cases. • Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason). • Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols).
Results in persistent or significant disability/incapacity.
Is a congenital anomaly/birth defect.
Is an important medical event (defined as a medical event[s] that may not be immediately life threatening or results in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the participant or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above). Examples of such events include, but are not limited to, intensive treatment in an emergency department or at home for allergic bronchospasm and blood dyscrasias or convulsions that do not result in hospitalization. Potential drug-induced liver injury (DILI) is also considered an important medical event. (See Section 9.2.7: Potential Drug-induced Liver Injury of the protocol for the definition of a potential DILI.)

Pregnancy and DILI must follow the same transmission timing and processes to BMS as those used for SAEs. (See Section 9.2.5: Pregnancy of the protocol for reporting pregnancies.)

EVALUATING AES AND SAES

Assessment of Causality

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

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study using National Cancer Institute Common Terminology Criteria for Adverse Events v 5.0 (NCI CTCAE v 5.0).

Follow-up of AEs and SAEs

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports must include the same investigator term[s] initially reported.)

If an ongoing SAE changes in its intensity or relationship to study intervention or if new information becomes available, the SAE report must be updated and submitted within 24 hours to BMS (or the designee) using the same procedure used for transmitting the initial SAE report.

All AEs/SAEs must be followed to resolution or stabilization.

REPORTING OF SAES TO SPONSOR OR DESIGNEE

- SAEs, whether related or not related to study intervention, and pregnancies must be reported to BMS (or the designee) promptly and not to exceed 24 hours of awareness of the event.
- SAEs must be recorded on the SAE Report Form.

The required method for SAE data reporting is through the electronic Case Report Form (eCRF).

- The paper SAE Report Form is intended only as a back-up option when the electronic data capture system is unavailable/not functioning for transmission of the eCRF to BMS (or the designee).
  - In this case, the paper form is transmitted via email or confirmed fax transmission.
  - When paper forms are used, the original paper forms are to remain on site.
- Pregnancies must be recorded on paper Pregnancy Surveillance Forms and transmitted via email or confirmed fax transmission.

SAE Email Address: [redacted]

SAE Fax Number: *Will be provided by local site monitor.*

SAE Telephone Contact (required for SAE and pregnancy reporting): *Will be provided by local site monitor.*

APPENDIX 4 WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION

Appendix 4 provides general information and definitions related to Women of Childbearing Potential (WOCBP) and methods of contraception that can be applied to most clinical trials. For information specific to this study regarding acceptable contraception requirements for female and male participants, refer to Section 6.1: Inclusion Criteria of the protocol. Only the contraceptive methods described in Section 6.1: Inclusion Criteria of the protocol are acceptable for this study.

DEFINITIONS

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Pre-menopausal female with 1 of the following:
  - Hysterectomy
  - Bilateral salpingectomy
  - Bilateral oophorectomy
- Post-menopausal female
  - A post-menopausal state is defined as 12 months of amenorrhea in a woman over the age of 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle-stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

Note: Females treated with hormone replacement therapy (HRT) are likely to have artificially suppressed FSH levels and may require a washout period to obtain a physiologic FSH level. The duration of the washout period is a function of the type of HRT used. Suggested guidelines for the duration of the washout periods for HRT types are presented below. Investigators should use their judgment in checking serum FSH levels.

- 1-week minimum for vaginal hormonal products (rings, creams, gels)
- 4-week minimum for transdermal products
- 8-week minimum for oral products

Other parenteral products may require washout periods as long as 6 months. If the serum FSH level is > 40 mIU/mL at any time during the washout period, the woman can be considered postmenopausal.

End of Relevant Systemic Exposure

End of relevant systemic exposure is the time point at which the study intervention (Investigational Medicinal Product [IP/IMP] and other study interventions ie, Non-IMP/AxMP required for study) or any active major metabolites have decreased to a concentration that is no longer considered relevant for human teratogenicity or fetotoxicity. This should be evaluated in context of safety margins from the no-observed-adverse-effect level or the time required for 5 half-lives of the study intervention to pass.

METHODS OF CONTRACEPTION

Local laws and regulations may require use of alternative and/or additional contraceptive methods.

The use of hormonal contraception is prohibited in the protocol by female participants because of a possible drug-drug interaction which could increase the concentration of hormones in the body and expose these female participants to additional risk.

Highly Effective Contraceptive Methods That Are <u>User Dependent</u> *Failure rate of < 1% per year when used consistently and correctly.*[a]
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – Oral (birth control pills) – Intravaginal (rings) – Transdermal • Combined (estrogen- and progestogen-containing) hormonal contraception must begin at least 30 days prior to initiation of study therapy.
• Progestogen-only hormonal contraception associated with inhibition of ovulation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] – Oral – Injectable • Progestogen-only hormonal contraception must begin at least 30 days prior to initiation of study therapy.
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation and/or implantation. (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b] • Intrauterine device.

- Intrauterine system (IUS). (This method of contraception can only be used by WOCBP participants in studies in which hormonal contraception is permitted by the study protocol.)[b,c]
- Bilateral tubal occlusion.

- Vasectomized partner.

Having a vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

A vasectomy is a highly effective contraception method provided that the participant 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.

Male participants will be required to always use a latex or other synthetic condom during any sexual activity (eg, vaginal, anal, oral) with WOCBP, even if the participants have undergone a successful vasectomy or if their partner is pregnant or breastfeeding.

- 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.

- Continuous abstinence must begin at least 30 days prior to initiation of study therapy.
- It is not necessary to use any other method of contraception when complete abstinence is elected.
- WOCBP participants who choose complete abstinence must continue to have pregnancy tests, as specified in Section 2 of the protocol.
- Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP participant chooses to forego complete abstinence.
- Periodic abstinence (including, but not limited to, calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactation amenorrhea method (LAM) are not acceptable methods of contraception for this study.

NOTES:

[a] Typical use failure rates may differ from failure rates when contraceptive methods are used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.

[b] Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the Investigational Medicinal Product and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments of the protocol.

[c] IUSs are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness. For information specific to this study regarding permissibility of hormonal contraception, refer to Section 6.1: Inclusion Criteria and Section 7.7.1: Prohibited and/or Restricted Treatments of the protocol.

Less Than Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of > 1% per year when used consistently and correctly.*
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously. • Diaphragm with spermicide. • Cervical cap with spermicide. • Vaginal sponge with spermicide. • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action. (This method of contraception cannot be used by WOCBP participants in studies in which hormonal contraception is prohibited.)
Unacceptable Methods of Contraception
• Periodic abstinence (calendar, symptothermal, post-ovulation methods). • Withdrawal (coitus interruptus). • Spermicide only. • LAM.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of pregnancy information and outcome of pregnancy on the Pregnancy Surveillance Form is provided in Section 9.2.5: Pregnancy of the protocol and Appendix 3.

APPENDIX 5 ECOG PERFORMANCE STATUS

Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;Dec;5(6):649-55. PMID: 7165009.

APPENDIX 6 RESPONSE EVALUATION CRITERIA IN SOLID TUMORS GUIDELINES (VERSION 1.1) WITH BMS MODIFICATIONS

1 EVALUATION OF LESIONS

Solid tumors will be evaluated using Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) guideline with BMS modifications.[1]

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT/MRI scan (scan slice thickness no greater than 5 mm), or ≥2x slice thickness if greater than 5mm.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT/MRI scan (scan slice thickness recommended to be no greater than 5 mm).

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT/MRI scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.2 Non-Measurable

All other lesions are considered non-measurable, including small lesions (longest diameter < 10mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Note: Lesions on X-Ray are not to be selected as Target or Non-Target Lesions.

1.3 SPECIAL considerations REGARDING LESION MEASURABILITY

1.3.1 Bone lesions

- Bone scan, PET scan and plain films are ***not*** considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components*, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

1.4 Baseline Documentation Of 'Target' And 'Non-Target' Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Note: A maximum of two lesions can be selected per organ system. For example, a maximum of two lung lesions can be selected (selected from one lung or one lesion from each). A maximum of two lymph nodes can be selected at baseline, as the lymphatic system is considered one organ.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2 RESPONSE CRITERIA

2.1 Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.
- **Not Evaluable (NE):** If one or more target lesions cannot be measured or adequately assessed as either fully resolved or too small to measure (due to missing or poor quality images), and the sum of diameters of the remaining measured target lesions (if any) has not increased sufficiently to meet Progressive Disease as defined above.

2.1.1 Special Notes on the Assessment of Target Lesions

2.1.1.1 Lymph nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

2.1.1.2 Target lesions that become 'too small to measure'

While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned as the reference diameter. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This

default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

2.1.1.3 Lesions that split or coalesce on treatment

When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.2 Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s)
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions.

2.2.1 Special Notes on Assessment of Progression of Non-Target Disease

The concept of progression of non-target disease requires additional explanation as follows:

2.2.1.1 When the patient also has measurable disease

In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. Pleural effusions, pericardial effusions and ascites will not be followed as target or non-target lesions and will not contribute to response or progression. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

2.2.1.2 When the patient has only non-measurable disease

This circumstance arises in some trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition:

if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: ie, an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include, an increase in lymphangitic disease from localized to widespread, or may be described as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be substantial.

2.2.2 New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: ie, not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

NOTE: Fluid collections (pleural effusions, pericardial effusions, and ascites) will not be considered new lesions and will not contribute to response or progression. In the event a new fluid collection is seen on a post-baseline imaging exam, a comment may be made, but the appearance of a new fluid collection alone should not result in an assessment of Progressive Disease (PD). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. A lesion identified on Chest X-Ray that was not present in prior CT can be considered a new lesion and will result in Progressive Disease (PD).

If a new lesion is equivocal, for example because of its small size, continued follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up

CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.3 Response Assessment

2.3.1 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until disease progression or the last response recorded, taking into account any requirement for confirmation and censoring rules regarding subsequent therapy. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement.

2.3.2 Time Point Response

At each protocol specified time point, a response assessment occurs. Table 2.3.2-1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable (therefore non-target) disease only, Table 2.3.2-2 is to be used.

Table 2.3.2-1: Time Point Response: Patients With Target (± Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Abbreviations: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease and NE = inevaluable

Table 2.3.2-2: Time Point Response: Patients with Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Abbreviations: CR = complete response, PD = progressive disease and NE = inevaluable

[a] Non-CR/non-PD is preferred over SD for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

2.3.3 Best Overall Response

Best response determination of complete or partial response requires confirmation: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point of ≥ 4 weeks (28 days) later. In this circumstance, the best overall response can be interpreted as in Table 2.3.3-1. When SD is believed to be best response, it must meet the protocol specified minimum time from the date of first treatment or randomization date.

For example, if the first scheduled follow-up imaging visit is Week 6 (± 7 days) for a particular protocol, a Best Response of SD can only be made after the subject is on-study for a minimum of 6 weeks (42 days) minus 7 days, for an absolute minimum time on-study of 35 days from the reference start date (reference date is considered Day 1 on study). If the subject is not on-study for at least this amount of time, any tumor assessment indicating stable disease before this time period will have a Best Response of NE unless PD is identified.

Special note on response assessment: When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	CR	CR
CR	PR	SD, PD OR PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD

Table 2.3.3-1: Best Overall Response (Confirmation of CR and PR Required)

Overall Response First Time Point	Overall Response Subsequent Time Point	Best Overall Response
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Abbreviations: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

[a] If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

2.3.4 Confirmation Scans

Verification of Response: To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by consecutive or subsequent repeat assessments that should be performed no less than 28 days after the criteria for response are first met. Subsequent documentation of a CR may provide confirmation of a previously identified CR even with an intervening NE or PR (eg, CR NE CR or CR PR CR). Subsequent documentation of a PR may provide confirmation of a previously identified PR even with an intervening NE or SD (eg, PR NE PR or PR SD PR). However, only one (1) intervening time point will be allowed between PR/CRs for confirmation.

Verification of Progression: Progression of disease should be verified in cases where progression is equivocal. If repeat scans confirm PD, then progression should be declared using the date of the initial scan. If repeat scans do not confirm PD, then the subject is considered to not have progressive disease.

REFERENCES:

[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-47.

APPENDIX 7 TITE-BOIN DECISION TABLE

To assign a dose to the next cohort of patients, count the number of treated patients (# Patients), the number of patients who experienced dose-limiting toxicity (# DLTs observed), and the number of pending patients ("# Pending patients") and their standardized total follow-up time (STFT) at the current dose, and then make the dose escalation/de-escalation decision according to the rule displayed in Table 1.

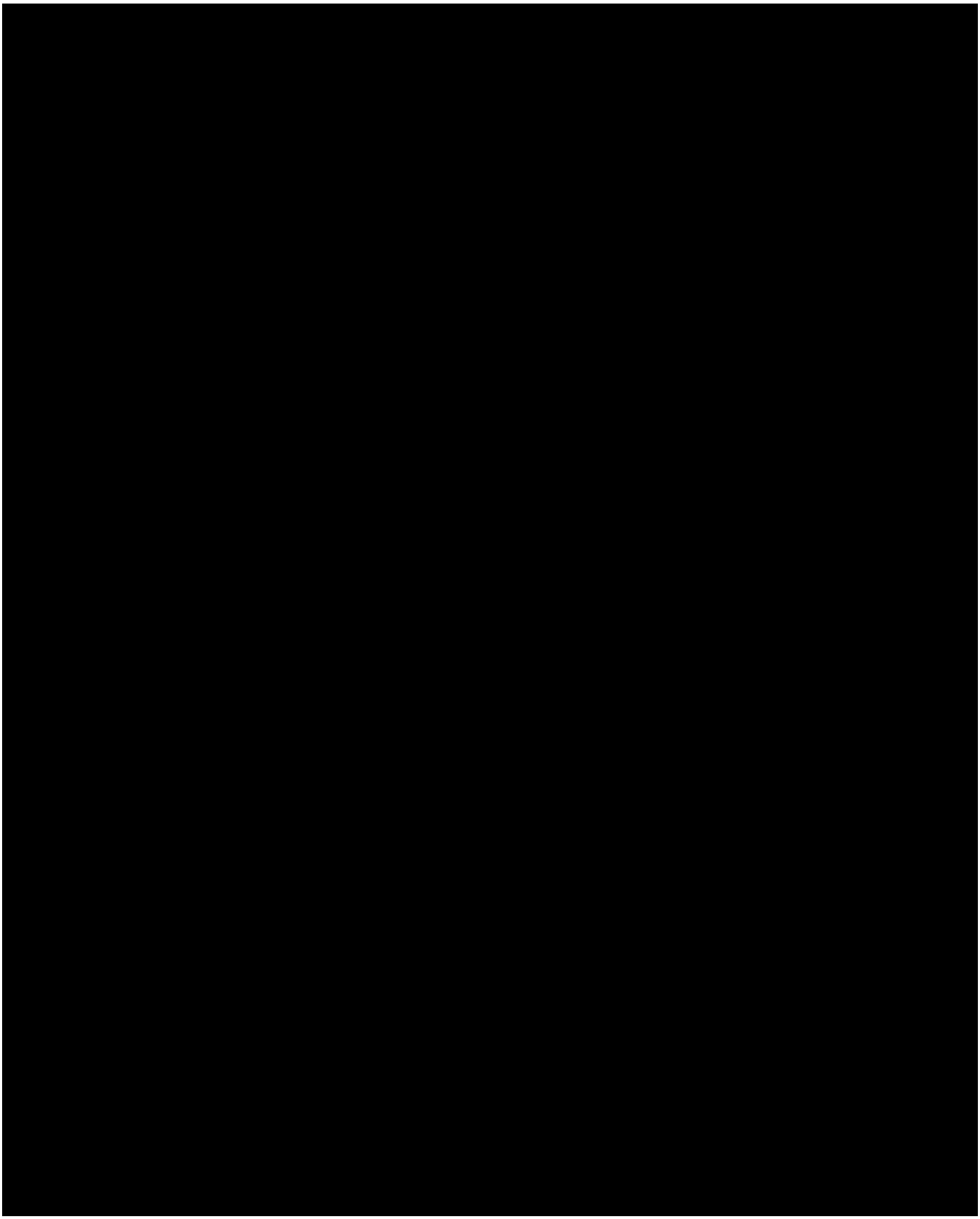
The STFT is defined as

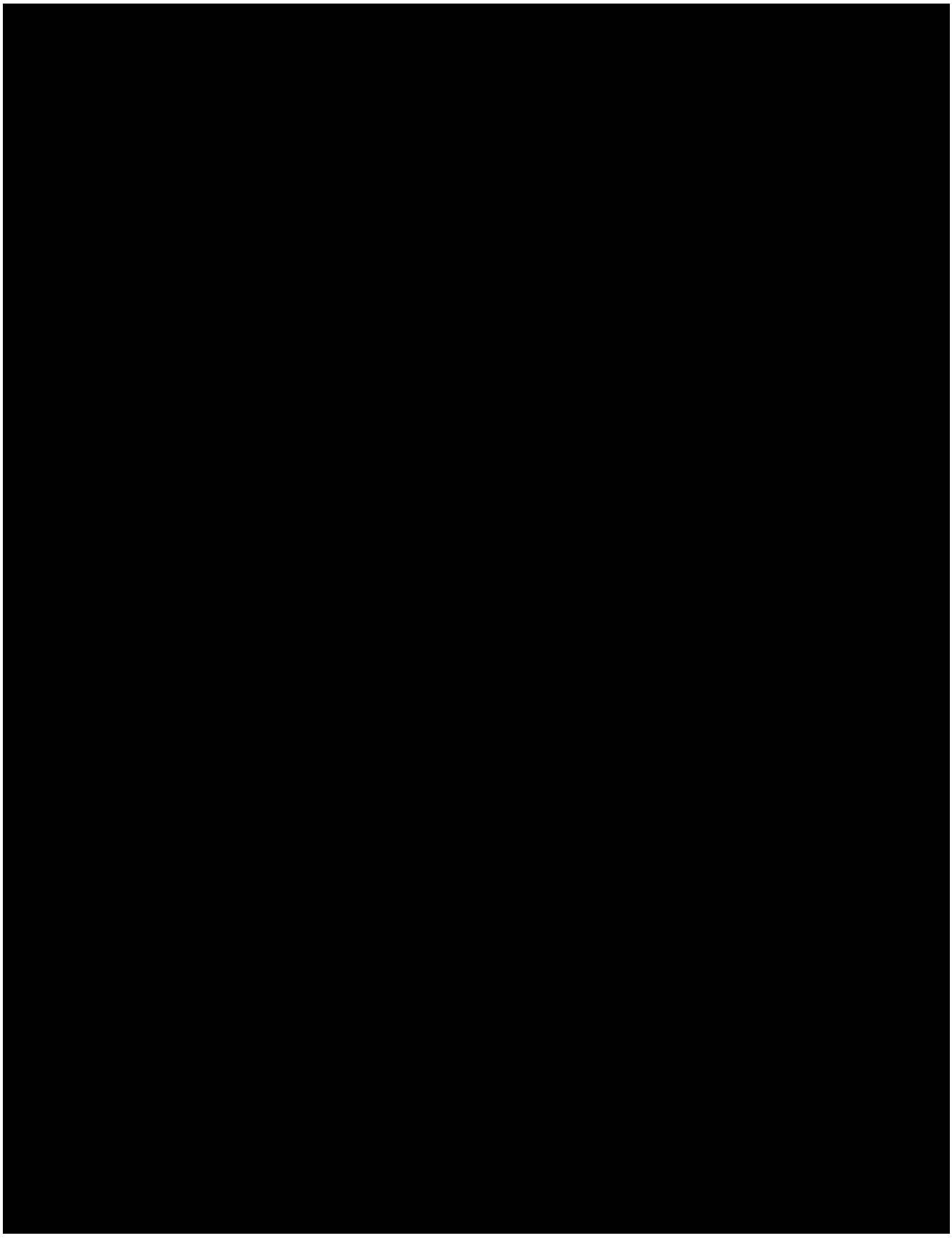
$$\text{STFT} = \frac{\text{sum of the followup time for pending patients at the current dose}}{\text{length of the DLT assessment window}}$$

Please also note the following when using Table 1:

1) "Yes & Eliminate" means de-escalating to the next lower dose and eliminating the current and higher doses from the trial to prevent treating any future patients at these doses because they are overly toxic. When the lowest dose is eliminated, stop the trial for safety. In this case, no dose should be selected as the MTD.
2) If the current dose is the lowest dose and the decision table indicates dose de-escalation but no elimination, treat the new patients at the lowest dose.
3) If the current dose is the highest dose and the rule indicates dose escalation, treat the new patients at the highest dose.
4) For patient safety, if at the current dose, more than 50% of the patients' DLT outcomes are pending, suspend the accrual to wait for more data to become available. This rule corresponds to "Suspend" in Table 1.
5) Dose escalation will stop if the maximum number of treated patients at the current dose level has been reached.

[redacted]





APPENDIX 8 MEDICATIONS ASSOCIATED WITH QT PROLONGATION

The list below is not meant to be all inclusive. Please consult individual drug labels for further information.

Table 1: Medications Associated with QT Prolongation

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Sevoflurane	Ultane, Sojourn	Anesthetic, general	Anesthesia
Propofol	Diprivan, Propoven	Anesthetic, general	Anesthesia
Bepridil	Vascor	Antianginal	Angina Pectoris (heart pain)
Ibutilide	Corvert	Antiarrhythmic	Arrhythmia
Dronedarone	Multaq	Antiarrhythmic	Arrhythmia
Sotalol	Betapace, Sotalex, Sotacor, Sotalol-AF	Antiarrhythmic	Arrhythmia
Quinidine	Quinaglute, Duraquin, Quinact, Quinidex, Cin-Quin, Quinora	Antiarrhythmic	Arrhythmia
Procainamide	Pronestyl, Procan	Antiarrhythmic	Arrhythmia
Flecainide	Tambocor, Almarytm, Apocard, Ecrinal, Flécaine	Antiarrhythmic	Arrhythmia
Disopyramide	Norpace	Antiarrhythmic	Arrhythmia
Dofetilide	Tikosyn	Antiarrhythmic	Arrhythmia
Amiodarone	Cordarone, Pacerone, Nexterone	Antiarrhythmic	Arrhythmia
Hydroquinidine (Dihydroquinidine) (Only on Non US Market)	Serecor	Antiarrhythmic	Arrhythmia
Nifekalant (Only on Non US Market)	Shinbit	Antiarrhythmic	Arrhythmia
Levofloxacin	Levaquin, Tavanic	Antibiotic	Bacterial infection
Moxifloxacin	Avelox, Avalox, Avelon	Antibiotic	Bacterial infection
Clarithromycin	Biaxin, Prevpac	Antibiotic	Bacterial infection
Roxithromycin (Only on Non US Market)	Rulide, Xthrocin, Roxl-150, Roxo, Surlid, Rulide, Biaxsig, Roxar, Roximycinv, Roxomycin, Rulid, Tirabicin, Coroxin	Antibiotic	Bacterial infection
Azithromycin	Zithromax, Zmax	Antibiotic	Bacterial infection
Ciprofloxacin	Cipro, Cipro-XR, Neofloxin	Antibiotic	Bacterial infection
Erythromycin	E.E.S., Robimycin, EMycin, Erymax, Ery-Tab, Eryc Ranbaxy, Erypar, Eryped, Erythrocin Stearate Filmtab, Erythrocot, E-Base, Erythroped, Ilosone, MY-E, Pediamycin, Abboticin, Abboticin-ES, Erycin, PCE	Antibiotic	Bacterial infection, increase GI motility

Table 1: Medications Associated with QT Prolongation

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
	Dispertab, Stiemycine, Acnasol, Tiloryth		
Arsenic trioxide	Trisenox	Anti-cancer	Cancer (leukemia)
Vandetanib	Caprelsa	Anti-cancer	Cancer (thyroid)
Oxaliplatin	Eloxatin	Anti-cancer	Cancer
Aclarubicin (Only on Non US Market)	Aclacin, Aclacinomycine, Aclacinon, Aclaplastin, Jaclacin	Anti-cancer	Cancer
Escitalopram	Cipralex, Lexapro, Nexito, Anxiset-E, Exodus, Esto, Seroplex, Elicea, Lexamil, Lexam, Entact, Losita, Reposil, Animaxen, Esitalo, Lexamil	Antidepressant, SSRI	Depression (major), anxiety disorders
Citalopram	Celexa, Cipramil	Antidepressant, SSRI	Depression
Domperidone (Only on Non US Market)	Motilium, Motillium, Motinorm Costi, Nomit	Antiemetic	Nausea, vomiting
Ondansetron	Zofran, Anset, Ondemet, Zuplenz, Emetron, Ondavell, Emeset, Ondisolv, Setronax	Antiemetic	Nausea, vomiting
Fluconazole	Diflucan, Trican	Antifungal	Fungal infection
Pentamidine	Pentam	Antifungal	Fungal infection (Pneumocystis pneumonia)
Chloroquine	Aralen	Antimalarial	Malaria
Halofantrine (Only on Non US Market)	Halfan	Antimalarial	Malaria
Hydroxychloroquine	Plaquenil, Quineprox	Antimalarial, Anti-inflammatory	Malaria, SLE, rheumatoid arthritis
Meglumine antimoniate (Only on Non US Market)	Glucantime	Antiparasitic	Leishmaniasis
Haloperidol	Haldol, Aloperidin, Bioperidolo, Brotopon, Dozic, Duraperidol, Einalon S, Eukystol, Halosten, Keselan, Linton, Peluces, Serenace, Serenase, Sigaperidol	Antipsychotic	Schizophrenia, agitation
Thioridazine	Mellaril, Novoridazine, Thioril	Antipsychotic	Schizophrenia
Pimozide	Orap	Antipsychotic	Tourette's Disorder
Levomepromazine (Methotrimeprazine) (Only on Non US Market)	Nosinan, Nozinan, Levoprome	Antipsychotic	Schizophrenia
Levosulpiride (Only on Non US Market)	Lesuride, Levazeo, Enliva	Antipsychotic	Schizophrenia

Table 1: Medications Associated with QT Prolongation

Generic Name	Brand Names (Partial List)	Drug Class	Therapeutic Use
Chlorprothixene (Only on Non US Market)	Truxal	Antipsychotic	Schizophrenia
Droperidol	Inapsine, Droleptan, Dridol, Xomolix	Antipsychotic / Antiemetic	Anesthesia (adjunct), nausea
Chlorpromazine	Thorazine, Largactil, Megaphen	Antipsychotic / Antiemetic	Nausea, Schizophrenia, many others
Sertindole (Only on Non US Market)	Serdolect, Serlect	Antipsychotic, atypical	Schizophrenia, anxiety
Sulpiride (Only on Non US Market)	Dogmatil, Dolmatil, Eglonyl, Espiride, Modal, Sulpor	Antipsychotic, atypical	Schizophrenia
Sultopride (Only on Non US Market)	Barnetil, Barnotil, Topral	Antipsychotic, atypical	Schizophrenia
Donepezil	Aricept	Cholinesterase inhibitor	Dementia (Alzheimer's Disease)
Cocaine	Cocaine	Local anesthetic	Anesthesia (topical)
Terodiline (Only on Non US Market)	Micturin, Mictrol	Muscle relaxant	Bladder spasm
Methadone	Dolophine, Symoron, Amidone, Methadose, Physeptone, Heptadon	Opioid agonist	Narcotic dependence, pain
Anagrelide	Agrylin, Xagrid	Phosphodiesterase 3 inhibitor	Thrombocythemia
Cilostazol	Pletal	Phosphodiesterase 3 inhibitor	Intermittent claudication
Ibogaine (Only on Non US Market)		Psychedelic	Narcotic addiction, unproven
Cesium Chloride	Energy Catalyst	toxin	Alternative therapy cancer
Terlipressin (Only on Non US Market)	Teripress, Glypressin, Terlipin, Remestyp, Tresil, Teriss	Vasoconstrictor	Septic shock
Papaverine HCl (Intra-coronary)		Vasodilator, Coronary	Diagnostic adjunct

Source: CredibleMeds. https://crediblemeds.org, accessed 04-Oct-2021.
Marketed drugs only.
Known QTc risk only.