Official Protocol Title:	A Phase 3 Randomized, Open-label Study to Evaluate the Efficacy and Safety of Olaparib Alone or in Combination With Bevacizumab Compared to Bevacizumab with a Fluoropyrimidine in Participants with Unresectable or Metastatic Colorectal Cancer
NCT number:	NCT04456699
Document Date:	September 8, 2022

Title Page

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Protocol Title: A Phase 3 Randomized, Open-label Study to Evaluate the Efficacy and Safety of Olaparib Alone or in Combination With Bevacizumab Compared to Bevacizumab with a Fluoropyrimidine in Participants with Unresectable or Metastatic Colorectal Cancer who Have Not Progressed Following First-line Induction (LYNK-003)

Protocol Number: 003-05

Compound Number: MK-7339

Sponsor Name:

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

Legal Registered Address:

126 East Lincoln Avenue

P.O. Box 2000

Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

IND	141,560
EudraCT	2019-000698-22

Approval Date: 08 September 2022

Sponsor Signatory

Typed Name: Title:	Date

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

Investigator Signatory

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

Typed Name: Title:	Date

DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	08-SEP-2022	Protocol is amended consistent with recommendations of the eDMC after an interim review of the data; specifically, to discontinue the study enrollment due to futility. Study participants randomized to one of the two experimental arms (olaparib plus bevacizumab [Arm 1] or olaparib monotherapy [Arm 2]) must discontinue the therapy. No crossover from either experimental arm to Standard of Care (SOC) arm (Arm 3A and Arm 3B) within the study is allowed. Participants on SOC have the option to continue receiving study intervention until criteria for discontinuation are met.
Amendment 04	29-NOV-2021	Update 5-FU information in Schedule of Activities table
Amendment 03	14-OCT-2021	Addition of CAPOX as allowed induction therapy; require BICR confirmation of non-PD prior to randomization; allow use of leucovorin
Amendment 02	13-APR-2020	Response to agency request for protocol changes
Amendment 01	28-AUG-2019	Response to agency request for protocol changes
Original Protocol	05-JUL-2019	N/A

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 05

Overall Rationale for the Amendments:

Protocol is amended consistent with recommendations of the eDMC after an interim review of the data; specifically, to discontinue the study enrollment due to futility. Study participants randomized to one of the two experimental arms (olaparib plus bevacizumab [Arm1] or olaparib monotherapy [Arm 2]) must discontinue the therapy. No crossover from either experimental arm to SOC arm (Arm 3A and Arm 3B) within the study is allowed. Participants on SOC have the option to continue receiving study intervention until criteria for discontinuation are met.

Summary of Changes Table:

Section # and Name	Description of Change	Brief Rationale
5 Study Population 6.1 Study Intervention(s) Administered 9.1 Statistical Analysis Plan Summary	Added statement: "As of Amendment 05, study enrollment is being stopped for futility. Study participants randomized to one of the two experimental arms (olaparib plus bevacizumab [Arm 1] or olaparib monotherapy [Arm2]) must discontinue study intervention. No crossover from either experimental arm to SOC arm (Arm 3A and Arm 3B) within the study is allowed. Participants on SOC have the option to continue receiving study intervention until criteria for discontinuation is met at the discretion of the investigator."	To clarify that participants randomized to one of the two experimental arms (olaparib plus bevacizumab [Arm 1] or olaparib monotherapy [Arm2]) must discontinue and participants on SOC may continue to receive treatment

Section # and Name	Description of Change	Brief Rationale
2.3 Benefit/Risk Assessment 4.1 Overall Design	Added statement that as of Amendment 05, the study enrollment is being stopped due to futility. The prespecified analyses (IA 2, 3, 4 and FA) described in the SAP will not be performed. In Section 2.3, added that selected analyses of safety endpoints will be performed at the end of the study.	To inform of the decision to stop this clinical study
1.1 Synopsis - Hypotheses, Objectives, and Endpoints 3 Hypotheses, Objectives, and Endpoints	The following statement was added: "NOTE: As of Amendment 05, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue as per local institutional guidelines. In addition, PRO assessments will no longer be performed. Blood for RNA analysis and serum and plasma biomarker analysis will no longer be collected. Updated analyses are described in Section 9. Post-treatment follow-up visits are no longer required except for safety and efficacy follow-up requirements (refer to Sec 8.11.4). The section below is retained for reference."	As the result of the efficacy IA indicated futility, further tumor scans and response assessments by BICR, and PRO assessments, and collection of blood for RNA analysis and serum and plasma biomarker analysis are considered unnecessary.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	In Sections 1.3.1, 1.3.2, and 1.3.3, added Statement: "NOTE: As of Amendment 05, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue as per local institutional guidelines. In addition, PRO assessments (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D-5L) will no longer be performed. Blood for RNA analysis and serum and plasma biomarker analysis will no longer be collected. Updated analyses are described in Section 9. Post-treatment follow-up visits are no longer required except for safety and efficacy follow-up requirements (refer to Section 8.11.4). The section below is retained for reference."	As of Amendment 05, these assessments and sample collections are considered unnecessary.
Title page 10.1.1 Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
5.1 Inclusion Criteria	For Criterion #10, updated the time needed for male participants to continue contraception after the last dose of each individual study intervention. For Criterion #11, updated the time needed for female participants to continue contraception after the last dose of each individual study intervention, and clarified that the contraceptive methods should be consistent with local regulations.	To correct the time required for contraception after the last dose of each study intervention for males and females

Section # and Name	Description of Change	Brief Rationale
7.1 Discontinuation of Study Intervention	Under the bullet "Documented radiographic disease progression outlined in Section 8.2.1", added a note to clarify the criteria for participants remaining on SOC to discontinue	To clarify the criteria for participants on SOC arm to discontinue from study intervention after Amendment 05
8.2.1 Tumor Imaging and Assessment of Disease	Added text: "As of Amendment 05, central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to iCRO nor read by BICR. The subsections below are retained for reference. However, for participants who are still receiving and will continue receiving SOC treatment until criteria for discontinuation are met, local tumor imaging should continue per local institutional guidelines."	To clarify that as of Amendment 05, further efficacy assessments are considered unnecessary. Participants who are still receiving SOC at the time of this amendment will continue with local tumor imaging as per local institutional guidelines.
8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information	In bullet "All AEs meeting serious criteria", changed the time period required for SAE reporting from 90 to 30 days after the last dose of study intervention	To be consistent with Section 4.1 where the time period required for AE and SAE reporting is 30 days
8.6 Pharmacokinetics	Added statements that as of Amendment 05, sample collection for PK has been completed and is no longer applicable	To update that this analysis is complete
8.8 Biomarkers	Added statements that as of Amendment 05, sample collections for biomarkers (blood for RNA analysis, serum and plasma biomarker analysis) will be discontinued.	As of Amendment 05, collection of these samples is considered unnecessary.

Section # and Name	Description of Change	Brief Rationale
8.9 Future Biomedical Research Sample Collection	Clarified the types of specimens that will be obtained for future biomedical research	To be consistent with Section 8.8
8.10 Medical Resource Utilization and Health Economics	Added statement: "As of Amendment 05: medical resource utilization and health economics data collection will be discontinued. The section below is retained for reference."	As of Amendment 05, assessment of these data is considered unnecessary.
8.10 Medical Resource Utilization and Health Economics	Changed the time period required for all-cause hospitalization and emergency room visits be reported in the eCRF (90 days to 30 days).	For correction
8.11.4.1 Safety Follow-up Visit	Added a statement to clarify that once the safety follow-up is completed, all participants will be discontinued from the study.	To clarify the requirement for safety follow-up
8.11.4.2 Follow-up Visits 8.11.4.3 PFS2 Follow-up	Added statement that as of Amendment 05, efficacy follow-up visits and PFS2 follow-up visits will be discontinued for all participants, and all participants will move into survival follow-up phase.	As of Amendment 05, these assessments are considered unnecessary.
8.11.4.4 Survival Follow-up	Added statement to clarify the time period for survival follow-up visits.	To clarify the periods for survival follow-up visits for all participants and for participants on SOC.

Section # and Name	Description of Change	Brief Rationale
9 Statistical Analysis Plan 9.1 Statistical Analysis Plan Summary 9.6 Statistical Methods 9.7 Interim Analyses 9.7.2 Safety Interim Analyses 9.8 Multiplicity 9.9 Sample Size and Power Calculations	In Sections 9 and 9.1, updated text with the status of data unblinding. In Section 9.1, a note was added describing the results of the safety and efficacy IA1 that led to the decision to stop the study enrollment due to futility. In Sections 9.1, and 9.6, added statement: "Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy and PRO endpoints." In Sections 9.1, 9.6, 9.7, 9.8, and 9.9, a statement was added that the prespecified interim analyses 2, 3, 4, and final analysis of the study described in the SAP will not be performed. In Section 9.7.2, a note was added to indicate that no further analysis to the eDMC is warranted as of Amendment 05.	To describe the results of the IA1 and to specify which analyses will be conducted as of Amendment 05

Section # and Name	Description of Change	Brief Rationale
4.4 Beginning and End-of-Study Definition 5 Study Population 6.1 Study Intervention(s) Administered 8.4 Adverse Events, Serious Adverse Events, and Other Reportable Safety Events 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	In Section 4.4, clarified when the overall study ends for analysis and reporting, and the local start of the study in the EEA In Section 5, second paragraph, added additional text to clarify the collection and use of demographic data provided by the participants In Section 6.1, Table 2 Study Interventions, in the "Use" column, changed "Experimental" to "Test Product"; changed the column heading from "IMP/NIMP" to "IMP or NIMP/AxMP" In Section 6.1 Table 2, added abbreviations EEA, IMP, NIMP/AxMP, and added clarifications that the classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA In Section 8.4, added that investigators need to document when an SAE is associated with a medication error, misuse, or abuse Added Section 10.3.1 Definitions of Medication Error, Misuse, and abuse	To align with EU CTR
1.1 Synopsis	In the Table Intervention Groups and Duration, in the "Use" column, changed "Experimental" to "Test Product"	To be consistent with Section 6.1 Table 2

Section # and Name	Description of Change	Brief Rationale
6.1 Study Intervention(s) Administered	Added reference to Appendix 7 country-specific differences	To align with PMDA regulation
6.1 Study Intervention(s) Administered	In Table 2, changed the dose formulation for capecitabine from capsule to tablet	To correct a typographical error
8.3.5 Pregnancy test	To clarify the requirements for pregnancy testing	To clarify the timeline requirements for pregnancy testing and be consistent with Section 5.1 Inclusion Criterion #11.
8.8.1 Planned Genetic Analysis Sample Collection	Stated the time point and acceptable window for collection of planned genetic analysis samples	For clarification of genetic analysis sample collection
10.2 Appendix 2 Clinical Laboratory Tests	In Table 16, added a reference to the footnote next to Reticulocytes to clarify that test is only performed if it is considered as local SOC	To comply with local regulation
10.7 Country-specific Requirements	Deleted 10.7.2 Argentina	For correction, given that the study was not conducted in Argentina

Section # and Name	Description of Change	Brief Rationale
10.7 Country-specific Requirements	10.7.1 France For Section 1.3 Schedule of Activities, clarified when pregnancy testing must be performed For Section 5.2 Exclusion Criteria, added additional exclusion criteria related to dihydropyrimidine dehydrogenase deficient participants and brivudine administration Added 10.7.2 Japan For Section 6.1 Study Intervention(s) Administered, clarified the classification of study intervention (bevacizumab) in Japan Added 10.7.4 Germany For Section 1.3 Schedule of Activities, added requirements for dihydropyrimidine dehydrogenase deficiency testing at screening For Section 5.2 Exclusion Criteria, added additional exclusion criteria related to dihydropyrimidine dehydrogenase deficient participants and brivudine administration For Section 6.5.3 Rescue Medications and Supportive Care, clarified the requirements for live vaccines administration Clarified that all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany	To update based on local health authority feedbacks for similar studies
Throughout Document	Minor administrative, formatting, grammatical, and typographical changes were made throughout the document	To ensure clarity and accurate interpretation of the intent of the protocol

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 Randomized, Open-label Study to Evaluate the Efficacy and Safety of Olaparib Alone or in Combination With Bevacizumab Compared to Bevacizumab with a Fluoropyrimidine in Participants with Unresectable or Metastatic Colorectal Cancer who Have Not Progressed Following First-line Induction (LYNK-003)

Short Title: Olaparib ± bevacizumab in CRC with SD/PR/CR from FOLFOX or CAPOX with bevacizumab

Acronym: Not applicable.

Hypotheses, Objectives, and Endpoints:

NOTE: As of Amendment 05, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue as per local institutional guidelines. In addition, PRO assessments will no longer be performed. Blood for RNA analysis and serum and plasma biomarker analysis will no longer be collected. Updated analyses are described in Section 9. Post-treatment follow-up visits are no longer required except for safety and survival follow-up requirements (refer to Section 8.11.4). The section below is retained for reference.

In male or female participants with unresectable or metastatic CRC who have not progressed following prior FOLFOX + bevacizumab or CAPOX + bevacizumab induction.

The study is considered to have met its primary objective if at least 1 primary hypothesis test is significant.

Primary Objectives	Primary Endpoints
• To compare PFS using RECIST 1.1 as assessed by BICR between the following treatments: - Olaparib + Bevacizumab versus a fluoropyrimidine + Bevacizumab - Olaparib versus A fluoropyrimidine + Bevacizumab Hypotheses: H1 – Olaparib + Bevacizumab is superior to a fluoropyrimidine + Bevacizumab with respect to PFS using RECIST 1.1 as assessed by BICR. H2 – Olaparib is superior to a fluoropyrimidine + Bevacizumab with respect to PFS using RECIST 1.1 as assessed by BICR.	• PFS: the time from randomization to first documented disease progression (PD) or death due to any cause, whichever occurs first

Secondary Objectives	Secondary Endpoints
• To compare OS between the following treatments: - Olaparib + Bevacizumab versus a fluropyrimidine + Bevacizumab - Olaparib versus a fluoropyrimidine + Bevacizumab Hypotheses: H3 – Olaparib + Bevacizumab is superior to a fluoropyrimidine + Bevacizumab with respect to OS. H4 – Olaparib is superior to a fluorpyrimidine + Bevacizumab with respect to OS.	• OS: the time from randomization to death due to any cause
• To evaluate ORR, and DOR using RECIST 1.1 as assessed by BICR following administration of: - Olaparib + Bevacizumab - Olaparib - Fluoropyrimidine + Bevacizumab	• OR: CR or PR • DOR: the time from first response (CR or PR) to subsequent disease progression or death due to any cause, whichever occurs first
• To evaluate the safety and tolerability of: - Olaparib + Bevacizumab - Olaparib	• AEs • Study intervention discontinuation due to AEs

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	The treatment of participants with unresectable or metastatic CRC that has not progressed following an induction course of FOLFOX + bevacizumab or CAPOX + bevacizumab
Population	Participants with unresectable or metastatic CRC that has not progressed following an induction course of FOLFOX + bevacizumab or CAPOX + bevacizumab
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.

Type of Control	Active Control Without Placebo
Study Blinding	Unblinded Open-label
Masking	Outcomes Assessor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 6 years from the time the first participant provides documented informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 525 participants with CRC that has not progressed following prior CAPOX + bevacizumab or FOLFOX + bevacizumab induction will be enrolled in this study.

Intervention Groups and Duration:

Intervention Groups

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Arm 1	Olaparib	300 mg	Twice daily	Oral	Until progressive disease or end of study	Test Product
	Bevacizumab[a]	5 mg/kg	Q2W	IV Infusion		
Arm 2	Olaparib	300 mg	Twice daily	Oral		
Arm 3a	Leucovorin[b] or Levoleucovorin	400 mg/m^2 (leucovorin) or 200 mg/m^2 (levoleucovorin)	Q2W	IV Infusion	Until progressive disease or end of study	Comparator
	Bevacizumab[a]	5 mg/kg	Q2W	IV Infusion		
	5-FU	2400 mg/m^2 over 46 to 48 hours[c]	Q2W	IV Infusion		
Arm 3b	Capecitabine	1000 mg/m^2	BID 14 days on, 7 days off Q3W	Oral		
	Bevacizumab[a]	7.5 mg/kg	Q3W	IV Infusion		

Abbreviations: 5-FU: 5-Fluorouracil, BID: Twice daily, IV: Intravenous, QXW: Every X weeks

a. Participants who begin study treatment with bevacizumab must remain on bevacizumab throughout the study. Participants who begin study treatment with biosimilar bevacizumab must remain on the same biosimilar throughout the study.
b. Leucovorin/levoleucovorin may be added to Arm 3a per investigator's discretion.
c. 5-FU regimen may include a bolus of 5-FU prior to infusion: 400mg/m^2 IV infusion on Day 1 based on local standards, investigator preference, and participant experience with the bolus during the induction phase.

Total Number	3 Arms

Duration of Participation	Each participant will participate in the study from the time the participant provides documented informed consent through the final protocol-specified contact. After a Screening phase of up to 28 days, each participant will be randomized to receive study intervention until disease progression is radiographically documented, unacceptable AEs, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, or administrative reasons requiring cessation of treatment. After the end of study treatment, each participant will be followed for the occurrence of AEs and spontaneously reported pregnancy as described under Section 8.4.1. Participants who discontinue study intervention for reasons other than radiographically documented disease progression will have post-treatment follow-up imaging for disease status until disease progression is documented radiographically per RECIST 1.1. All participants will then be followed for disease status until second disease progression during reintroduction of investigator-choice of anticancer therapy. All participants will be followed for OS until death, withdrawal of consent, or the end of the study. Once the participant has achieved all study objectives or the study has ended, the participant is discontinued from this study.

Study Governance Committees:

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

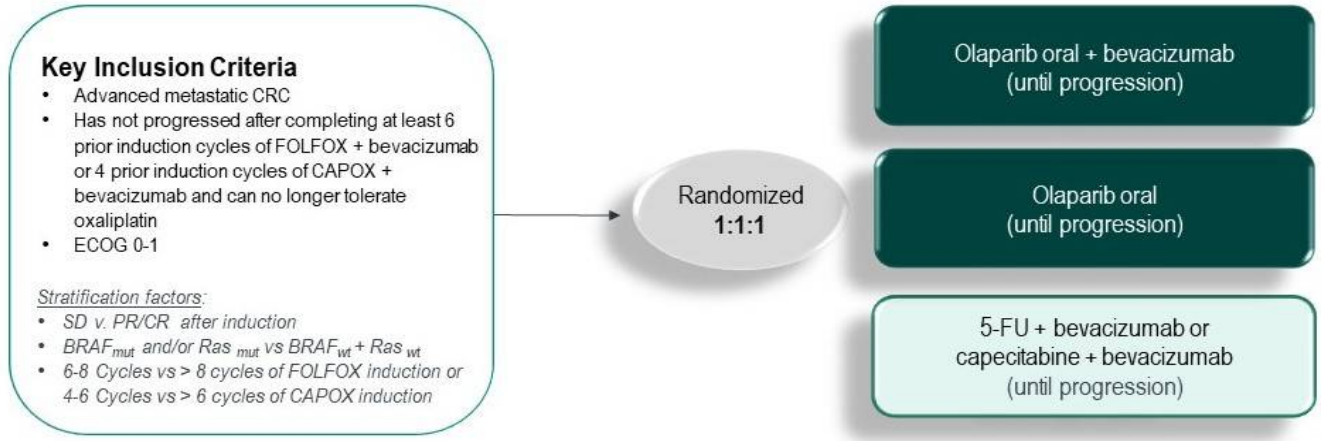
Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The design for the study is depicted in Figure 1.

Figure 1 Study Schema



- Randomized, open label, N= approx. 525
- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DOR, Safety
- Exploratory endpoints: PFS2, QOL (EORTC QLQ C30 + EORTC QLQ CR29 + EQ5D)

Abbreviations: CR = complete response; CRC = colorectal cancer; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; FOLFOX = folinic acid/fluorouracil (5-FU)/oxaliplatin; mut = mutant; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; R = randomization; SD = stable disease; wt = wildtype.

Note: For the purpose of this study a cycle of FOLFOX is given every 2 weeks, and a cycle of CAPOX is given every 3 weeks, such that 1 administration of oxaliplatin is 1 cycle.

1.3 Schedule of Activities (SoA)

1.3.1 Arm 1 (Olaparib + Bevacizumab) & Arm 3a (Bevacizumab + 5-FU)

NOTE: As of Amendment 05, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue as per local institutional guidelines. In addition, PRO assessments (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D-5L) will no longer be performed. Blood for RNA analysis and serum and plasma biomarker analysis will no longer be collected. Updated analyses are described in Section 9. Post-treatment follow-up visits are no longer required except for safety and survival follow-up requirements (refer to Section 8.11.4). The section below is retained for reference.

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Administrative Procedures													
ICF	X												Consent must be obtained prior to performing any protocol-specific procedures.
FBR ICF	X												Participation in FBR is optional and consent must be obtained before collection of samples.
Inclusion/Exclusion Criteria	X												
Participant ID card	X	X											At the time of Visit 1, site personnel should add the randomization number to the Participant ID card.
Demographics and medical history	X												

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Cancer history	X												
Prior/concomitant medication review	X	X	X	X	X	X	X	X	X	X			
Induction history	X												Including history of response while on or after completing the regimen as well as documented reason for discontinuation of oxaliplatin.
Provide radiographic image(s) from induction	X												Sites must submit to the iCRO 1 set of radiographic images including chest/abdomen/pelvis taken before or during the induction period and at least 42 days prior to the imaging taken during Screening. The site must receive the iCRO's determination that the images are of diagnostic quality and confirmation of non-PD by BICR prior to randomization.
Randomization number/study treatment assignment using IRT		X											Visit 1 study treatment must be administered within 3 days after obtaining randomization number.

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Subsequent anti-neoplastic therapy status including disease status								X	X	X	X		PFS2 assessment will be performed by the investigator and defined according to local standard clinical practice and may involve radiological or symptomatic progression or death. Subsequent therapy will be collected for participants from the time of study intervention discontinuation until second progression.
Survival status		←----------										X	Continue after investigator determined PD or start of post-maintenance investigator-choice anticancer therapy. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Administration of Study Treatment													
Olaparib dispensed		X		X		X							Arm 1. Continuous daily dose of 300 mg BID.
Olaparib container returned				X		X		X					Day 1 of every Cycle starting in Cycle 2

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Bevacizumab Administration		X	X	X	X	X	X						Arms 1 and 3. Participants who begin study treatment with bevacizumab must remain on bevacizumab throughout the study. Participants who begin study treatment with biosimilar bevacizumab must remain on the same biosimilar throughout the study.
5-FU Administration		X	X	X	X	X	X						Arm 3a only.

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Efficacy Procedures													**Imaging should continue to be performed until PD is documented, withdrawal of consent, or death, whichever occurs first.**
Tumor imaging	X	X						X		X			Images will be performed every 56 days (8 weeks, ± 7 days) for the first 12 months, and every 84 days (12 weeks, ± 7 days) thereafter. Imaging timing should be calculated from the date of randomization, should follow **calendar days,** and should not be adjusted for delays in cycle starts. For participants who have an outcome of a confirmed curative surgery (Section 4.1), imaging must be performed at a minimum of (no less than) 4 weeks after surgery and no more than 8 weeks prior to the next treatment cycle. Subsequent post-operative images will be assessed every 8 weeks (56 days ± 7 days) for 12 months and every 12 weeks (84 days ± 7 days) thereafter

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Safety Procedures													
AE monitoring	X	X	X	X	X	X	X	X	X	X			New diagnoses of MDS and AML should be reported throughout the study, including follow-up phase.
Height	X												
Weight	X	X	X	X	X	X	X	X					
Complete physical examination	X							X					
Directed physical examination		X	X	X	X	X	X						
Vital Signs (HR, DBP, SBP, RR, temperature)	X	X	X	X	X	X	X	X	X				
12-lead ECG	X							X					12-lead ECG performed using local standard procedures. Additional ECGs performed as clinically indicated.
Hematology	X	X	X	X	X	X	X	X	X				Screening samples must be collected within 10 days of treatment initiation.
Chemistry	X	X	X	X	X	X	X	X	X				
Urinalysis	X	X	X	X	X	X	X		X				Perform 24-hour urine protein analysis if dipstick is ≥2+. Screening samples must be collected within 10 days of treatment initiation.
CEA testing	X	X				X		X					Perform every other cycle
HBV, HCV, and HIV testing	X												Not required unless mandated by local health authority.

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Urine or Serum β-hCG - WOCBP only	X	X		X		X		X	X				WOCBP require a negative urine test within 24 hours prior to the first dose of study treatment. Serum test is only required if urine test is positive or is not evaluable. During the Treatment Period, pregnancy testing is conducted every 4 weeks. Additional urine pregnancy testing can be conducted if required by local regulations or clinically indicated.
PT/INR and aPTT	X												Screening samples collected within 10 days of treatment initiation. PT/INR and aPTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and safety follow-up period.
ECOG performance status	X	X		X		X		X					Screening assessment must be performed within 10 days of randomization.

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Patient-reported Outcomes													**PROs are to be administered in the order listed**
EQ-5D-5L		X		X		X		X	X				During the Treatment Period, PROs will be assessed at Cycles 1 through 3, 5, 7, and every 3 cycles thereafter (C10, C13, etc).
EORTC QLQ-C30		X		X		X		X	X				
EORTC QLQ-CR29		X		X		X		X	X				
Pharmacokinetics													
Blood for olaparib pharmacokinetics		X		X									At Visit 1 (Day 1), the PK sample will be collected at 2 hours (±1 hour) postdose. At Visit 2 (Day 1), PK samples will be collected predose (30 minutes prior to the planned dose [±15 min]) and at 30 min (±15 min) and 2 hours (±1 hour) postdose.

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Biomarkers													
Blood for Genetic Analysis (DNA)[a]		X											Cycles 1 through 3 only. *Final samples for RNA, serum, plasma, and ctDNA analysis should be collected at the time of PD. Collect at Discontinuation/EOT if participant discontinues study intervention due to PD, or at final visit in follow-up if participant discontinues follow-up due to PD. Sample is not collected at every follow-up visit.
Blood for RNA analysis		X		X		X		X*		X*			
Blood for serum biomarker analysis		X		X		X		X*		X*			
Blood for plasma biomarker analysis		X		X		X		X*		X*			
Blood for ctDNA Analysis	X	X		X		X		X*		X*			
Mandatory Tissue collection (New or Archival)	X												A new tumor specimen is preferred to archival samples.

Trial Period	**Screening**	**Treatment Cycle = 28 days**						**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**		**2**		**3+**		**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	
Cycle Day		**1**	**15**	**1**	**15**	**1**	**15**						General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Ras/BRAF Mutation Testing	X												Only perform if status is not already known. Perform at the local laboratory unless it does not have this capability. Results must be obtained by the site prior to randomization.

Abbreviations: 5-FU = fluorouracil; AE = adverse event; aPTT = activated partial thromboplastin time; β-HCG = β-human chorionic gonadotropin; ctDNA = circulating tumor DNA; BID = twice daily; CEA = carcinoembryonic antigen; DBP = diastolic blood pressure; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Cancer Group; EORTC QLQ-C29= European Organisation for Research and Treatment of Cancer Quality of Life Core 29; EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Core 30; EOT = end of therapy; FBR = Future Biomedical Research; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; HRT = hormone replacement therapy; ICF = informed consent form; iCRO = imaging contract research organization; ID = identification; INR = International Normalized Ratio; interactive response technology (IRT) = interactive response system; PD = progressive disease; PK = pharmacokinetics; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; PFS2 = second progression-free survival; Q3W = every 3 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SBP = systolic blood pressure; SOC = standard of care; WOCBP = women of childbearing potential.

a. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research. If the planned genetic analyses are not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

b. Participants who discontinue treatment for reasons other than disease progression will be monitored in the follow-up phase and will then move into the PFS2 follow-up period after progression is documented. Participants who discontinue treatment due to disease progression will move directly into the PFS2 follow-up period.

1.3.2 Arm 2 Olaparib Monotherapy

NOTE: As of Amendment 05, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue as per local institutional guidelines. In addition, PRO assessments (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D-5L) will no longer be performed. Blood for RNA analysis and serum and plasma biomarker analysis will no longer be collected. Updated analyses are described in Section 9. Post-treatment follow-up visits are no longer required except for safety and survival follow-up requirements (refer to Section 8.11.4). The section below is retained for reference.

Trial Period	**Screening**	**Treatment Period 1 Cycle = 28 Days**			**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥ 30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days**	**Q12W (± 14 days)**	
Administrative Procedures										
ICF	X									Consent must be obtained prior to performing any protocol-specific procedures.
FBR ICF	X									Participation in FBR is optional and consent must be obtained before collection of samples.
Inclusion/Exclusion Criteria	X									
Participant ID card	X	X								At the time of Visit 1, site personnel should add the randomization number to the Participant ID card.
Demographics and medical history	X									
Cancer history	X									

Trial Period	**Screening**	**Treatment Period 1 Cycle = 28 Days**			**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥ 30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days**	**Q12W (± 14 days)**	
Prior/concomitant medication review	X	X	X	X	X	X	X			
Induction history	X									Including history of response while on or after completing the induction regimen as well as documented reason for discontinuation of oxaliplatin.
Provide radiographic image(s) from during induction	X									Sites must submit to the iCRO 1 set of radiographic images including chest/abdomen/pelvis taken before or during the induction period and at least 42 days prior to the imaging taken during Screening. The site must receive the iCRO's determination that the images are of diagnostic quality and confirmation of non-PD by BICR prior to randomization.
Obtain randomization number and study treatment assignment using interactive response technology (IRT)		X								Visit 1 study treatment must be administered within 3 days after obtaining randomization number.

Trial Period	**Screening**	**Treatment Period 1 Cycle = 28 Days**			**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥ 30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days**	**Q12W (± 14 days)**	
Subsequent anti-neoplastic therapy status including disease status					X	X	X	X		PFS2 assessment will be performed by the investigator and defined according to local standard clinical practice and may involve radiological or symptomatic progression or death. Subsequent therapy will be collected for participants from the time of study intervention discontinuation until second progression.
Survival status		←----------							X	Continue after investigator determined PD or start of post-maintenance investigator-choice anticancer therapy. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Administration of Study Treatment										
Olaparib dispensed		X	X	X						Continuous daily dose of 300 mg BID.
Olaparib container returned			X	X	X					Day 1 of every cycle starting in Cycle 2

Trial Period	**Screening**	**Treatment Period 1 Cycle = 28 Days**			**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥ 30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days**	**Q12W (± 14 days)**	
Efficacy Procedures										**Imaging should continue to be performed until PD is documented, withdrawal of consent, or death, whichever occurs first.**
Tumor imaging	X	X			X		X			Images will be performed every 56 days (8 weeks, ± 7 days) for the first 12 months, and every 84 days (12 weeks, ± 7 days) thereafter. Imaging timing should be calculated from the date of randomization, should follow **calendar days,** and should not be adjusted for delays in cycle starts. For participants who have an outcome of a confirmed curative surgery (described in Section 4.1), imaging must be performed at a minimum of (no less than) 4 weeks after surgery and no more than 8 weeks prior to the next treatment cycle. Subsequent post-operative images will be assessed every 8 weeks (56 days ± 7 days) for 12 months and every 12 weeks (84 days ± 7 days) thereafter

Trial Period	**Screening**	**Treatment Period 1 Cycle = 28 Days**			**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥ 30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days**	**Q12W (± 14 days)**	
Safety Procedures										
AE monitoring	X	X	X	X	X	X	X			New diagnoses of MDS and AML should be reported throughout the study, including follow-up phase.
Height	X									
Weight	X	X	X	X	X					
Complete physical examination	X				X					
Directed physical examination		X	X	X						
Vital Signs (HR, DBP, SBP, RR, temperature)	X	X	X	X	X	X				
12-lead ECG	X				X					12-lead ECG performed using local standard procedures. Additional ECGs performed as clinically indicated.
Hematology	X	X	X	X	X	X				Screening samples must be collected within 10 days of treatment initiation.
Chemistry	X	X	X	X	X	X				
Urinalysis	X	X	X	X		X				Perform 24-hour urine protein analysis if dipstick is ≥2+. Screening samples must be collected within 10 days of treatment initiation.
CEA testing	X	X		X	X					Perform every other cycle.
HBV, HCV, and HIV testing	X									Not required unless mandated by local health authority.

Trial Period	**Screening**	**Treatment Period 1 Cycle = 28 Days**			**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥ 30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days**	**Q12W (± 14 days)**	
Urine or Serum β-hCG – WOCBP only	X	X	X	X	X	X				WOCBP require a negative urine test within 24 hours prior to the first dose of study treatment. Serum test is only required if urine test is positive or is not evaluable. During the Treatment Period, pregnancy testing is conducted every 4 weeks. Additional urine pregnancy testing can be conducted if required by local regulations or clinically indicated.
PT/INR and aPTT	X									Screening samples collected within 10 days of treatment initiation. PT/INR and aPTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and safety follow-up period.
ECOG performance status	X	X	X	X	X					Screening assessment must be performed within 10 days of randomization.

Trial Period	**Screening**	**Treatment Period 1 Cycle = 28 Days**			**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥ 30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days**	**Q12W (± 14 days)**	
Patient-Reported Outcomes										**PROs are to be administered in the order listed**
EQ-5D-5L		X	X	X	X	X				During the Treatment Period, PROs will be assessed at Cycles 1 through 3, 5, 7, and every 3 cycles thereafter (C10, C13, etc).
EORTC QLQ-C30		X	X	X	X	X				
EORTC QLQ-CR29		X	X	X	X	X				
Pharmacokinetics										
Blood for olaparib pharmacokinetics		X	X							At Visit 1 (Day 1), the PK sample will be collected at 2 hours (±1 hour) postdose. At Visit 2 (Day 1), PK samples will be collected predose (30 minutes prior to the planned dose [±15 min]) and at 30 min (±15 min) and 2 hours (±1 hour) postdose.
Biomarkers										
Blood for Genetic Analysis (DNA)[a]		X								

Trial Period	**Screening**	**Treatment Period 1 Cycle = 28 Days**			**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥ 30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days**	**Q12W (± 14 days)**	
Blood for RNA analysis		X	X	X	X*		X*			Cycles 1 through 3 only. *Final samples for RNA, serum, plasma, and ctDNA analysis should be collected at the time of PD. Collect at Discontinuation/EOT if participant discontinues study intervention due to PD, or at final visit in follow-up if participant discontinues follow-up due to PD. Sample is not collected at every follow-up visit.
Blood for serum biomarker analysis		X	X	X	X*		X*			
Blood for plasma biomarker analysis		X	X	X	X*		X*			
Blood for ctDNA Analysis	X	X	X	X	X*		X*			
Mandatory Tissue collection (New or Archival)	X									A new tumor specimen is preferred to archival samples.

Trial Period	**Screening**	**Treatment Period 1 Cycle = 28 Days**			**EOT**	**Post-Treatment**				**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥ 30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+ 3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days**	**Q12W (± 14 days)**	
Ras/BRAF Mutation Testing	X									Only perform if status is not already known. Perform at the local laboratory unless it does not have this capability. Results must be obtained by the site prior to randomization.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; β-hCG = β-human chorionic gonadotropin; ctDNA = circulating tumor DNA; BID = twice daily; DBP = diastolic blood pressure; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Cancer Group; EORTC QLQ-C29= European Organisation for Research and Treatment of Cancer Quality of Life Core 29; EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Core 30; EOT = end of therapy; FBR = Future Biomedical Research; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; HRT = hormone replacement therapy; ICF = informed consent form; iCRO = imaging contract research organization; ID = identification; INR = International Normalized Ratio; IRT = interactive response system; PD = progressive disease; PK = pharmacokinetics; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; Q3W = every 3 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SBP = systolic blood pressure; SOC = standard of care; WOCBP = women of childbearing potential.

a. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research. If the planned genetic analyses are not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

b. Participants who discontinue treatment for reasons other than disease progression will be monitored in the follow-up phase and will then move into the PFS2 follow-up period after progression is documented. Participants who discontinue treatment due to disease progression will move directly into the PFS2 follow-up period.

1.3.3 Arm 3b Bevacizumab + Capecitabine

NOTE: As of Amendment 05, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue as per local institutional guidelines. In addition, PRO assessments (EORTC QLQ-C30, EORTC QLQ-CR29, EQ-5D-5L) will no longer be performed. Blood for RNA analysis and serum and plasma biomarker analysis will no longer be collected. Updated analyses are described in Section 9. Post-treatment follow-up visits are no longer required except for safety and survival follow-up requirements (refer to Section 8.11.4). The section below is retained for reference.

Trial Period	**Screening**	**Treatment Cycle = 21 days**					**EOT**	**Post-Treatment**		**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Administrative Procedures										
ICF	X									Consent must be obtained prior to performing any protocol-specific procedures.
FBR ICF	X									Participation in FBR is optional and consent must be obtained before collection of samples.
Inclusion/Exclusion Criteria	X									
Participant ID card	X	X								At the time of Visit 1, site personnel should add the randomization number to the Participant ID card.
Demographics and medical history	X									
Cancer history	X									

Trial Period	**Screening**	**Treatment Cycle = 21 days**					**EOT**	**Post-Treatment**		**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Prior/concomitant medication review	X	X	X	X	X	X	X			
Induction history	X									Including history of response while on or after completing the induction regimen as well as documented reason for discontinuation of oxaliplatin.
Provide radiographic image(s) from induction	X									Sites must submit to the iCRO 1 set of radiographic images including chest/abdomen/pelvis taken before or during the induction period and at least 42 days prior to the imaging taken during Screening. The site must receive the iCRO's determination that the images are of diagnostic quality and confirmation of non-PD by BICR prior to randomization.
Randomization number/study treatment assignment using IRT		X								Visit 1 study treatment must be administered within 3 days after obtaining randomization number.

Trial Period	**Screening**	**Treatment Cycle = 21 days**					**EOT**	**Post-Treatment**		**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Subsequent anti-neoplastic therapy status including disease status					X	X	X	X		PFS2 assessment will be performed by the investigator and defined according to local standard clinical practice and may involve radiological or symptomatic progression or death. Subsequent therapy will be collected for participants from the time of study intervention discontinuation until second progression.
Survival status		←----------							X	Continue after investigator determined PD or start of post-maintenance investigator-choice anticancer therapy. In addition, upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
Administration of Study Treatment										
Bevacizumab administration		X	X	X						Bevacizumab 7.5mg/kg IV on Day 1 Q3W.
Capecitabine administration		X	X	X						Capecitabine 1000mg/m^2 BID for 14 days, then 7 days off, Q3W.

Trial Period	**Screening**	**Treatment Cycle = 21 days**					**EOT**	**Post-Treatment**		**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Efficacy Procedures										**Imaging should continue to be performed until PD is documented, withdrawal of consent, or death, whichever occurs first.**
Tumor imaging		X			X		X			Images will be performed every 56 days (8 weeks, ± 7 days) for the first 12 months, and every 84 days (12 weeks, ± 7 days) thereafter. Imaging timing should be calculated from the date of randomization, should follow **calendar days,** and should not be adjusted for delays in cycle starts. For participants who have an outcome of a confirmed curative surgery (Section 4.1), imaging must be performed at a minimum of (no less than) 4 weeks after surgery and no more than 8 weeks prior to the next treatment cycle. Subsequent post-operative images will be assessed every 8 weeks (56 days ± 7 days) for 12 months and every 12 weeks (84 days ± 7 days) thereafter

Trial Period	**Screening**	**Treatment Cycle = 21 days**					**EOT**	**Post-Treatment**		**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Safety Procedures										
AE monitoring	X	X	X	X	X	X	X			New diagnoses of MDS and AML should be reported throughout the study, including follow-up phase.
Height	X									
Weight	X	X	X	X	X					
Complete physical examination	X				X					
Directed physical examination		X	X	X						
Vital Signs (HR, DBP, SBP, RR, temperature)	X	X	X	X	X	X				
12-lead ECG	X				X					12-lead ECG performed using local standard procedures. Additional ECGs performed as clinically indicated.
Hematology	X	X	X	X	X	X				Screening samples must be collected within 10 days of treatment initiation.
Chemistry	X	X	X	X	X	X				
Urinalysis	X	X	X	X		X				Perform 24-hour urine protein analysis if dipstick is ≥2+. Screening samples must be collected within 10 days of treatment initiation.
CEA testing	X	X		X	X					Perform every other cycle
HBV, HCV, and HIV testing	X									Not required unless mandated by local health authority.

Trial Period	**Screening**	**Treatment Cycle = 21 days**					**EOT**	**Post-Treatment**		**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Urine or Serum β-hCG - WOCBP only	X	X	X	X	X	X				WOCBP require a negative urine test within 24 hours prior to the first dose of study treatment. Serum test is only required if urine test is positive or is not evaluable. During the Treatment Period, pregnancy testing is conducted every 4 weeks. Additional urine pregnancy testing can be conducted if required by local regulations or clinically indicated.
PT/INR and aPTT	X									Screening samples collected within 10 days of treatment initiation. PT/INR and aPTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and safety follow-up period.
ECOG performance status	X	X	X	X	X					Screening assessment must be performed within 10 days of randomization.

Trial Period	**Screening**	**Treatment Cycle = 21 days**					**EOT**	**Post-Treatment**		**Notes**
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Patient-Reported Outcomes										**PROs are to be administered in the order listed**
EQ-5D-5L		X	X	X	X	X				During the Treatment Period, PROs will be assessed at Cycles 1, 2, 4, 6, 9 and every 4 cycles thereafter (C13, C17, etc).
EORTC QLQ-C30		X	X	X	X	X				
EORTC QLQ-CR29		X	X	X	X	X				
Biomarkers										
Blood for Genetic Analysis (DNA)[a]		X								
Blood for RNA analysis		X	X	X	X*		X*			Cycles 1 through 3 only. *Final samples for RNA, serum, plasma, and ctDNA analysis should be collected at the time of PD. Collect at Discontinuation/EOT if participant discontinues study intervention due to PD, or at final visit in follow-up if participant discontinues follow-up due to PD. Sample is not collected at every follow-up visit.
Blood for serum biomarker analysis		X	X	X	X*		X*			
Blood for plasma biomarker analysis		X	X	X	X*		X*			
Blood for ctDNA Analysis	X	X	X	X	X*		X*			
Mandatory Tissue collection (New or Archival)	X									A new tumor specimen is preferred to archival samples.

Trial Period	Screening	Treatment Cycle = 21 days					EOT	Post-Treatment		Notes
Cycle Number/Visit Title	**Screening**	**1**	**2**	**3+**	**DC**	**Safety Follow-up**	**Follow-up Visits[b]**	**PFS2 Follow-up[b]**	**Survival Follow-up**	General Notes: • All assessments/ procedures should be performed prior to treatment administration unless otherwise indicated. • If the DC visit occurs ≥30 days from last dose of study intervention, a Safety Follow-up Visit is not required. • Follow-up visits may be scheduled to coincide with follow-up imaging.
Cycle Day		**1**	**1**	**1**						
Scheduling Window (Days):	**–28 to -1**	**+3**	**± 3**	**± 3**	**At time of DC**	**30 Days After Last Dose (+ 7 days)**	**Q8W for 12 months and Q12W thereafter (± 7 days)**	**Q8W (± 14 days)**	**Q12W (± 14 days)**	
Ras/BRAF Mutation Testing	X									Only perform if status is not already known. Perform at the local laboratory unless it does not have this capability. Results must be obtained by the site prior to randomization.

Abbreviations: AE = adverse event; aPTT = activated partial thromboplastin time; β-HCG = β-human chorionic gonadotropin; ctDNA = circulating tumor DNA; BID = twice daily; CEA = carcinoembryonic antigen; DBP = diastolic blood pressure; DC = discontinuation; ECG = electrocardiogram; ECOG = Eastern Cooperative Cancer Group; EORTC QLQ-C29= European Organisation for Research and Treatment of Cancer Quality of Life Core 29; EORTC QLQ-C30= European Organisation for Research and Treatment of Cancer Quality of Life Core 30; EOT = end of therapy; FBR = Future Biomedical Research; FSH = follicle stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; HRT = hormone replacement therapy; ICF = informed consent form; iCRO = imaging contract research organization; ID = identification; INR = International Normalized Ratio; interactive response technology (IRT) = interactive response system; PD = progressive disease; PK = pharmacokinetics; PRO = patient-reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; PFS2 = second progression-free survival; Q3W = every 3 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; RECIST = Response Evaluation Criteria in Solid Tumors; RR = respiratory rate; SBP = systolic blood pressure; SOC = standard of care; WOCBP = women of childbearing potential.

a. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research. If the planned genetic analyses are not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

b. Participants who discontinue treatment for reasons other than disease progression will be monitored in the follow-up phase and will then move into the PFS2 follow-up period after progression is documented. Participants who discontinue treatment due to disease progression will move directly into the PFS2 follow-up period.

2 INTRODUCTION

This clinical trial will study the PARP inhibitor, olaparib, alone or in combination with bevacizumab compared to bevacizumab with 5-FU in participants with unresectable or metastatic CRC that has not progressed following prior CAPOX + bevacizumab or FOLFOX + bevacizumab.

2.1 Study Rationale

Human cancers show genomic instability and an increased mutation rate due to underlying defects in DNA repair. The deficiencies render cancer cells more dependent on the remaining DNA repair pathways, and targeting these pathways is expected to have much greater impact on the survival of the tumor cells than on normal cells. PARP1 and PARP2, the most abundant of the PARP enzymes, play a crucial role in repairing single-strand DNA breaks. The cells with inhibited PARP activity heavily depend on other DNA repair pathways, mainly HRR of DNA double strand breaks. A subset of patients with CRC have HRD and may be more sensitive to PARP inhibitors. Platinum-based chemotherapy regimens are the predominant first-line option for patients with advanced/metastatic CRC, similar to ovarian cancer. It is well documented that platinum sensitivity in ovarian cancer predicts sensitivity to PARP inhibition possibly related to the need for similar repair mechanism to repair their drug-induced DNA damage. This study will evaluate the antitumor effect of maintenance therapy with olaparib in participants with unresectable or metastatic CRC that has not progressed following prior CAPOX + bevacizumab or FOLFOX + bevacizumab.

Platinum-based regimens, specifically CAPOX or FOLFOX, with or without bevacizumab, are the most frequently used standard of care in metastatic CRC as frontline therapy. CAPOX and FOLFOX are considered interchangeable in the NCCN guidelines, and equivalent efficacy has been shown in several clinical trials [Zhang, C., et al 2012] [Buchler, T., et al 2014]. Historically, these regimens are given until disease progression or unacceptable toxicity. However, long exposure to oxaliplatin results in significant treatment-limiting associated toxicity, specifically neuropathy. Oxaliplatin toxicity is cumulative and regressive to some degree after drug discontinuation although it can be disabling and persistent [Esin, E. 2016]. A stop-and-go approach, employing shorter durations of oxaliplatin containing regimens, interrupted by periods of oxaliplatin-free therapy, has been shown to have equivalent efficacy to continuous treatment with oxaliplatin, with reduced toxicity [Seymour, M. 2012] [Berry, S. R., et al 2015]. Maintenance treatment options aiming to enhance clinical benefit and reduce the associated toxicity derived from long exposures to oxaliplatin are an attractive modality in the management of first-line metastatic CRC.

In general, this approach involves intensive first-line therapy, followed by less intensive therapy until progression in patients who did not progress during the first-line induction chemotherapy [Aprile, G., et al 2016]. This concept is gaining credibility, and recent data in the literature suggest that maintenance treatment may play a key role in different cancer types such as CRC, lung, breast, and ovarian carcinomas [Fidias, P. M., et al 2009] [Paz-Ares, L. G., et al 2013] [Gligorov, J., et al 2014] [Burger, R. A., et al 2011] [Perren, T. J., et al 2011].

Currently there are no approved drugs as maintenance after first-line therapy in metastatic CRC. However, both NCCN and ESMO guidelines recommend that oxaliplatin may be discontinued after 12 weeks of therapy with FOLFOX (six 2-week cycles) or CAPOX (four 3-week cycles) when subjects experience unacceptable neurotoxicity. In clinical practice, after discontinuation of oxaliplatin patients are switched to a maintenance regimen of fluoropyrimidine and bevacizumab based on the results from clinical trials such as CAIRO3, PRODIGE 9, and AIO KRK 0207 [Goey, K. K. H., et al 2017] [Hegewisch-Becker, S., et al 2015] [Aparicio, T., et al 2018]. These trials showed a significant PFS benefit and a trend in OS benefit when maintenance was adopted.

The CAIRO3 study was an open-label, Phase 3, multicenter randomized controlled trial assessing maintenance therapy with capecitabine/bevacizumab versus observation (no drug) in 558 patients with metastatic CRC and with SD or better after first-line treatment with CAPOX/bevacizumab [Goey, K. K. H., et al 2017]. After first progression, both groups were to receive CAPOX/bevacizumab again until PFS2. After a median follow-up of 48 months, the primary endpoint of PFS2 was significantly better in the maintenance arm (8.5 vs. 11.7 months; HR, 0.67; 95% CI, 0.56 to 0.81; $p<0.0001$), with 54% of patients overall receiving CAPOX/bevacizumab the second time. A nonsignificant trend toward improved OS was seen in the maintenance arm (18.1 vs. 21.6 months; adjusted HR, 0.83; 95% CI, 0.68 to 1.01; $p=0.06$).

The AIO 0207 trial was an open-label, noninferiority, randomized Phase 3 trial that randomized 472 patients whose disease did not progress on induction FOLFOX/bevacizumab or CAPOX/bevacizumab to no maintenance therapy or to maintenance therapy with fluoropyrimidine/bevacizumab or with bevacizumab alone [Hegewisch-Becker, S., et al 2015]. The planned protocol included reintroduction of primary therapy after first progression. The primary endpoint was time to failure of strategy, defined as time from randomization to second progression, death, and initiation of treatment with a new drug. After a median follow-up of 17 months, the median time to failure of strategy was 6.4 months (95% CI, 4.8 to 7.6) for the no treatment group, 6.9 months (95% CI, 6.1 to 8.5) for the fluoropyrimidine/bevacizumab group, and 6.1 months (95% CI, 5.3 to 7.4) for the bevacizumab alone group. Compared with fluoropyrimidine/bevacizumab, bevacizumab alone was noninferior, whereas the absence of maintenance therapy was not. However, only approximately one-third of trial participants received the reinduction therapy, thus limiting the interpretation of results. Overall survival was one of the secondary endpoints of the trial, and no relevant difference was seen between the arms.

The randomized Phase 3 noninferiority SAKK 41/06 trial provides historical data regarding bevacizumab monotherapy as maintenance after first-line treatment [Koeberle, D., et al 2015]. In this study, the primary endpoint of time to progression was not met (4.1 months for bevacizumab continuation vs. 2.9 months for no continuation; HR, 0.74; 95% CI, 0.58 to 0.96), and no difference in OS was observed (25.4 vs. 23.8 months; HR, 0.83; 95% CI, 0.63 to 1.1; $p=0.20$). Therefore, the value of bevacizumab monotherapy as maintenance was not demonstrated.

PRODIGE 9 trial is a randomized Phase 3 open-label trial that assessed bevacizumab maintenance versus no maintenance during CFI chemotherapy-free intervals in metastatic

CRC [Aparicio, T., et al 2018]. The primary endpoint was TCD, defined as the time elapsed between randomization and tumor progression during a chemotherapy sequence. The study randomized 494 participants assigned to either FOLFIRI plus bevacizumab induction chemotherapy followed by bevacizumab maintenance during CFI (n=247) or to the same induction chemotherapy followed by observation during CFI (n=247). The median TCD was 15 months in both arms (HR, 1.07; 95% CI, 0.85 to 1.34; *p*=0.57). The median PFS was 9.2 months in the maintenance arm and 8.9 months in the observation arm (HR, 0.91; 95% CI, 0.76 to 1.09; *p*=0.316). The 12-month PFS was 30.2% (± 2.9) in the maintenance arm and 21.0% (± 2.6) in the observation arm. The median time to treatment failure was 11.1 months in the maintenance arm and 12.1 months in the observation arm (HR, 1.17; 95% CI, 0.97 to 1.40; *p*=0.092). The trial failed to demonstrate a treatment difference in TCD between the 2 treatment strategies of administering and not administering bevacizumab monotherapy during the maintenance period.

The current study (MK-7339-003) aims to compare the combination of fluoropyrimidine and bevacizumab to olaparib or olaparib plus bevacizumab as a maintenance strategy following discontinuation of CAPOX or FOLFOX in patients with CRC with the goal to improve the overall outcome in terms of efficacy and safety of first-line therapy in metastatic CRC.

2.2 Background

2.2.1 Olaparib

Olaparib (AZD2281, KU-0059436) is a potent PARP inhibitor (PARP1, 2, and 3) that is being developed as an oral anticancer therapy, both as monotherapy (including maintenance) and for combination with chemotherapy and other anticancer agents.

PARP inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA SSBs. Inhibiting PARPs leads to the persistence of SSBs, which are then converted to the more serious DNA DSBs during the process of DNA replication. During the process of cell division, DSBs can be efficiently repaired in normal cells by HRR. Tumors with HRD, such as ovarian cancers in patients with BRCAm, cannot accurately repair the DNA damage, which may become lethal to cells as it accumulates. In such tumor types, olaparib may offer a potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens.

Olaparib traps the inactive form of PARP on DNA at sites of SSBs, thereby preventing their repair [Helleday, T. 2011] [Murai, J., et al 2012]. Olaparib has demonstrated efficacy in ovarian, prostate, and pancreatic tumors with *BRCA1* and *BRCA2* mutations and has shown proof of concept in tumors with ATM and other indicators of HRD. The specificity of olaparib for binding PARP at the replication fork during DNA replication is believed to have applicability to tumors associated with mutations in HRR.

Refer to the IB/approved labeling for detailed background information on olaparib.

2.2.2 Pharmaceutical and Therapeutic Background

2.2.2.1 Inhibition of PARP as a Target for Cancer

PARP1 and PARP2 are zinc-finger DNA-binding enzymes that play a critical role in DNA repair [Ame, J. C., et al 2004] by sensing single-strand DNA damage and converting it into intracellular signals that activate the BER and SSB repair pathways. When a break in DNA occurs, PARP enzymes are recruited to, and bind at, the end of the broken DNA strands, activating their enzymatic activity. PARP subsequently catalyzes the addition of long polymers of ADP-ribose onto several other proteins associated with chromatin (eg, PARP, histones, DNA repair proteins), resulting in chromatin relaxation, rapid recruitment of DNA repair proteins, and efficient repair of the break. In the absence of repair of SSBs, during subsequent DNA replication these breaks are converted to double strand breaks [Fong, Peter C., et al 2009].

Under normal conditions, HRR is the preferred pathway for repairing double strand DNA damage as it is associated with a lower rate of errors compared with other forms of DNA repair [Prakash, R., et al 2015]. Cells unable to perform HRR (eg, due to inactivation of genes required for homologous recombination, such as occur with deleterious mutations of *BRCA1* or *BRCA2*) are more likely to use the error-prone NHEJ or alternative NHEJ pathways to repair these DSBs and risk accumulating multiple lesions or LOH due to an increase in deletions and accompanying genomic instability. Over time, the accumulation of excessive DNA errors in combination with the inability to complete S phase (ie, because of stalled replication forks due to PARP inhibitor administration), leads to cell death demonstrating that PARP inhibition is synthetic lethal in the context of *BRCA* mutations [Farmer, H., et al 2005] [Bryant, H. E., et al 2005]. Cells without SSBs or with intact HRR, such as somatic tissue, replicate normally in the presence of a PARP inhibitor, thereby minimizing toxicity.

2.2.2.2 PARP Inhibition in Platinum-sensitive Cancers

Cisplatin, carboplatin and oxaliplatin are the backbone of platinum-based therapy for several malignancies, such as lung, ovarian, head and neck, colorectal, breast, genitourinary, and pancreatic cancers [Kelland, Lloyd 2007]. General mechanisms of action that are common among platinum agents are the formation of DNA cross-links, induction of DNA replicative stress, mitotic arrest, and ultimate cell death [Dilruba, S. 2016]. Hence, cancers with deficiencies in DNA damage repair pathways are particularly sensitive to platinum-based chemotherapies.

These cancer types are also sensitive to PARP inhibitors. PARP inhibitors have been shown to be effective in ovarian, prostate, breast, and pancreatic cancers [Ledermann, J., et al 2012] [Moore, K., et al 2018] [Robson, M., et al 2017] [Mirza, M. R., et al 2016] [Swisher, E. M., et al 2017]. See the olaparib IB for more information.

Sensitivity to platinum-based chemotherapy is a good predictor of response to PARP inhibition as demonstrated by these trials and therefore, it has been used as a biomarker for patient selection in PARP inhibitor maintenance clinical trials [Gelmon, K. A., et al 2011].

Olaparib is approved as maintenance therapy for patients with platinum-sensitive relapsed ovarian cancer. Pancreatic cancer is another malignancy where platinum sensitivity is used as a selection criterion for testing PARP inhibitor efficacy in patients with g*BRCA* mutant cancers (POLO trial; NCT02184195).

The cross-sensitivity between PARP inhibitors and platinum-based chemotherapies is predicted to be due to similar repair mechanisms being used to repair the DNA damage resulting from exposure to both classes of drugs.

Correlating platinum sensitivity to response to PARP inhibition is also being explored in other malignancies, such as breast cancer. Germline *BRCA1/2* mutations are frequent in HER2-negative breast cancers, particularly the TNBC subtype. TNBC's biology, like in ovarian cancer, features high frequency of *TP53* mutations, genomic instabilities and HRD signatures [Paik, S., et al 2012]. These similarities with ovarian cancer led to a number of clinical trials exploring PARP inhibitor's efficacy in HER2-negative breast cancer and TNBC. Olaparib has been recently approved for the treatment of patients with g*BRCA*m HER2-negative metastatic breast cancer who have been treated with chemotherapy (neoadjuvant, adjuvant or metastatic setting). In the OlympiAD trial (NCT02000622), an open-label, multicenter study evaluating olaparib monotherapy efficacy in patients with gBRCAm, HER2-negative metastatic breast cancer, the median PFS was significantly longer in the olaparib group than in the standard-therapy group (7.0 months vs. 4.2 months; HR 0.58; 95% CI, 0.43 to 0.80; $p<0.001$) [Robson, M., et al 2017]. Approximately 30% of the participants in this trial were previously treated with platinum-based chemotherapy.

In SCLC, a Phase 1 trial testing the PARP inhibitor talazoparib in participants with multiple indications (NCT01286987) demonstrated preliminary efficacy in participants with platinum-sensitive cancers. In this cohort of 23 participants, 2 participants (9%) had a PR and 4 participants (17%) had stable disease [de Bono, J., et al 2017]. A Phase 2 trial is currently exploring talazoparib in combination with low-dose temozolomide in platinum-sensitive participants (NCT03672773).

2.2.2.2.1 Rationale for PARP Inhibition in CRC

Similar to ovarian cancer, platinum-based chemotherapy is the standard of care in CRC as the frontline treatment. In numerous clinical studies (eg, PAOLA-1, SOLO, PROfound as monotherapy and in combination with bevacizumab) evaluating the PARP inhibitors' efficacy in ovarian cancer patients, platinum sensitivity was a valuable predictor of response to PARP inhibition. Hence, the patient selection was based on participants whose CRC had not progressed following prior CAPOX or FOLFOX induction with bevacizumab. The oxaliplatin-free interval of ≥6 months in CRC patients is associated with better ORR, PFS, and OS, and often this patient subpopulation responds well to second-line platinum treatment [Venook, A. P. 2015]. Given that the platinum efficacy is the highest in tumors with defects in DNA damage repair pathways, it was not surprising that the ovarian cancer patients with platinum-sensitive tumors responded well to PARP inhibition in the maintenance setting.

2.2.2.2.2 Rationale for Combining Olaparib and Bevacizumab in CRC

There are several data suggesting that olaparib and bevacizumab may be synergistic. One mechanism of bevacizumab resistance is hypoxia induction as a response to vessel regression caused by the anti-angiogenic agent, resulting in an increase of DNA damage and genetic instability [Chan, N., et al 2010]. This observation that tumor cells exposed to chronic hypoxia acquire defects in HR and increased sensitivity to PARP inhibition [Hegan, D. C., et al 2010] is an example of 'contextual synthetic lethality' in which hypoxia-induced repair-deficient tumor cells can be targeted by disrupting backup pathways. Therefore, the premise of combining olaparib and bevacizumab is based on the rationale that direct targeting of PARP by olaparib and indirect sensitization to olaparib by acquisition of HR defects by bevacizumab will be therapeutically beneficial.

The potential synergy between olaparib and anti-VEGF therapy has been recently supported by the results of randomized Phase 2 trial showing that the combination of the antiangiogenic cediranib (30 mg daily po) plus olaparib (200 mg capsules BID) for the treatment of recurrent platinum-sensitive HGSOC compared to olaparib alone prolonged PFS from a median of 8.2 months to 16.5 months (HR 0.50; 95% CI, 0.30 to 0.83, p=0.007) [Liu, J. F., et al 2017]. However, the combination treatment elicited frequent toxicities leading to dose modifications in 77% of participants (compared to 24% in the single-agent arm), with increased occurrence of severe hypertension, fatigue and diarrhea which were previously reported toxicities for cediranib.

A Phase 1 study established the safety and tolerability of olaparib alone and in combination with bevacizumab. Participants with advanced solid tumors received oral olaparib (100 mg, 200 mg, or 400 mg BID) in combination with bevacizumab (5 mg/kg IV Q2W). In the 12 participants treated, the most common AEs related to olaparib were Grade 1/2 nausea and fatigue. No serious drug-related AEs or DLTs were reported. This study demonstrated that the combination of olaparib with bevacizumab was generally well tolerated with no DLTs observed and that it warranted additional investigations [Dean, E., et al 2012]. The PAOLA trial (NCT02477644) is evaluating the combination of olaparib (300 mg BID) and bevacizumab as maintenance therapy after response to first platinum-based therapy of advanced ovarian cancer.

2.2.3 Preclinical and Clinical Studies

The preclinical experience with olaparib is fully described in the IB.

SOLO1

SOLO1 is a randomized, double-blinded, placebo-controlled trial designed to evaluate the efficacy and safety of olaparib (tablets, 300 mg BID) as maintenance monotherapy in newly diagnosed *BRCA*m ovarian cancer patients that are platinum-sensitive. Compared to placebo, olaparib significantly reduced the risk of disease progression. The median total treatment duration in the olaparib arm (106.9 weeks [approximately 25 months], reflecting the 2-year treatment cap) was almost double that of the placebo arm (60.3 weeks [approximately 14 months], reflecting median PFS in the placebo arm); equating to an exposure advantage

for patients in the olaparib arm of approximately 47 weeks (approximately 11 months). At 41 months follow-up, the median PFS for the olaparib-treated cohort was not reached, compared to 13.8 months for the placebo control (HR 0.30; 95% CI, 0.23 to 0.41; $p<0.0001$). At the 3-year timepoint, 60.4% of patients in the olaparib-treated group had no disease progression versus 26.9% in the placebo group. Olaparib as maintenance monotherapy led to a substantial improvement in PFS in patients with newly diagnosed advanced *BRCA* mutant ovarian cancer patients, with a difference in median PFS for olaparib versus placebo of approximately 3 years [Moore, K., et al 2018].

SOLO2

SOLO2 is a randomized, double-blind, placebo-controlled Phase 3 study that evaluated olaparib (300 mg BID) for the maintenance treatment of platinum-sensitive, relapsed ovarian cancer in patients with gBRCAm. Compared to placebo, olaparib significantly improved investigator-assessed median PFS from 5.5 months to 19.1 months (HR 0.30; 95% CI, 0.22 to 0.41; $p<0.0001$). Overall survival data were immature at the data cutoff [Pujade-Lauraine, E., et al 2017].

Study 19

Study 19 is a Phase 2, randomized, double-blind, multicenter study that assessed the efficacy of olaparib monotherapy in the maintenance treatment of patients with platinum-sensitive serous ovarian cancer, following treatment with 2 or more platinum containing regimens [Friedlander, M., et al 2018]. Thirty-two patients (24%) in the study continued receiving olaparib maintenance for over 2 years, and 15 patients (11%) received olaparib maintenance for over 6 years. Long-term treatment with olaparib was demonstrated to be well tolerated, with no new safety signals observed.

OlympiAD

OlympiAD was a randomized, open-label, Phase 3 study that evaluated olaparib monotherapy (300 mg BID) versus TPC chemotherapy for the treatment of metastatic, HER2-, gBRCAm breast cancer in patients who had received no more than 2 previous chemotherapy regimens. Compared to TPC, olaparib significantly improved mPFS as assessed by BICR (7.0 months vs. 4.2 months; HR= 0.58; 95% CI, 0.43 to 0.80; $p<0.001$). Additionally, olaparib significantly improved the median PFS2 (13.2 months vs. 9.3 months; HR: 0.57; 95% CI, 0.40 to 0.83; $p=0.003$). Finally, the ORR for olaparib was 59.9% (95% CI: 52.0 to 67.4; 9% CR) compared to 28.8% (95% CI: 18.3 to 41.3; 1.5% CR) for TPC [Robson, M., et al 2017].

TOPARP

TOPARP was an open-label, multicenter, Phase 2 investigator-initiated single arm study (NCT01682772) of olaparib (400 mg BID) for the treatment of mCRPC in patients who had progressed after 1 or 2 prior treatment regimens. All patients must have received prior docetaxel. The primary endpoint, composite RR, was defined as an OR by RECIST 1.1, a reduction in PSA ≥50%, or a decrease in the number of CTC from ≥5 to <5 per 7.5 mL

blood. The secondary endpoints included safety, tolerability, PFS, and OS. Of 49 evaluable patients, 16 (32.7%) responded to olaparib (95% CI: 20.0 to 47.5), and 12 patients remained on treatment for greater than 6 months. Six of 32 patients with RECIST 1.1-measurable disease had radiological responses (18.8 %) and 11 patients had a biochemical response (≥50% decrease in PSA). Four responses lasted more than 1 year. Next generation sequencing identified homozygous deletions and/or deleterious mutations in DNA repair genes in 16/49 (32.7%) cases, including 7 patients with *BRCA2* mutations and 5 patients with *ATM* alterations. Of the 16 patients with DNA repair mutations, 14 patients (87.5%) responded to olaparib by RR including all 7/7 patients with *BRCA2* loss (4 bi-allelic somatic loss; 3 germline mutations) and 4/5 patients with *ATM* aberrations. Few responses were observed in biomarker-negative patients (2/33 = 6% ORR). Median PFS of the 16 biomarker-positive patients was 9.8 months with a median OS of 13.8 months. In contrast, in the biomarker-negative group, mPFS was 2.7 months and median OS was 7.5 months [Mateo, J., et al 2015].

Study 42

Study 42 was a nonrandomized, open-label, multicenter, Phase 2 study of olaparib in patients with advanced ovarian, breast, pancreatic, or prostate cancers and gBRCAm. The ORRs reported were 26.2% (78/298, 95% CI, 21.3 to 31.6) for the total study population, 31.1% (60/193; 95% CI, 24.6 to 38.1) for ovarian, 12.9% (8/62; 95% CI, 5.7 to 23.9) for breast, 21.7% (5/23; 95% CI, 7.5 to 43.7) for pancreas, and 50.0% (4/8; 95% CI, 15.7 to 84.3) for prostate cancer [Kaufman, B., et al 2015].

In summary, olaparib monotherapy treatment has resulted in favorable ORRs in a variety of HRRm advanced solid tumors including breast, ovarian, and prostate cancers. This broad response suggests that a strong association between HRRm and olaparib response may be tumor-agnostic.

2.2.4 Ongoing Clinical Studies

The Phase 3 PROfound clinical trial (NCT02987543) is evaluating olaparib in participants with mCRPC who progressed on prior nonhormonal treatments. Participants are randomly assigned based on mutations in genes associated with HRD by the Lynparza™ HRR assay to Cohort A (*BRCA1*, *BRCA2*, or *ATM* mutations) or Cohort B (men with a mutation in 1 of the 12 other HRR genes). Participants are randomly assigned (2:1) to receive either olaparib or physician's choice of enzalutamide or abiraterone. The primary endpoint is radiographic PFS, and secondary efficacy endpoints include ORR, time to pain progression, and OS.

The Phase 3 POLO clinical trial (NCT02184195) is evaluating olaparib as monotherapy in participants with metastatic pancreatic cancer with gBRCAm and whose tumors have not progressed on at least 16 weeks of platinum-base chemotherapy. Participants are randomly assigned in a 3:2 ratio to either olaparib (300 mg BID) or placebo. The primary endpoint is PFS, and secondary efficacy endpoints include OS, time from randomization to PFS2, TFST, TSST, TDT, ORR, and DCR.

The Phase 3 SOLO3 clinical trial (NCT02282020) is evaluating olaparib in participants with relapsed gBRCAm ovarian cancer who have progressed at least 6 months after their last platinum treatment and have received at least 2 prior platinum treatments. Participants are randomly assigned to either olaparib 300 mg BID or physician's choice of chemotherapy. The primary endpoint is ORR, and secondary efficacy endpoints include OS, PFS2, time to earliest progression by RECIST 1.1, CA-125, or death, time to deterioration of HRQoL, TFST, TSST, and TDT.

The Phase 3 PAOLA-1 clinical trial (NCT02477644) is evaluating olaparib in maintenance therapy in participants with high-grade serous or endometrioid advanced ovarian cancer (including patients with primary peritoneal and/or fallopian tube cancer) who have responded following first-line platinum-paclitaxel based chemotherapy plus bevacizumab concomitant with chemotherapy and in maintenance (planned for 15 months). Participants must have completed a minimum of 6 and maximum of 9 cycles of first-line platinum-paclitaxel based chemotherapy, including a minimum of 3 cycles of bevacizumab in combination with the 3 last cycles of chemotherapy. Participants were randomly assigned in 2:1 ratio to olaparib 300 mg BID or placebo. The primary endpoint is PFS, and secondary efficacy endpoints include: PFS2, time to earliest progression (by RECIST 1.1) or CA-125, TFST, TSST, OS, effects of olaparib maintenance compared to placebo, and safety/tolerability.

For a summary of ongoing clinical study data and results for olaparib, refer to the IB.

2.3 Benefit/Risk Assessment

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

As olaparib has been found to be well tolerated across various tumor types, a positive benefit/risk profile is anticipated.

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

NOTE: Based on the data from IA1 of safety and efficacy for LYNK-003 (data cutoff 10-MAY-2022), the eDMC recommended stopping the study enrollment for futility based on prespecified futility boundary of IA1. The prespecified final analysis of the study described in the SAP will not be performed.

Selected analyses of safety endpoints will be performed at the end of the study. There will be no further analyses of efficacy and PRO endpoints.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

NOTE: As of Amendment 05, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue as per local institutional guidelines. In addition, PRO assessments will no

longer be performed. Blood for RNA analysis and serum and plasma biomarker analysis will no longer be collected. Updated analyses are described in Section 9. Post-treatment follow-up visits are no longer required except for safety and survival follow-up requirements (refer to Section 8.11.4). The section below is retained for reference.

In male or female participants with unresectable or metastatic CRC who have not progressed following prior FOLFOX + bevacizumab or CAPOX + bevacizumab induction.

The study is considered to have met its primary objective if at least 1 primary hypothesis test is significant.

Objectives	Endpoints
Primary	
• To compare PFS using RECIST 1.1 as assessed by BICR between the following treatments: - Olaparib + Bevacizumab versus a fluoropyrimidine + Bevacizumab - Olaparib versus A fluoropyrimidine + Bevacizumab Hypotheses: **H1** – Olaparib + Bevacizumab is superior to a fluoropyrimidine + Bevacizumab with respect to PFS using RECIST 1.1 as assessed by BICR. **H2** – Olaparib is superior to a fluoropyrimidine + Bevacizumab with respect to PFS using RECIST 1.1 as assessed by BICR.	• PFS: the time from randomization to first documented disease progression (PD) or death due to any cause, whichever occurs first

Objectives	Endpoints
Secondary	
• To compare OS between the following treatments: - Olaparib + Bevacizumab versus a fluropyrimidine + Bevacizumab - Olaparib versus a fluoropyrimidine + Bevacizumab Hypotheses: **H3** – Olaparib + Bevacizumab is superior to a fluoropyrimidine + Bevacizumab with respect to OS. **H4** – Olaparib is superior to a fluorpyrimidine + Bevacizumab with respect to OS.	• OS: the time from randomization to death due to any cause
• To evaluate ORR, and DOR using RECIST 1.1 as assessed by BICR following administration of: - Olaparib + Bevacizumab - Olaparib - Fluoropyrimidine + Bevacizumab	• OR: CR or PR • DOR: the time from first response (CR or PR) to subsequent disease progression or death due to any cause, whichever occurs first
• To evaluate the safety and tolerability of: - Olaparib + Bevacizumab - Olaparib	• AEs • Study intervention discontinuation due to AEs
Tertiary/Exploratory	
• To evaluate progression-free survival 2 (PFS2) by investigator assessment following administration of: - Olaparib + Bevacizumab - Olaparib - 5-FU + Bevacizumab	• PFS2: the time from randomization to second documented disease progression (PD2) or death due to any cause, whichever occurs first

Objectives	Endpoints
• To evaluate DCR using RECIST 1.1 as assessed by BICR following administration of: - Olaparib + Bevacizumab - Olaparib - Fluoropyrimidine + Bevacizumab	• Disease control: stable disease (SD), PR or CR
• To evaluate mean changes from baseline in HRQoL scores and characterize health utilities	• The global health status/QoL scores of the EORTC QLQ-C30 (items 29 and 30) • The multi-item and single-item scales of the EORTC QLQ-C30 • The multi-item and single-item scales of the EORTC QLQ-CR29 • Health utilities as assessed using the EQ-5D 5L
• To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamics activity, and or the mechanism of action of olaparib with or without bevacizumab	• Germline genetic variation
• To evaluate pharmacokinetics of olaparib in the following treatment groups: - Olaparib + Bevacizumab - Olaparib	• Olaparib plasma concentrations (C_{max} and C_{trough})

4 STUDY DESIGN

4.1 Overall Design

NOTE: Based on the data from IA1 of safety and efficacy for LYNK-003 (data cutoff 10-MAY-2022), the eDMC recommended stopping the study enrollment for futility based on prespecified futility boundary of IA1. As a result the study team was unblinded and study enrollment was stopped (as of 18-JUL-2022). The prespecified analysis (IA 2,3,4 and FA) of the study described in the SAP will not be performed. Study participants randomized to one of the two experimental arms (olaparib plus bevacizumab [Arm 1] or olaparib monotherapy [Arm 2]) must discontinue study intervention. No crossover from either experimental arm to

SOC arm (Arm 3A and Arm 3B) within the study is allowed. Participants on SOC have the option to continue receiving study intervention until criteria for discontinuation is met at the discretion of the investigator. Participants on SOC will no longer have tumor response assessments by BICR. However, local tumor imaging assessments should continue as per local institutional guidelines.

This is a Phase 3 randomized, open-label study of olaparib alone or in combination with bevacizumab compared to bevacizumab + 5-FU or capecitabine in participants with unresectable or metastatic CRC that has not progressed following an induction course of CAPOX + bevacizumab or FOLFOX + bevacizumab. Approximately 525 participants will be enrolled and randomized to 1 of 3 intervention arms in a 1:1:1 ratio as follows:

- Arm 1: Olaparib (300 mg BID) + bevacizumab (5 mg/kg IV Q2W)
- Arm 2: Olaparib (300 mg BID)
- Arm 3: Bevacizumab (5 mg/kg IV Q2W) + 5-FU (2400 mg/m^2 IV over 46 to 48 hours Q2W) (Arm 3a) or bevacizumab (7.5mg/kg IV Q3W) + capecitabine (1000mg/m^2 BID for 14 days, then 7 days off, Q3W) (Arm 3b). The 5-FU regimen may include a bolus of 5-FU prior to infusion: 400mg/m^2 IV infusion on Day 1 based on local standards, investigator preference, and participant experience with the bolus during the induction phase.

Participants who begin study treatment with bevacizumab must remain on bevacizumab throughout the study. Participants who begin study treatment with biosimilar bevacizumab must remain on the same biosimilar throughout the study.

Randomization will be stratified based on whether the participant experienced SD versus a PR or CR to prior CAPOX + bevacizumab or FOLFOX + bevacizumab whether they have BRAF and/or Ras mutations versus wild type for both, and whether they received 4 to 6 cycles or >6 cycles of CAPOX + bevacizumab or 6 to 8 cycles or >8 cycles of FOLFOX + bevacizumab.

The study includes a non-binding futility analysis (Interim Analysis 1, IA1) to determine whether there is sufficient evidence to continue the experimental arms. If the PFS HR of either Arm 1 or Arm 2 compared to the control arm is less than the prespecified futility boundary, the study will continue as planned. Additional details regarding interim analyses can be found in Section 9.7.

Efficacy will be evaluated using PFS as the primary endpoint using RECIST 1.1 as determined by BICR. OS, ORR, DOR, and PFS2 will also be assessed. Participants will be evaluated with radiographic imaging to assess response to intervention at regular intervals. On study imaging will be assessed every 8 weeks (56 days ± 7 days) for 12 months and every 12 weeks (84 days ± 7 days) thereafter. After documented PD, participants will receive investigator-choice anticancer therapy and will continue to be followed for disease status until a PFS2 event is recorded.

All imaging obtained on study, including imaging showing investigator-assessed PD, will be submitted to the iCRO for BICR, which will assess the images using RECIST 1.1 for the determination of efficacy (Section 8.2.1). The iCRO will also collect scans taken before and during Screening and must determine the prior scans are of diagnostic quality and confirmation of non-PD by BICR prior to randomization.

Participants may undergo resection of the primary tumor and/or metastasectomy with curative intent after achieving a response to trial therapy that converts previously unresectable disease to resectable disease if deemed eligible per the investigator's discretion in a multidisciplinary approach according to his/her institutional standard and with Sponsor consultation. After surgery, participants may resume the same therapy that they were receiving pre-operatively, when clinically appropriate and after the surgical wound is fully healed.

The first post-operative tumor imaging should be performed at a minimum of (no less than) 4 weeks after surgery and no more than 8 weeks prior to the next treatment cycle (Section 8.2.1.2). If treatment does not resume within 8 weeks after surgery the investigator should consult with the Sponsor.

For participants who undergo surgery with curative intent, a new baseline of tumor burden will be established as described in Section 8.2.1.2.

Adverse event monitoring will be ongoing throughout the trial and AEs will be graded in severity according to the guidelines outlined in the NCI CTCAE v5. Adverse events and SAEs will be reported by the investigator or delegate from allocation through 30 days following cessation of study intervention, or until initiation of reintroduction of investigator-choice of anticancer therapy, whichever is earlier.

Study intervention will continue until documented PD, unacceptable AEs, intercurrent illness that prevents further administration of study intervention, investigator's decision to discontinue the participant, participant withdrawal of consent, pregnancy of the participant, or administrative reasons requiring cessation of study intervention (Section 7.1).

Participants who discontinue study intervention for reasons other than documented PD will have post-treatment follow-up for disease status (including imaging) until PD. All participants will then be followed for disease status until second documented PD, withdrawing consent for study participation, or becoming lost to follow-up. Investigator assessment of disease status as part of routine clinical practice during the reintroduction of investigator-choice of anticancer therapy will be reported to assess for PFS2. No imaging will be collected as part of the study to assess or verify PFS2. Investigators will also provide information regarding all anticancer therapies given during the PFS2 follow-up period.

After second documented PD, each participant will be contacted (eg, by telephone) approximately every 12 weeks (84 ± 7 days) for survival until withdrawal of consent to participate in the study, becoming lost to follow-up, death, or end of the study, whichever occurs first.

CAPOX is a permitted induction regimen. Participants who received CAPOX/bevacizumab as induction, and who are subsequently randomized to the control arm, will receive capecitabine and bevacizumab as maintenance. The rationale for this change is based on the high utilization of CAPOX as an induction regimen in the community, to the point where allowing only FOLFOX/bevacizumab does not represent real-world practice.

FOLFOX and CAPOX are used interchangeably in CRC, both in the adjuvant and the metastatic setting. The NCCN guidelines recommend both of these regimens for first-line therapy as equivalent.

BICR confirmation of non-PD: the inclusion criteria in this study require a response of SD or better to first-line induction. In order to maintain population homogeneity, reduce interobserver variability, and ensure all participants enter the trial with the same clinical status, BICR confirmation of non-PD is required prior to randomization.

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

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

This study will use PFS based on RECIST 1.1 criteria as assessed by BICR as the primary endpoint. Progression-free survival is an acceptable measure of clinical benefit for a late stage study that demonstrates superiority of a new antineoplastic therapy, especially if the magnitude of the effect is large and the therapy has an acceptable risk/benefit profile. The use of BICR and RECIST 1.1 to assess PFS is typically considered acceptable by regulatory authorities. Images will be submitted to an imaging CRO (iCRO) and read by an independent central review blinded to treatment assignment to minimize bias in the response assessments. In addition, the final determination of radiologic progression will be based on the central assessment of progression, rather than a local site investigator/radiology assessment. Expedited verification of radiologic progression as determined by central review will be communicated to the site.

Overall survival will be assessed as a key secondary endpoint, and ORR and DOR will be assessed as additional secondary efficacy endpoints. PFS2 and DCR will be assessed as exploratory efficacy endpoints.

Overall survival has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies and will therefore be assessed as a key secondary endpoint in the study. However, the anticipated duration needed to collect adequate OS data to make an accurate conclusion precludes the use of OS as the primary endpoint in this study.

Objective response rate, DOR, and DCR together are considered acceptable measures of clinical benefit and will be assessed. PFS2 is an additional measure of clinical benefit and is most useful in a disease setting where most participants go on to receive similar subsequent therapies. It is expected for this study that most participants will be restarted on a platinum-based chemotherapy regimen at progression on study therapy. However, all participants will be followed for PFS2 regardless of subsequent therapy.

4.2.1.1.1 RECIST 1.1

RECIST 1.1, which allows a maximum of 5 target lesions in total (2 per organ), will be used by the BICR and the local site when assessing images for efficacy measures and when determining eligibility and for all protocol guidelines related to disease status (eg, discontinuation of study intervention) (Section 8.2.1).

4.2.1.2 Safety Endpoints

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

4.2.1.3 Patient-reported Outcomes

Symptomatic improvement is considered a clinical benefit and accepted by health authorities as additional evidence of the risk-benefit profile of any new study intervention. As part of the analyses for this trial, HRQoL and disease-related symptoms will be investigated among all participants via the following assessment tools:

- EORTC QLQ C30
- EORTC QLQ CR29
- EQ-5D-5L

These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and study intervention tolerability. EQ-5D-5L will also be used to calculate health utilities for health economic models.

4.2.1.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 was developed to assess the QoL of participants with cancer. It has been translated and validated in over 100 languages and used in more than 3000 studies worldwide. It contains 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, and pain), and 6 single symptom items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) [Aaronson, N. K., et al 1993]. It is scored on a 4-point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much).

The EORTC QLQ-C30 instrument also contains 1 global health status/QoL scale that uses 7-point scale scoring with anchors (1=very poor and 7=excellent).

4.2.1.3.2 EORTC QLQ-CR29

The EORTC QLQ-CR29, a supplemental colorectal cancer-specific module, comprises multi-item and single-item measures of colorectal cancer-associated symptoms and impact. It includes 4 scales assessing urinary frequency, fecal seepage, stool consistency, and body image, and single items assessing other common problems following colorectal cancer therapy.

4.2.1.3.3 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome. The EQ-5D-5L will provide data for use in economic models and analyses including developing health utilities or quality-adjusted life-years [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions addressed in this instrument are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates his or her general state of health at the time of the assessment. The EQ-5D-5L will always be completed by participants first, prior to completing any other PRO instruments. This instrument has been used extensively in cancer studies and published results from these studies support its validity and reliability [Pickard, A. S., et al 2007].

4.2.1.4 Pharmacokinetic Endpoints

Collection of olaparib PK samples in a limited number of patients (n = 50 in Arm 1 and n = 50 in Arm 2) is proposed to determine the exposure to olaparib. Exposure data along with other participant factors can be used to evaluate any potential differences compared to established olaparib PK.

4.2.1.5 Planned Exploratory Biomarker Research

PARP inhibitors represent an important class of antitumor agents. However, the mechanism of action of these new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer therapy and other treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/PD biomarkers and generate information that may better guide single-agent and combination therapy. To identify novel biomarkers, biospecimens (ie, blood components, tumor material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations of biomarkers that correlate with response or resistance to treatment may include but are not limited to:

Germline (blood) genetic analyses (eg, SNP analyses, whole exome sequencing, whole genome sequencing)

CCI [redacted]

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. CCI [redacted] irculating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and blood RNA analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment. CCI [redacted]

Proteomics and immunohistochemistry (IHC) using blood or tumor

Tumor and blood samples from this study may undergo proteomic analyses to identify tumor or blood-derived proteins that may also correlate with response. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay (ELISA) measure such proteins in serum. Correlation of expression with response to therapy may identify new approaches for predictive biomarkers in blood, representing a major advance

from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

4.2.1.6 Future Biomedical Research

The Sponsor will conduct future biomedical research on specimens for which consent was provided during this study. This research may include genetic analyses (DNA), gene expression profiling (ribonucleic acid [RNA]), proteomics, metabolomics (serum, plasma), and/or the measurement of other analytes, depending on which specimens are consented for future biomedical research.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main study) and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for future biomedical research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that participants receive the correct dose of the correct drug/vaccine at the correct time. The details of this future biomedical research are presented in Appendix 6.

4.2.2 Rationale for the Use of Comparator

Maintenance therapy with bevacizumab and a fluoropyrimidine is frequently used for patients with unresectable or metastatic CRC who do not progress following an induction course of CAPOX or FOLFOX with or without bevacizumab. Both the ESMO consensus guidelines and NCCN practice guidelines for unresectable or metastatic CRC recommend the consideration of active maintenance with a fluoropyrimidine and bevacizumab for patients with a good response following first-line chemotherapy and who are experiencing unacceptable neurotoxicity due to oxaliplatin . Refer to the approved labeling for bevacizumab, 5-FU, and capecitabine for more information.

4.3 Justification for Dose

4.3.1 Rationale for Olaparib Dosing

The dose of olaparib used in this study is 300 mg BID (tablet formulation), which is the currently approved dose.

4.3.2 Rationale for 5-FU Dosing Regimen

5-FU will be administered at an approved dose and schedule (2400 mg/m^2 IV over 46 to 48 hours Q2W). The 5-FU regimen may include a bolus of 5-FU prior to infusion: 400mg/m^2 IV infusion on Day 1 based on local standards, investigator preference, and participant experience with the bolus during the induction phase. Refer to its approved labeling for more information.

4.3.3 Rationale for Capecitabine Dosing Regimen

Capecitabine will be administered at an approved dose and schedule (1000 mg/m^2 BID 2 weeks on, 1 week off, Q3W). Refer to its approved labeling for more information.

4.3.4 Rationale for Bevacizumab Dosing Regimen

Bevacizumab will be administered at an approved dose and schedule (5 mg/kg IV Q2W with 5-FU or 7.5 mg/kg IV Q3W with capecitabine). Refer to its approved labeling for more information.

4.3.4.1 Rationale for Combination Dosing Regimen of Olaparib + Bevacizumab

In a Phase 1 study to assess the safety and tolerability of the combination of olaparib with bevacizumab, 12 participants with advanced solid tumors received increasing doses of continuous oral olaparib (100, 200, and 400 mg BID) in combination with bevacizumab (10 mg/kg Q2W) [Dean, E., et al 2012]. No SAEs related to treatment or DLTs were reported. The authors concluded the combination of olaparib 400 mg BID (capsule formulation) with bevacizumab 10 mg/kg Q2W was generally well tolerated with no DLTs and could be considered for future clinical investigation. This study will treat participants with 300 mg olaparib BID, the current approved dose for olaparib, and 5 mg/kg of bevacizumab Q2W as this is the standard recommended dose in combination with FOLFOX for unresectable or metastatic CRC. It is expected that combination treatment at these dose levels should be safe as they are lower doses than those previously tested.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant (or their legally acceptable representative) provides documented informed consent. The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator). For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last participant, whichever comes last. If the study includes countries in the European Economic Area (EEA), the local start of the study in the EAA is defined as First Site Ready (FSR) in any Member State.

4.4.1 Clinical Criteria for Early Study Termination

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

5 STUDY POPULATION

As of Amendment 05, study enrollment is being stopped for futility. Study participants randomized to one of the two experimental arms (olaparib plus bevacizumab [Arm 1] or olaparib monotherapy [Arm 2]) must discontinue study intervention. No crossover from either experimental arm to SOC arm (Arm 3A and Arm 3B) within the study is allowed. Participants on SOC have the option to continue receiving study intervention until criteria for discontinuation is met at the discretion of the investigator.

As stated in the Code of Conduct for Clinical Trials (Appendix 1, Section 10.1.1) this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Male/Female participants of at least 18 years of age with unresectable or metastatic CRC who have not progressed following prior CAPOX + bevacizumab or FOLFOX + bevacizumab will be enrolled in this study.

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

5.1 Inclusion Criteria

A participant is eligible for inclusion in the study if the participant:

Type of Participant and Disease Characteristics

1. Has a histologically-confirmed metastatic or unresectable (Stage IV as defined by AJCC eighth edition) colorectal adenocarcinoma (NCCN 2018).

2. Has not progressed (ie, achieved a SD, PR, or CR) after a first-line induction course of at least 6 cycles of FOLFOX + bevacizumab or 4 cycles of CAPOX + bevacizumab as first-line therapy.

    - Participants must not have received an investigational agent during their induction course.

    - Determination of best overall response (SD/PR/CR) will be made by the investigator.

    - Non-PD will be verified by BICR prior to randomization based on the images submitted to iCRO as described in inclusion criterion 4.

    - “First-line therapy” is defined as the first systemic chemotherapy regimen given for the diagnosis of unresectable or metastatic CRC. Participants may have received prior adjuvant/neoadjuvant chemotherapy for CRC as long as it was completed at least 6

months prior to initiation of first-line CAPOX + bevacizumab or FOLFOX + bevacizumab induction treatment.

3. Has experienced unacceptable toxicity to oxaliplatin that, in the opinion of the treating physician, requires/required the discontinuation of oxaliplatin. Note: As an example, unacceptable toxicity may include (but is not limited to) severe or prolonged neurotoxicity.

    - Participants must be randomized within a minimum of 2 weeks and a maximum of 6 weeks after their last dose of CAPOX + bevacizumab or FOLFOX + bevacizumab (last dose is the day of the last infusion that contained oxaliplatin).

4. Has provided to the iCRO 1 set of baseline radiographic images taken before or during the CAPOX + bevacizumab or FOLFOX + bevacizumab induction period and at least 42 days prior to the imaging performed during Screening. Tumor imaging at Screening must be performed within 28 days prior to the date of randomization.

5. Has an ECOG performance status of 0 to 1 within 10 days prior to randomization.

6. Has the ability to swallow and retain oral medication and not have any clinically significant gastrointestinal abnormalities that might alter absorption.

7. Has adequate organ function, as detailed in Table 1; all Screening laboratory tests should be performed within 10 days of randomization.

Table 1 Adequate Organ Function Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100 000/µL
Hemoglobin	≥10.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Estimated creatinine clearance using the Cockcroft-Gault equation[b]	≥51 mL/min
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for participants with liver metastases)
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

Abbreviations: ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); ULN=upper limit of normal.

[a] Criteria must be met without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Estimated creatinine clearance using Cockcroft-Gault:

$$\frac{(140\text{-age [years]} \times \text{weight [kg]})}{\text{Serum creatinine (mg/dL)} \times 72} \quad (\times F)^*$$

*where F = 0.85 for females and F = 1 for males

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

8. Has provided a tumor tissue sample to the central lab for biomarker analysis.

    - If a sample is not available at Screening, a new tissue sample is required to be collected during Screening.

Demographics

9. Is male or female, at least 18 years of age, at the time of providing documented informed consent.

Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

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

    - Olaparib: 90 days
    - 5-FU: 90 days
    - Capecitabine: 90 days
    - Leucovorin/levoleucovorin: 90 days.
    - Bevacizumab: none.

    • Refrain from donating sperm

    PLUS either:

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

    OR

    • Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 5]) as detailed below:

    - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.

    • Male participants must also agree to use male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

Female Participants

11. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

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

    • Is not a WOCBP

    OR

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

  - Olaparib: 180 days
  - 5-FU: 180 days
  - Capecitabine: 180 days
  - Leucovorin/levoleucovorin: 180 days.
  - Bevacizumab: 120 days.

- The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 72 hours (serum) or 24 hours (urine) before the first dose of study intervention.

- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Appendix 2.

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

Informed Consent

12. The participant (or legally acceptable representative if applicable) provides documented informed consent for the study. The participant may also provide consent for future biomedical research. However, the participant may participate in the main study without participating in future biomedical research.

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Medical Conditions

1. Has known hypersensitivity to the components and/or excipients in bevacizumab, 5-FU, capecitabine, or olaparib.

2. Has known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable (ie, without evidence of progression for at least 28 days by repeat imaging - note that the repeat imaging should be performed during study Screening), clinically stable and without requirement of steroid intervention for at least 14 days prior to first dose of study intervention.

3. Has an active infection requiring systemic therapy.

4. Has a known history of HIV infection. No HIV testing is required unless mandated by local health authority.

5. Has a known history of or is positive for hepatitis B (HBsAg reactive) or hepatitis C (HCV RNA [qualitative] is detected).

   Note: No testing for hepatitis B and hepatitis C is required unless mandated by local health authority.

6. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.

7. Has MDS/AML or with features suggestive of MDS/AML.

8. Has hemoptysis or hematemesis within 28 days prior to randomization.

9. Has evidence of bleeding diathesis or significant coagulopathy (in the absence of anticoagulation).

10. Has clinically significant bleeding within 28 days prior to randomization.

11. Is considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, extensive interstitial bilateral lung disease on HRCT scan or any psychiatric disorder that prohibits obtaining informed consent.

12. Has 1 or more conditions that, in the opinion of the treating physician, make the participant ineligible for treatment with bevacizumab. These conditions may include:

    - Uncontrolled hypertension (SBP >150 mm Hg or DBP >100 mm Hg) or a history of hypertensive crisis or hypertensive encephalopathy
    - Arterial thromboembolic events (eg, myocardial infarction, cerebral infarction)
    - History of nephrotic syndrome or moderate proteinuria
    - History of gastrointestinal perforation
    - History of non-gastrointestinal fistula formation
    - History of RPLS

Prior/Concomitant Therapy

13. Has received prior systemic anticancer therapy (other than CAPOX + bevacizumab or FOLFOX + bevacizumab induction) including investigational agents within 28 days prior to randomization.

    Note: Participants must have recovered from all AEs due to previous therapies to ≤Grade 1 or baseline. Participants with persistent alopecia or Grade ≤3 neuropathy are eligible.

14. Has received prior therapy with olaparib or with any other PARP inhibitor.

15. Is currently receiving either strong (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil) inhibitors of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period prior to randomization is 2 weeks.

16. Is currently receiving either strong (phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine and St John's Wort) or moderate (eg, bosentan, efavirenz, modafinil) inducers of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period prior to randomization is 5 weeks for phenobarbital and 3 weeks for other agents.

Note: A current list of strong/moderate inhibitors or inducers of CYP3A4 can be found at the following website:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

17. Has undergone major surgery within 2 weeks of randomization or has not recovered adequately from toxicities and/or complications from any major surgery prior to randomization.

18. Has received prior radiotherapy within 2 weeks of start of study intervention. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease.

Prior/Concurrent Clinical Study Experience

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

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

Diagnostic Assessments

20. Has a known additional malignancy that is progressing or has required active therapy within the past 5 years.

    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded.

21. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the participant's participation for the full duration of the study, or is not in the best interest of the participant to participate, in the opinion of the treating investigator.

22. Has clinically significant (eg, active) cardiovascular disease, including:

    - Myocardial infarction or unstable angina within ≤6 months of randomization
    - CHF ≥Grade 2 (as per New York Heart Association)
    - The presence of uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >450 ms on 2 or more time points within

a 24 hour period, electrolyte disturbances, etc), or patients with congenital long QT syndrome

- Peripheral vascular disease ≥Grade 3 (eg, symptomatic and interfering with activities of daily living requiring repair or revision)

23. Has known dihydropyrimidine dehydrogenase (DPD) deficiency

Other Exclusions

24. This criterion was removed as a result of updates to the pregnancy and contraception language in Inclusion Criteria #10 and #11.

25. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines are allowed.

    Refer to Section 6.5.2 for information on COVID-19 vaccines.

Refer to Appendix 7 for country-specific requirements.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants receiving olaparib should avoid grapefruit, grapefruit juice, Seville oranges, Seville orange juice, and St. John's Wort (tablet or tea) while receiving study intervention. Otherwise, participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.3.2 Driving or Operating Machinery

Because the AEs related to olaparib may include asthenia, fatigue and dizziness, participants receiving olaparib should be advised to use caution while driving or operating machinery if these symptoms occur.

5.3.3 Pregnancy

If a participant inadvertently becomes pregnant during the study, the participant will be immediately discontinued from study intervention. The site will contact the participant at least monthly and document the participant's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is an SAE (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male participant impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 8.4.5.

5.4 Screen Failures

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

5.5 Participant Replacement Strategy

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

6 STUDY INTERVENTION

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

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

6.1 Study Intervention(s) Administered

As of Amendment 05, study enrollment is being stopped for futility. Study participants randomized to one of the two experimental arms (olaparib plus bevacizumab [Arm 1] or olaparib monotherapy [Arm 2]) must discontinue study intervention. No crossover from either experimental arm to SOC arm (Arm 3A and Arm 3B) within the study is allowed. Participants on SOC have the option to continue receiving study intervention until criteria for discontinuation is met at the discretion of the investigator.

The study interventions to be used in this study are outlined in Table 2.

Country-specific requirements are noted in Appendix 7.

Table 2 Study Interventions

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 1	Experimental	Olaparib	Drug	Tablet	150 mg	300 mg	Oral	Twice Daily	Test Product	IMP	Centrally by the Sponsor, or locally by the trial site, subsidiary, or designee
Arm 1	Experimental	Bevacizumab	Drug	Vial	Variable	5 mg/kg	IV Infusion	Q2W	Test Product	IMP	Centrally by the Sponsor, or locally by the trial site, subsidiary, or designee
Arm 2	Experimental	Olaparib	Drug	Tablet	150 mg	300 mg	Oral	Twice Daily	Test Product	IMP	Centrally by the Sponsor, or locally by the trial site, subsidiary, or designee
Arm 3a/3b	Active Comparator	Bevacizumab	Drug	Vial	Variable	5 mg/kg or 7.5 mg/kg	IV Infusion	Q2W or Q3W	Comparator	IMP	Centrally by the Sponsor, or locally by the trial site, subsidiary, or designee

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
Arm 3a	Active Comparator	5-FU	Drug	Vial	Variable	2400 mg/m^2 over 46 to 48 hours	IV Infusion	Q2W	Comparator	IMP	Centrally by the Sponsor, or locally by the trial site, subsidiary, or designee
Arm 3b	Active Comparator	Capecitabine	Drug	Tablet	Variable	1000mg/m^2	Oral	BID 14 days on, 7 days off Q3W	Comparator	IMP	Centrally by the Sponsor, or locally by the trial site, subsidiary, or designee
Arm 3a	Active Comparator	Leucovorin/ levoleucovorin	Drug	Vial	Variable	400 mg/m^2 (leucovorin) or 200 mg/m^2 (levoleucovorin)	IV Infusion	Q2W	Comparator	IMP	Centrally by the Sponsor, or locally by the trial site, subsidiary, or designee

5-FU=fluorouracil; BID=twice daily; EEA=European Economic Area; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; Q2W=every 2 weeks; Q3W=every 3 weeks.

The classification of IMP and NIMP/AxMP in this table is based on guidance issued by the European Commission and applies to countries in the EEA. Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed.

Note: 100 mg olaparib tablets will also be made available and are to be used only in the event of dose modifications.

Participants who received CAPOX will receive a dose of 7.5 mg/kg of bevacizumab (Arm 3b), while those who received FOLFOX will receive 5 mg/kg of bevacizumab (Arm 3a).

5-FU regimen may include a bolus of 5-FU prior to infusion: 400mg/m^2 IV infusion on Day 1 based on local standards, investigator preference, and participant experience with the bolus during the induction phase

Participants who begin study treatment with bevacizumab must remain on bevacizumab throughout the study. Participants who begin study treatment with biosimilar bevacizumab must remain on the same biosimilar throughout the study.

Leucovorin/levoleucovorin may be added to Arm 3a per investigator's discretion.

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (eg, not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.9 for details regarding administration of the study intervention.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Bevacizumab, leucovorin, and 5-FU should be prepared per local and institutional guidelines according to the approved product labels. Refer to the Pharmacy Manual for more details regarding olaparib administration.

Capecitabine will be given at 1000 mg/m^2 po BID for Days 1-14 only of a 21-day cycle.

As capecitabine is an oral drug available in fixed doses, the dose administered may not exactly match the calculated dose. Determination of the rounding of capecitabine doses for administration should be made according to local institutional practices, with documentation of both the calculated and administered dose.

Capecitabine should be prepared and administered per instructions in the package insert. Capecitabine will be administered po based on instructions provided by the investigator. Per package insert, it is recommended that capecitabine be administered with food.

The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

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

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

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

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

investigator is responsible for ensuring that a local discard/destruction procedure is documented.

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

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

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 3 study intervention arms. Participants will be assigned randomly in a 1:1:1 ratio to Arm 1 (olaparib + bevacizumab), Arm 2 (olaparib monotherapy), or Arm 3a/Arm 3b (bevacizumab + fluoropyrimidine [5-FU or capecitabine]).

6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factors:

1. SD versus PR/CR to prior FOLFOX + bevacizumab or CAPOX + bevacizumab induction
2. $BRAF_{mut}$ and/or Ras_{mut} versus $BRAF_{wt}$ + Ras_{wt}
3. Number of induction cycles
    - For FOLFOX-based induction, 6 to 8 cycles versus >8 cycles
    - For CAPOX-based induction, 4 to 6 cycles versus >6 cycles

    Note: Stratification is based on the number of cycles of FOLFOX or CAPOX with or without bevacizumab.

6.3.3 Blinding

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

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan for ≥4 weeks (28 days) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Participants should be given clear instructions on how and when to take their study intervention. Participants will self-administer olaparib except when a clinic visit is scheduled. Study site staff will make tablet counts at regular intervals during treatment. After the tablet count has been performed, the remaining tablets will not be returned to the participant but will be retained by the investigative site until reconciliation is completed by the study monitor. Olaparib compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. All participants must return their bottle(s) of olaparib at the appropriate scheduled visit, when a new bottle will be dispensed. Participants will be instructed to notify study site personnel of missed doses.

6.5 Concomitant Therapy

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. Concomitant medications administered >30 days after the last dose of study intervention should be recorded for SAEs and ECIs as defined in Section 8.4.7.

Based on limited in vitro data, olaparib may increase the exposure to substrates of CYP3A4, organic-anion-transporting polypeptide (OATP)1B1, organic cation transporter (OCT)1/2/3, and multidrug and toxic compound extrusion (MATE)1/2 and reduce exposure to substrates of CYP2B6. Caution should be observed if substrates of these isoenzymes or transporter proteins are co-administered. A current list of substrates can be found at the following website:

https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

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

6.5.1 Leucovorin/Levoleucovorin

Leucovorin (calcium folinate/folinic acid/calcium leucovorin, 400 mg/m^2, IV infusion Q2W) or levoleucovorin (200 mg/m^2, IV infusion, Q2W) may be used in Arm 3a with 5-FU at the investigator's discretion, and in accordance with local standards.

6.5.2 Prohibited Concomitant Medications

Medications or vaccinations specifically prohibited in the exclusion criteria (Section 5.2) are not allowed during Screening and during the study intervention phase of the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any

questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

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

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol.

- Investigational agents other than olaparib.

- Radiation therapy for disease control.

  Note: Radiation therapy to symptomatic lesions or to the brain may be allowed following Sponsor consultation.

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

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

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

- Anticancer hormonal therapy (eg, androgen deprivation, androgen receptor blockade, anti-estrogens)

  Note: Hormonal replacement therapy is allowed.

- Strong and moderate inducers or inhibitors of CYP3A4 that cannot be discontinued for the duration of the study.

  Note: a current list of strong/moderate inducers/inhibitors of CYP3A4 can be found at the following website:

  https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers

  Note: Exceptions are outlined in Section 6.6.1.3.4.

Participants who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from treatment but continue in trial for assessment of disease status and survival.

There are no prohibited therapies during the post-treatment follow-up phase.

For participants being treated with capecitabine, bevacizumab, leucovorin or 5-FU, refer to their approved labeling for additional prohibited therapies.

6.5.3 Rescue Medications and Supportive Care

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

6.6 Dose Modification Guidelines

NCI CTCAE v5.0 must be used to grade the severity of AEs. If appropriate, the investigator may attribute each toxicity event to olaparib, bevacizumab, capecitabine or 5-FU alone, or to any combination of these agents, and follow the dose modification guidelines accordingly below. If a participant experiences several toxicities and there are conflicting recommendations, following the most conservative dose adjustment is recommended (dose reduction appropriate for the most severe toxicity).

Reduction or holding of 1 agent and not the other agents is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study drugs. If, in the opinion of the investigator, the toxicity is related to a combination of agents, both drugs should be held according to recommended dose modifications.

If toxicity does not revolve to Grade 0 or 1 within 12 weeks after the last dose, study treatment should be discontinued after consultation with the Sponsor. With investigator and Sponsor agreement, participants with a laboratory AE still at Grade 2 after 12 weeks may continue treatment in the study if the AE is asymptomatic and controlled. After any Grade 4 drug-related AE, participants should not restart study treatment without consultation with the Sponsor.

6.6.1 Olaparib Dosing Modifications

Any toxicity observed during the course of the study that the investigator believes attributable to olaparib could be managed by interruption of olaparib treatment or dose reduction. Repeated interruptions, not exceeding 4 weeks (28 days) duration, are allowed as required. If the interruption is any longer, it must be agreed to by the Sponsor.

The dose of olaparib can be reduced to 250 mg BID initially and then to 200 mg BID as needed (except in specific instances as described in Sections 6.6.1.1 through 6.6.1.3). If the 200 mg BID dose is not tolerable, no further dose reduction is allowed, and study intervention should be discontinued. Once the dose has been reduced, escalation is not permitted (except following concomitant treatment with CYP3A4 inhibitors – see Section 6.6.1.3.4).

All dose reductions and interruptions (including any missed doses) and the reason(s) for the dose interruption/reduction should be captured on the appropriate eCRF.

In Arm 1, if olaparib is discontinued due to toxicity the participant must discontinue study treatment and enter the follow-up phase of the study. If bevacizumab is discontinued due to toxicity, the participant may remain on study treatment receiving olaparib alone.

In Arm 3a/Arm 3b, if 5-FU or capecitabine is discontinued due to toxicity the participant must discontinue study treatment and enter the follow-up phase of the study. If bevacizumab is discontinued due to toxicity, the participant may remain on study treatment receiving 5-FU or capecitabine alone.

6.6.1.1 Management of Hematological Toxicities

Dose modification guidelines and supportive care guidelines for hematological toxicities that are attributed to olaparib by the investigator are in Table 3 and Table 4.

Table 3 Management of Anemia Attributed to Olaparib

Toxicity	NCI CTCAE Grade	Action Taken
Hemoglobin (Hb)	Grade 2 (<10 but ≥8 g/dL)	**First Occurrence:** Give appropriate supportive treatment and investigate causality. • Investigator judgment to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for a maximum of 4 weeks (28 days). Treatment can be restarted if Hb has recovered to >9 g/dL. **Subsequent Recurrence:** • Hb <10 but ≥9 g/dL: Investigator judgment to either continue olaparib with supportive treatment (eg, transfusion) or interrupt olaparib dosing for maximum of 4 weeks (28 days). Upon recovery, a dose reduction to 250 mg BID as a first step or 200 mg BID as a second step may be considered. • Hb <9 but ≥8 g/dL: Interrupt olaparib for a maximum of 4 weeks (28 days) until Hb improves to >9 g/dL. Upon recovery, reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional decreases in Hb occur.
	Grade 3 (<8 g/dL)	Give appropriate supportive treatment (eg, transfusion) and investigate causality. • Interrupt olaparib, for a maximum of 4 weeks (28 days), until Hb improves to ≥9 g/dL. • Upon recovery, reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional decreases in Hb occur.
Abbreviations: BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; Hb = hemoglobin; NCI = National Cancer Institute. Note: Common treatable causes of anemia (eg, iron, vitamin B12 or folate deficiencies and hypothyroidism) should be investigated and appropriately managed. In some cases, management of anemia may require blood transfusions. The management of prolonged hematological toxicities is detailed in Section 6.6.1.2.		

Table 4 Management of Neutropenia, Leukopenia, and Thrombocytopenia Attributed to Olaparib

Toxicity	NCI CTCAE Grade	Action Taken
Neutropenia, Leukopenia, or Thrombocytopenia	Grades 1 or 2	Investigator judgment to either continue olaparib or interrupt dosing for a maximum of 4 weeks (28 days). Give appropriate supportive treatment and investigate causality.
	Grades 3 or 4	• Interrupt olaparib, for a maximum of 4 weeks (28 days), until event recovers to ≤Grade 1. • Repeated incidence: reduce the dose of olaparib to 250 mg BID. A second dose reduction to 200 mg BID may be considered if additional Grade 3 or 4 events occur.

Abbreviations: AE = adverse event; BID = twice daily; CTCAE = Common Terminology Criteria for Adverse Events; G-CSF = granulocyte colony-stimulating factor; NCI = National Cancer Institute.

- AEs of neutropenia and leukopenia should be managed as deemed appropriate by the investigator with close follow-up and interruption of study intervention if CTCAE Grade 3 or worse neutropenia occurs.
- Primary prophylaxis with G-CSF is not recommended; however, if a participant develops febrile neutropenia, study intervention should be stopped and appropriate management including G-CSF should be given according to local hospital guidelines. Please note that G-CSF should not be used within at least 24 hours (7 days for PEGylated G-CSF) of the last dose of study intervention unless absolutely necessary.
- Platelet transfusions, if indicated, should be done according to local hospital guidelines.
- The management of prolonged hematological toxicities is detailed in Section 6.6.1.2.

6.6.1.2 Management of Prolonged Hematological Toxicities

If a participant develops prolonged hematological toxicity such as:

- ≥2 week interruption/delay in study intervention due to Grade 3 or worse anemia and/or the development of blood transfusion dependence
- ≥2 week interruption/delay in study intervention due to Grade 3 or worse neutropenia (absolute neutrophil count <1 × 109/L)
- ≥2 week interruption/delay in study intervention due to Grade 3 or worse thrombocytopenia and/or development of platelet transfusion dependence (platelets <50 × 109/L)

Differential blood count, including reticulocytes and peripheral blood smear, should be checked weekly. If any blood parameters remain clinically abnormal after the dosing of olaparib has been interrupted for ≥4 weeks (≥28 days), the participant should be referred to a hematologist for further investigations. Bone marrow analysis and/or blood cytogenetic analysis should be considered, according to local regulation and/or standard institutional hematological practice. Study intervention should be discontinued if blood counts do not recover to NCI CTCAE v5 Grade 1 or better within 4 weeks (28 days) of dose interruption.

Development of confirmed MDS or other clonal blood disorder should be reported as an SAE and full reports must be provided by the investigator to the Sponsor as outlined in Section 8.4.4. Olaparib intervention should be discontinued for confirmed MDS and/or AML (Section 7.1).

6.6.1.3 Management of Non-hematologic Toxicity

Repeated dose interruptions, not exceeding 4 weeks (28 days) duration, are allowed as required. If toxicity reoccurs following rechallenge with study intervention, and where further dose interruptions are considered inadequate for management of toxicity, either a dose reduction should be considered (Section 6.6.1) or the participant must permanently discontinue study intervention.

Treatment must be interrupted if any Grade 3 or 4 AE occurs that the investigator considers to be related to administration of olaparib.

6.6.1.3.1 Management of New or Worsening Pulmonary Symptoms

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormalities occur in the absence of a clear diagnosis, an interruption in study intervention dosing is recommended and further diagnostic workup (including a high-resolution CT scan) should be performed to exclude pneumonitis.

Following investigation, if no evidence of abnormality is observed on CT imaging and symptoms resolve, then study intervention can be restarted, if deemed appropriate by the investigator. If significant pulmonary abnormalities are identified, these must be discussed with the Sponsor.

6.6.1.3.2 Management of Nausea and Vomiting

Events of nausea and vomiting are known to be associated with olaparib intervention. These events are generally mild to moderate (Grade 1 or 2) in severity, intermittent, and manageable on continued treatment. The first onset generally occurs in the first month of intervention for nausea and within the first 6 months of intervention for vomiting. For nausea, the incidence generally plateaus at around 9 months, and for vomiting at around 6 to 7 months.

No routine prophylactic anti-emetic treatment is required at the start of study intervention; however, participants should receive appropriate anti-emetic treatment at the first onset of nausea or vomiting and as required thereafter, in accordance with local regulations or institutional guidelines. Alternatively, olaparib tablets can be taken with a light meal/snack (ie, 2 pieces of toast or a couple of biscuits).

As per international guidance on anti-emetic use in cancer patients, generally a single agent anti-emetic should be considered (eg, dopamine receptor antagonist, antihistamines, or dexamethasone).

6.6.1.3.3 Management of Renal Impairment

If after study entry and/or while still on study therapy, a participant's estimated CrCl falls below the threshold for study inclusion (≥50 mL/min), retesting should be performed promptly.

A dose reduction is recommended for participants who develop moderate renal impairment (calculated CrCl between 31 and 50 mL/min as calculated by Cockcroft-Gault equation) for any reason during the course of the study (Table 5).

Table 5 Dose Reduction of Olaparib to Manage Moderate Renal Impairment

Initial Dose	**Moderate Renal Impairment[a]**
300 mg BID	200 mg BID
Abbreviation: BID = twice daily. a. Creatinine clearance of 31 to 50 mL/min as calculated by Cockcroft-Gault equation.	

Because the CrCl determination is only an estimate of renal function, in instances where the CrCl falls to between 31 and 50 mL/min, the investigator should use his or her discretion in determining whether a dose change or discontinuation of therapy is warranted.

Olaparib has not been studied in participants with severe renal impairment (CrCl ≤30 mL/min) or end-stage renal disease; if participants develop severe impairment or end-stage disease, it is recommended that olaparib be discontinued.

6.6.1.3.4 Dose Reductions for Concurrent CYP3A4 Inhibitor Use

Strong or moderate CYP3A inhibitors should not be taken with olaparib. If there is no suitable alternative concomitant medication, then the dose of olaparib should be reduced for the period of concomitant administration as described in Table 6. After the washout of the inhibitor is complete (Section 5.2), the olaparib dose can be re-escalated. Note: After washout of the CYP3A4 drug, dosing of olaparib can immediately resume at the normal dosing level – no step-wise titration needed). The dose reduction of olaparib should be recorded in the eCRF with the reason documented as concomitant CYP3A4 inhibitor use.

Table 6 Dose Reduction of Olaparib with a Strong or Moderate CYP3A Inhibitor

Initial Dose	**Strong CYP3A Inhibitor**	**Moderate CYP3A Inhibitor**
300 mg BID	100 mg BID	150 mg BID
Abbreviations: BID = twice daily; CYP = cytochrome P450.		

6.6.1.4 Interruptions for Non-toxicity Related Events

Olaparib dose interruptions for conditions other than toxicity resolution should be kept as short as possible. If a participant cannot restart study treatment within 4 weeks for resolution of intercurrent conditions not related to disease progression or toxicity, the case should be discussed with the Sponsor's clinical director. All dose reductions and interruptions (including any missed doses), and the reasons for the reductions/interruptions, per drug accountability and participant feedback reconciliation, are to be recorded in the eCRF. Study treatment should be stopped at least 3 days prior to planned surgery. After surgery, study treatment can be restarted when the wound has healed. Study treatment should be discontinued for a minimum of 3 days before a participant undergoes radiation treatment. Study treatment should be restarted within 4 weeks as long as any bone marrow toxicity has recovered.

6.6.2 Bevacizumab, Capecitabine, Leucovorin, and 5-FU Dose Modifications

Bevacizumab, capecitabine, leucovorin, and 5-FU doses may be modified in accordance with their approved labeling and local practice guidelines.

6.7 Intervention After the End of the Study

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

6.8 Clinical Supplies Disclosure

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

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.3.

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

performed at study intervention discontinuation are provided in Section 8.1.10 and Section 8.11.3.

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Documented radiographic disease progression outlined in Section 8.2.1.

  Note: As of Amendment 05, participants remaining on SOC (Arm 3A and Arm 3B) should be discontinued from study intervention based on investigator assessment of radiographic disease progression.
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy, that requires treatment.
- Bone marrow findings consistent with MDS or AML.
- The participant interrupts study intervention administration for more than 28 consecutive days without Sponsor consultation.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive pregnancy test.

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

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from future biomedical research, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly

fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

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

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician .

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

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

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The maximum amount of blood collected from each participant over the duration of the study can be found in the Laboratory Manual. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

8.1.1.1 General Informed Consent

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

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

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

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

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

8.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

8.1.2 Inclusion/Exclusion Criteria

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

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after the participant provides documented informed consent. At the time of intervention randomization, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Demographics and Medical History

Detailed participant demographics and medical history will be obtained by the investigator or qualified designee. The medical history will collect all active conditions and any condition diagnosed within the prior 10 years that the investigator considers to be clinically significant. In addition, significant and potentially relevant conditions that occurred >10 years previously should be collected. Details regarding the disease for which the participant has enrolled in this study will be recorded separately and not listed as medical history.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before first dose of study medication. Additionally, all prior chemotherapies administered (including neoadjuvant, adjuvant and first-line induction), their duration and reason for discontinuation (ie, disease progression, discontinuation of therapy for reason other than progression, completion of planned program without progression and toxicity) will be documented.

8.1.5.2 Induction History

The investigator or qualified designee will review and record the participant's prior induction history with CAPOX + bevacizumab or FOLFOX + bevacizumab including the participant's history of response while on or after completing the CAPOX + bevacizumab or FOLFOX + bevacizumab regimen.

8.1.5.3 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 Submitting Prior Radiographic Images

The investigator must review all prestudy (induction) imaging per RECIST 1.1 and confirm that the participant has not progressed (ie, SD, PR or CR) prior to entering the study.

The site must submit to the iCRO 1 set of radiographic images including chest/abdomen/pelvis taken before or during the CAPOX + bevacizumab or FOLFOX + bevacizumab induction period and at least 42 days prior to the imaging taken during Screening. The site must receive the iCRO's determination that the images are of diagnostic quality and confirmation of non-PD by BICR prior to randomization.

8.1.7 Assignment of Screening Number

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

Any participant who is screened multiple times will retain the original Screening number assigned at the initial Screening visit.

Specific details on the Screening visit requirements (Screening/rescreening) are provided in Section 8.11.1.

8.1.8 Assignment of Treatment/Randomization Number

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

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

8.1.9 Study Intervention Administration

Chemotherapy will be administered according to the specifications within the Pharmacy Manual.

Olaparib will be administered by the investigator and/or study staff on Day 1 of each cycle according to the specifications within the Pharmacy Manual. Participants will then self-administer olaparib orally for the remainder of the study intervention period.

Study intervention can be administered within ± 3 days of the targeted Day 1 for each cycle, except Cycle 1, when intervention can only be administered within + 3 days of the targeted Day 1.

8.1.9.1 Timing of Dose Administration

8.1.9.1.1 Olaparib

Olaparib will be administered at a dose of 300 mg po BID.

Olaparib tablets should be taken with one glass of water twice a day at the same time each day, approximately 12 hours (±2h) between doses. The tablets should be swallowed whole and not chewed, crushed, dissolved, or divided. Olaparib tablets can be taken with or without food. If vomiting occurs shortly after olaparib tablets are swallowed, the dose should only be replaced if all the intact tablets can be seen and counted. Should any participant enrolled on the study miss a scheduled dose for any reason (eg, because of forgetting to take the tablets or vomiting), the participant will be allowed to take the scheduled dose up to a maximum of 2 hours after that scheduled dose time. If it is more than 2 hours after the scheduled dose time, the missed dose is not to be taken, and the participant should take their allotted dose at the next scheduled time.

Participants must be instructed that if they miss a dose or vomit at any time after taking a dose, they should take their next dose at its scheduled time. The site will validate compliance with study intervention (including missed or vomited doses) at each site visit according to its standard operating procedure. If doses are missed or vomited, this must be indicated in the source documents and CRFs.

8.1.9.1.2 Bevacizumab and 5-FU

Bevacizumab will be administered at a dose of 5 mg/kg IV Q2W. 5-FU will be administered at a dose of 2400 mg/m^2 IV over 46 to 48 hours Q2W. The 5-FU regimen may include a bolus of 5-FU prior to infusion: 400mg/m^2 IV infusion on Day 1 based on local standards, investigator preference, and participant experience with the bolus during the induction phase. Bevacizumab and 5-FU will be administered after all predose assessments and procedures have been completed. The participant should self-administer olaparib at home prior to the infusion of bevacizumab. Detailed information regarding the dose regimen/ administration/modification is in the approved labeling for bevacizumab and 5-FU.

8.1.9.1.3 Capecitabine

Capecitabine will be administered at a dose of 1000 mg/m^2 BID 14 days on, 7 days off, Q3W. Detailed information regarding the dose regimen/administration/modification is in the approved labeling for capecitabine.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the end of treatment should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 and Section 8.11.4.

8.1.10.1 Withdrawal From Future Biomedical Research

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

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

8.1.11 Participant Blinding/Unblinding

This is an open-label study; there is no blinding for this study.

8.1.12 Calibration of Equipment

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

Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Tumor Imaging and Assessment of Disease

As of Amendment 05, central tumor response assessments will be discontinued. Imaging scans will no longer be submitted to iCRO nor read by BICR. The subsections below are retained for reference.

However, for participants who are still on SOC treatment and will continue receiving SOC treatment until criteria for discontinuation are met, local tumor imaging should continue per local institutional guidelines. .

The process for image collection and transmission to the iCRO is given in the SIM.

Tumor imaging should be acquired by CT of the chest, abdomen and pelvis, or contrast-enhanced MRI when CT is contraindicated or when mandated by local practice (CT is strongly preferred). MRI is the strongly preferred modality for imaging the brain. The same imaging modality, ideally the same scanner, and the use of contrast should be used in a participant throughout the study to optimize reproducibility of assessment of existing and new tumor burden and improve accuracy of assessment of response or progression based on imaging. Tumor imaging by CT (or MRI) of the chest, abdomen, and pelvis is required at every scheduled imaging time point. Brain imaging should only be performed as clinically indicated.

All scheduled images for all participants from the sites will be submitted to the iCRO. In addition, images (including via other modalities) obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but that demonstrate radiologic progression, should be submitted to the iCRO.

When the investigator identifies radiographic progression, the iCRO will perform expedited verification of radiologic PD and communicate the results to the study site and Sponsor. Study intervention should continue until PD has been verified. Images should continue to be submitted to the iCRO. In clinically stable participants, imaging should continue until PD has been verified by BICR (if initial site-assessed PD was not verified by BICR, each subsequent scan must be submitted to the iCRO for verification of PD until PD has been verified by BICR).

Assessment of treatment response will be according to RECIST 1.1 (some limitation is described in Section 8.2.1.2).

8.2.1.1 Tumor Imaging During Screening

Tumor imaging at Screening must be performed within 28 days prior to the date of randomization. Tumor imaging performed as part of routine clinical management is

acceptable for use in place of the Screening tumor imaging if it is of diagnostic quality and was performed within 28 days prior to the date of randomization and can be assessed by the iCRO.

Upon completion of the Screening tumor imaging, the investigator must confirm that the participant's disease did not progress prior to randomization. Non-PD must be verified by BICR prior to randomization, based on the images submitted to iCRO as described in inclusion criterion 4.

Participants who do not have measurable disease per RECIST 1.1 at Screening because of a CR or PR to the induction regimen are still eligible for the study.

8.2.1.2 Tumor Imaging During the Study

In the first year, on study imaging assessments must be performed every 8 weeks (56 days, ± 7 days) from the date of randomization. After the first year, imaging assessments must be performed every 12 weeks (84 days, ± 7 days). All supplemental imaging must also be submitted to the iCRO.

Timing of imaging should follow calendar days from the date of randomization and should not be adjusted for delays in cycle starts.

For participants who undergo surgery with curative intent, imaging must be performed at a minimum of (no less than) 4 weeks after surgery and no more than 8 weeks prior to the next treatment cycle. The last set of imaging prior to restart of treatment will be used to establish a new baseline of tumor burden. Subsequent imaging will be compared to this new baseline and the visit responses will be limited to PD, non-PD, or not evaluable; these new post-operative images will be assessed every 8 weeks (56 days ± 7 days) for 12 months and every 12 weeks (84 days ± 7 days) thereafter. After documented PD, participants will receive investigator-choice anticancer therapy and will continue to be followed for disease status until a PFS2 event is recorded.

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

For participants who discontinue study intervention, tumor imaging should be performed at the time of treatment discontinuation (± 4-week window). If previous imaging was obtained within 4 weeks prior to the date of discontinuation, imaging at treatment discontinuation is not mandatory.

For participants who discontinue study intervention without documented disease progression, every effort should be made to continue monitoring disease status by tumor imaging with the same schedule used while on treatment until the start of new anticancer treatment, disease progression, death, withdrawal of consent, or the end of the study, whichever occurs first.

8.3 Safety Assessments

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

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard during the Screening period. Clinically significant abnormal findings should be recorded as medical history. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs. Height and weight will also be measured and recorded.

At visits that do not require a full physical examination (Section 1.3), brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. New clinically significant abnormal findings should be recorded as AEs.

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

8.3.2 Vital Signs

Vital signs will be measured with the participant in a sitting, semirecumbent, or supine position after 5 minutes of rest, and will include temperature, systolic and diastolic BP, heart rate, and respiratory rate.

8.3.3 Electrocardiograms

A standard 12-lead ECG will be performed at the Screening visit and again at the Discontinuation Visit using local standard procedures.

8.3.4 Clinical Safety Laboratory Assessments

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

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

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the Laboratory Manual and the SoA.

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

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

8.3.4.1 Bone Marrow or Blood Cytogenetic Samples

Bone marrow or blood cytogenetic samples may be collected for participants with prolonged hematological toxicities as defined in Section 6.6.1.2.

Bone marrow analysis should include an aspirate for cellular morphology, cytogenetic analysis and flow cytometry, and a core biopsy for bone marrow cellularity. If it is not possible to conduct cytogenetic analysis or flow cytometry on the bone marrow aspirate, then attempts should be made to perform the tests on a blood sample.

8.3.5 Pregnancy Test

Pregnancy testing (urine or serum) should be conducted according to Section 1.3 (SoA) and at the end of relevant systemic exposure for all arms.

- Pregnancy testing requirements for study inclusion are described in Section 5.1.

- Pregnancy testing (urine or serum) should be conducted at monthly intervals during intervention.

- Pregnancy testing (urine or serum) should be conducted for the time required to eliminate systemic exposure after the last dose of study intervention and should correspond with the time frame for the participant's contraception, as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is:
  - Olaparib:180 days
  - 5-FU: 180 days
  - Capecitabine: 180 days
  - Leucovorin/levoleucovorin: 180 days.
  - Bevacizumab: 120 days.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator, or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 ECOG Performance Scale

The investigator or qualified designee will assess ECOG performance status as specified in the SoA.

8.3.7 Safety Considerations With Capecitabine and 5-FU

8.3.7.1 Photosensitivity

Investigators are advised to counsel participants assigned to receive capecitabine or 5-FU about the risk of photosensitivity and to take sun protection measures accordingly.

8.3.7.2 Ophthalmologic Complications Due to Capecitabine

Participants should be carefully monitored for ophthalmological complications such as keratitis and corneal disorders, especially if they have a prior history of eye disorders. Treatment of eye disorders should be initiated as clinically appropriate.

8.3.7.3 Severe Skin Reactions Due to Capecitabine

Capecitabine can induce severe skin reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis. Capecitabine should be permanently discontinued in participants who experience a severe skin reaction during treatment.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

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

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

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

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

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

- All AEs from the time of intervention allocation/randomization through 30 days following cessation of study intervention must be reported by the investigator.

- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 30 days following cessation of study intervention or 30 days following cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through 180 days following cessation of study intervention, or 30 days following cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.

- Any SAE of MDS/AML or new primary malignancy occurring 30 days after the last dose of olaparib should be reported regardless of the investigator's assessment of causality or knowledge of the treatment arm.

- Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 7.

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of olaparib's safety profile and require close monitoring and rapid communication by the investigators to the Sponsor. Adverse events of special interest for olaparib comprise the Important Identified Risk of MDS/AML and the Important Potential Risks of new primary malignancy (other than MDS/AML) and pneumonitis.

Table 7 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period:** Consent to Randomization/ Allocation	**Reporting Time Period:** Randomization/ Allocation through Protocol-specified Follow-up Period	**Reporting Time Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor:
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
Serious Adverse Event (SAE) including Cancer and Overdose	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - potential drug-induced liver injury (DILI) - require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

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

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

8.4.5 Pregnancy and Exposure During Breastfeeding

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

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

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 8.4.1.

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

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the participants in the study. Any suspected endpoint that upon review is not progression of the cancer under study will be forwarded to Global Pharmacovigilance as an SAE within 24 hours of determination that the event is not progression of the cancer under study.

8.4.7 Events of Clinical Interest (ECIs)

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

Events of clinical interest for this study include:

- An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

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

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

- Any event of MDS/AML, new primary malignancy, or pneumonitis should be reported whether it is considered a non-serious AE (eg non-melanoma skin cancer) or SAE and regardless of Investigator’s assessment of causality.

8.5 Treatment of Overdose

Olaparib must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be reported as an overdose.

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

Refer to the approved labeling for capecitabine, leucovorin, bevacizumab, and 5-FU regarding the definition of an overdose and recommended treatment for an overdose.

The Sponsor's medical monitor must be contacted in the event of a study intervention overdose.

8.6 Pharmacokinetics

As of Amendment 05, the collection of blood samples for PK was completed and is no longer applicable. The section below is retained for reference.

A minimum of 100 PK samples are anticipated to be collected. Pharmacokinetic sample collections are currently planned in a limited number of participants (n = 50 in Arm 1 and n = 50 in Arm 2). Based on known non-overlapping clearance pathways for bevacizumab and olaparib, PK drug-drug interaction is not expected. The PK of olaparib in combination with bevacizumab has been evaluated in patients with advanced solid tumors and no impact on PK of olaparib was seen in this study [Dean, E., et al 2012]. The PK profile of olaparib is well characterized and additional PK data will be available from ongoing studies in solid tumor indications (eg, SOLO3, PROfound, and LYNK-002).

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

As of Amendment 05, blood collections for RNA analysis and serum and plasma biomarker analysis will be discontinued. The section below is retained for reference.

To identify novel biomarkers, the following biospecimens to support exploratory analyses of cellular components (eg, protein, RNA, DNA, metabolites) and other circulating molecules will be collected from all participants as specified in the SoA:

- Blood for genetic analysis
- Blood for RNA analysis
- Blood for serum and plasma biomarker analysis
- Blood for ctDNA analysis
- Tumor Tissue

Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the Laboratory Manual.

8.8.1 Planned Genetic Analysis Sample Collection

The planned genetic analysis sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at the site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the participant provides documented informed consent for future biomedical research. If the planned genetic analysis is not approved, but future biomedical research is approved and consent is given, this sample will be collected for the purpose of future biomedical research.

The planned genetic analysis sample should be obtained predose on Day 1 but may be collected at the next scheduled blood draw, if needed. Sample collection, storage, and shipment instructions for planned genetic analysis samples will be in the Operations/Laboratory Manual.

8.9 Future Biomedical Research Sample Collection

If the participant provides documented informed consent for future biomedical research, the following specimens will be obtained as part of future biomedical research:

Leftover sample listed in Section 8.8 (including any extracted material from samples).

8.10 Medical Resource Utilization and Health Economics

As of Amendment 05: medical resource utilization and health economics data collection will be discontinued. The section below is retained for reference.

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

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

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

8.11 Visit Requirements

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

8.11.1 Screening

Approximately 28 days prior to intervention randomization, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor.

All Screening procedures are to be completed within 28 days prior to the date of randomization except for the following:

- Laboratory tests are to be performed within 10 days prior to the first dose of study intervention. An exception is HBV, HCV, and HIV testing which may be performed up to 28 days prior to the date of randomization if testing is required by local regulations. Refer to Appendix 7 for country-specific requirements.

- Evaluation of ECOG performance status is to be performed within 10 days prior to randomization.

- The radiographic images submitted to the iCRO during Screening must have been performed before or during the CAPOX + bevacizumab or FOLFOX + bevacizumab induction period and at least 42 days prior to the imaging performed during Screening.

8.11.2 Treatment Period

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

8.11.3 Discontinuation Visit

The Discontinuation Visit should occur at the time when study intervention is discontinued. If the Discontinuation Visit occurs 30 days after the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, procedures do not need to be repeated. Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.

8.11.4 Post-treatment Visits

8.11.4.1 Safety Follow-up Visit

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

Once the Safety Follow-up Visit is completed, all participants will be discontinued from the study.

8.11.4.2 Follow-up Visits

As of Amendment 05, follow-up visits for assessment of efficacy will be discontinued for all participants. All participants will move into survival follow-up phase (Section 8.11.4.4). The section below is retained for reference.

Participants who discontinue study intervention for a reason other than BICR-verified disease progression will move into the follow-up phase and should be assessed every 8 weeks (56 days ± 7 days) for the first year and every 12 weeks (84 days ± 7 days) thereafter, from the date of randomization, to coincide with the imaging schedule at the time of discontinuation from study intervention. to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, death, or the end of study, whichever occurs first. Information regarding post-study anticancer treatment will be collected if new treatment is initiated.

8.11.4.3 PFS2 Follow-up

As of Amendment 05, PFS2 follow-up visits will be discontinued for all participants. All participants will move into survival follow-up phase (Section 8.11.4.4). The section below is retained for reference.

After disease progression, sites should continue to provide updates regarding the participant's disease status until subsequent disease progression occurs, death, withdrawal of consent, or the end of the study, whichever occurs first.

Participants will be assessed every 8 weeks for a second progression (using the participant's status at first progression as the reference for assessment of second progression). A participant's progression status is defined according to local standard clinical practice and may involve radiological or symptomatic progression or death. Copies of the participants radiological scans are not required to be sent to the iCRO and RECIST measurements will not be collected for assessment of PFS2. The date of PFS2 assessment and investigator determination of progression status (progressed or non-progressed) at each assessment will be recorded in the eCRF.

8.11.4.4 Survival Follow-up

As of Amendment 05, for all participants, survival follow-up visits will continue until the final efficacy evaluation.. Those participants remaining on SOC (Arm 3A and Arm 3B) at the time of Amendment 05 should continue to be monitored in the study through the AE reporting period (Section 8.4). The section below is retained for reference.

Participants who experience second disease progression will move into the survival follow-up phase and should be contacted (eg, by telephone) approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first. Investigators will be directed to ask during the regular follow-up for OS if the participant has developed MDS/AML or a new primary malignancy and will be prompted to report any such cases.

8.11.5 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an eDMC review, interim and/or final analysis. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding participants that have a previously recorded death event in the collection tool).

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. The study team has been unblinded (as of 18-JUL-2022). Changes made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses that occurred prior to Amendment 05 were documented in previous protocol amendments(s) (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis, will be documented in an sSAP and referenced in the CSR for the study. A separate biomarker analysis plan will be provided. Post hoc exploratory analyses will be clearly identified in the CSR. The PRO analysis plan will also be included in the sSAP.

9.1 Statistical Analysis Plan Summary

As of Amendment 05: The SAP is amended as follows:

NOTE: Based on the data from IA1, an interim safety and efficacy analysis for LYNK-003 (data cutoff 10-MAY-2022), eDMC recommended stopping the study enrollment for futility based on prespecified futility boundary of IA1. Based upon the recommendation of the eDMC, the study team was unblinded (as of 18-JUL-2022). The prespecified interim analyses 2, 3, 4, and final analysis of the study described in the SAP will not be performed. Selected analyses of safety endpoints will be performed at the end of the study; there will be no further analyses of efficacy and PRO endpoints. The SAP summary has been updated accordingly.

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

Study Design Overview	A Phase 3 randomized, open-label study to evaluate the efficacy and safety of olaparib alone or in combination with bevacizumab compared to bevacizumab with a fluoropyrimidine in participants with unresectable or metastatic CRC who have not progressed following first-line induction.
Treatment Assignment	Approximately 525 participants will be randomized in a 1:1:1 ratio to 3 treatment groups (1) olaparib + bevacizumab, (2) olaparib and (3) bevacizumab + 5-FU or bevacizumab + capecitabine (Control). Stratification factors are 1) SD versus PR/CR to prior FOLFOX + bevacizumab or CAPOX + bevacizumab induction, 2) $BRAF_{mut}$ and/or Ras_{mut} versus $BRAF_{wt}$ + Ras_{wt}, and 3) 6 to 8 cycles of induction versus >8 cycles for FOLFOX-based induction, and 4 to 6 cycles versus >6 cycles for CAPOX-based induction. This is an open-label study. As of Amendment 05, study enrollment is being stopped for futility. Study participants randomized to one of the two experimental arms (olaparib plus bevacizumab [Arm 1] or olaparib monotherapy [Arm 2]) must discontinue study intervention. No crossover from either experimental arm to SOC arm (Arm 3A and Arm 3B) within the study is allowed. Participants on SOC have the option to continue receiving study intervention until criteria for discontinuation is met at the discretion of the investigator.
Analysis Populations	Efficacy: Intention-to-Treat (ITT) Safety: All Participants as Treated (APaT)
Primary Endpoint	Progression-free survival (PFS) based on RECIST 1.1 as assessed by BICR.
Key Secondary Endpoint	OS
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The primary and secondary hypotheses will be evaluated by comparing olaparib + bevacizumab versus 5-FU + bevacizumab or capecitabine + bevacizumab and olaparib versus 5-FU + bevacizumab or capecitabine + bevacizumab with respect to PFS and OS using a stratified log-rank test. The HR will be estimated using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. The tiers differ with respect to the analyses that will be performed. There is no Tier 1 safety endpoint for this study. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for between arm comparisons; only point estimates by treatment arm will be provided for Tier 3 safety parameters. The 95% CIs for the between-treatment differences in percentages will be provided using the Miettinen and Nurminen method [Miettinen, O. and Nurminen, M. 1985].

Interim Analyses	As of Amendment 05, the prespecified interim analyses 2, 3, 4, and final analysis described in the SAP will not be performed. The study includes a non-binding futility analysis (IA1) to determine whether there is sufficient evidence to continue the experimental arms. Three IAs beyond IA1 are planned in addition to the final analysis. • Interim analysis 1 (IA1): non-binding futility analysis (~ 119 PFS events have been observed for both treatment comparisons [119 events in Arm 1 plus Control; and 119 events in Arm 2 plus Control], expected to occur ~ 19 months after study start): - If the PFS HR of either Arm 1 or Arm 2 compared to the control arm is less than the prespecified futility boundary, the study may continue as planned. • Interim analysis 2 (IA2): ~ 238 PFS events have been observed for at least one treatment comparison (238 events in Arm1 plus Control or 238 events in Arm 2 plus Control), ~ 117 deaths are expected in these 2 arms (Arm 1 plus Control or Arm 2 plus Control) when ~ 238 PFS events are observed, expected to occur ~ 30 months after study start. - Interim PFS and OS analyses • Interim analysis 3 (IA3): ~297 PFS events have been observed for both treatment comparisons (297 events in Arm 1 plus Control; and 297 events in Arm 2 plus Control), ~ 174 deaths are expected for both treatment comparisons, expected to occur ~42 months after study start. - Final PFS analysis - Interim OS analysis • Interim analysis 4 (IA4): ~ 228 deaths have occurred for at least 1 treatment comparison (228 deaths in Arm 1 plus Control or 228 deaths in Arm 2 plus Control), expected to occur ~ 58 months after study start - Interim OS analysis • Final analysis: ~ 268 deaths have occurred for both treatment comparisons (268 deaths in Arm 1 plus Control; and 268 deaths in Arm 2 plus Control), expected to occur ~ 78 months after study start - Final OS analysis
Multiplicity	The Type-I error rate over the multiple treatment comparisons and primary and key secondary efficacy endpoints will be controlled at 2.5% (1-sided). A small alpha penalty of 0.01% will be paid for the futility analysis (split equally between the 2 treatment comparisons). The remaining alpha will be initially equally split between the 2 treatment comparisons to test PFS (1.245% for each treatment comparison: Arm 1 vs. Control and Arm 2 vs. Control). If a test for PFS is significant, then the secondary OS endpoint will be tested for that arm. The graphical approach of Maurer and Bretz [Bretz, F., et al 2009] will be applied to re-allocate alpha among the hypotheses of PFS and OS. Lan-DeMets O'Brien-Fleming group sequential methods will be used to allocate alpha among the interim and final analyses. The study will be considered positive if the PFS hypothesis test is positive for either treatment comparison (Arm 1 vs. Control, and/or Arm 2 vs. Control).

Sample Size and Power	As of Amendment 05, the prespecified interim analyses 2, 3, 4, and final analysis of the study described in the SAP will not be performed. The planned sample size is approximately 525 participants. For PFS, based on 297 events at IA3, the study has 88% power to detect an HR of 0.65 at α=1.245% (1-sided) for each treatment comparison (Arm 1 vs. Control, or Arm 2 vs. Control), with assumed PFS median of 7 months in the control arm. For OS, based on 268 events at the final analysis, the study has 53% (73%) power to detect an HR of 0.75 (0.70) at α=1.245% (1-sided) for each treatment comparison, with assumed OS median of 24 months in the control arm.

9.2 Responsibility for Analyses/In-house Blinding

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

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

This study is being conducted as an open-label study; therefore, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned. Although the study is open-label, analyses or summaries generated by randomized intervention assignment, or actual intervention received will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of intervention group assignment.

9.3 Hypotheses/Estimation

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

9.4 Analysis Endpoints

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

9.4.1 Efficacy Endpoints

Primary Endpoint:

- PFS: the time from randomization to the first documented PD per RECIST 1.1 as assessed by BICR or death due to any cause, whichever occurs first. See Section 9.6.1 for the definition of censoring.

Key Secondary Endpoint:

- OS: the time from randomization to death due to any cause.

Secondary Endpoint:

- **ORR**: the proportion of the participants in the analysis population who have a confirmed CR or PR per RECIST 1.1 as assessed by BICR.

- **DOR**: the time from first documented evidence of CR or PR until PD per RECIST 1.1 as assessed by BICR or death due to any cause, whichever occurs first, in participants who demonstrate CR or PR.

Exploratory Endpoint:

- **PFS2**: the time from randomization to second documented disease progression or death due to any cause, whichever occurs first, by investigator assessment.

- **DCR**: the proportion of the participants in the analysis population who have a confirmed CR or PR or SD per RECIST 1.1 as assessed by BICR.

The analysis of PFS2 and DCR will be described in the sSAP.

9.4.2 Safety Endpoints

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

9.4.3 PRO Endpoints

The following exploratory PRO endpoints will be evaluated as described in Section 4.2.1.3:

- Global health status/QoL of the EORTC QLQ-C30 (items 29 and 30)

- The multi-item and single-item scales of the EORTC QLQ-C30

- The multi-item and single-item scales of the EORTC QLQ-CR29

- Health utilities as assessed using the EQ-5D-5L

These analyses will be described in the sSAP.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Population

Analyses of the primary efficacy endpoint are based on the ITT population. All randomized participants will be included in this population. Participants will be analyzed in the treatment arm to which they are randomized. Details of the approach to handling missing data are provided in Section 9.6.

Participants who enter the study without measurable disease will be excluded from the ORR and DCR analysis.

9.5.2 Safety Analysis Population

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all randomized participants who receive at least 1 dose of study treatment. Participants will be analyzed in the treatment arm corresponding to the study treatment they actually received. For most participants, this will be the treatment group to which they are randomized. Participants who receive incorrect study treatment for the entire treatment period will be included in the treatment arm corresponding to the study treatment actually received.

At least 1 laboratory or vital sign measurement obtained after at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

9.5.3 PRO Analysis Population

The PRO analyses are based on the PRO FAS population, defined as participants who have at least 1 PRO assessment available and have received at least 1 dose of study treatment.

9.6 Statistical Methods

NOTE: As of Amendment 05, the prespecified interim analyses 2, 3, 4, and final analysis of the study described in the SAP will not be performed. Selected analyses of safety endpoints will be performed at the end of study; there will be no further analyses of efficacy and PRO endpoints. The subsections below are retained for reference.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary efficacy objectives. Methods related to exploratory objectives will be described in the sSAP. Efficacy results that will be deemed to be statistically significant after consideration of the Type-I error control strategy are described in Section 9.8. Nominal p-values will be computed for other efficacy analyses but should be interpreted with caution due to potential issues of multiplicity.

9.6.1.1 Progression-free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie-handling will be used to assess the magnitude of the treatment difference (ie, the HR) between the treatment arms (Arm 1 vs. Control, and Arm 2 vs. Control). The HR and its 95% CI from the stratified Cox model with Efron's method of tie-handling and with a single treatment covariate will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to

both the stratified log-rank test and the stratified Cox model. Descriptive statistics of the treatment difference (ie, the HR, 95% CI, and nominal p-value) between Arm 1 and Arm 2 will also be provided.

Since disease progression is assessed periodically, PD can occur any time in the interval between the last assessment when PD is not documented and the assessment when PD is documented. The true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 by BICR. Death is always considered as a confirmed PD event. Participants who do not experience a PFS event will be censored at the last disease assessment. A sensitivity analysis will be performed for a comparison of PFS based on the investigator's assessment.

In order to evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 1 primary and 2 sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than 1 missed disease assessment, the data are censored at the last disease assessment prior to the missed visits. Data after new anticancer therapy are censored at the last disease assessment prior to the initiation of new anticancer therapy. The first sensitivity analysis follows the ITT principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers discontinuation of treatment due to reasons other than CR or initiation of new anticancer treatment, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 8.

For participants who have a surgery with curative intent (described in Section 4.1), PFS will be defined using time from randomization to the disease recurrence after the surgery.

Table 8 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
PD or death documented after ≤1 missed disease assessment, and before new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessments and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than CR; otherwise censored at last disease assessment if participant is still receiving study treatment or has completed study treatment
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival.

9.6.1.2 Overall Survival (OS)

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

9.6.1.3 Objective Response Rate (ORR)

Stratified Miettinen and Nurminen method will be used for the comparison of the ORR between 2 treatment arms. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization (Section 6.3.2) will be applied to the analysis.

Participants who enter the study without measurable disease will be excluded from the ORR analysis.

9.6.1.4 Duration of Response (DOR)

For participants who demonstrate CR or PR, DOR is defined as the time from first documented evidence of CR or PR until PD or death due to any cause, whichever occurs first. Censoring rules for DOR are summarized in Table 9.

For each DOR analysis, a corresponding summary of the reasons for which responding participants are censored will also be provided. Responses in participants who are alive, have not progressed, have not initiated new anticancer treatment (reintroduction of investigator-choice of anticancer therapy), have not been determined to be lost to follow-up, and have had a disease assessment within approximately 5 months of the data cutoff date, are considered ongoing responders at the time of analysis. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied.

If the sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants with a confirmed CR or PR will be included in this analysis.

Table 9 Censoring Rules for Duration of Response

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy was initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anticancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anticancer therapy if any	PD or death	End of response (Event)

Abbreviation: PD = progressive disease.

A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.

9.6.1.5 Analysis Strategy for Key Efficacy Endpoints

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

Table 10 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
PFS (RECIST 1.1) by BICR	Testing: stratified log-rank test Estimation: stratified Cox model with Efron's tie-handling method	ITT	Censored according to rules in Table 8
Secondary Analyses			
OS	Testing: stratified log-rank test Estimation: stratified Cox model with Efron's tie-handling method	ITT	Censored at last known alive date
ORR (RECIST 1.1) by BICR	Estimation: Stratified Miettinen and Nurminen method	Participants who enter the study with measurable disease in ITT	Participants with missing data are considered nonresponders
DOR (RECIST 1.1) by BICR	Summary statistics using Kaplan-Meier method	All responders in ITT	Censored according to rules in Table 9
Abbreviations: BICR = blinded independent central review; DOR = duration of response; ITT = intention-to-treat; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors Version 1.1. Sensitivity analyses will be performed for PFS, ORR, and DOR based on investigator's assessment.			

9.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters, including AEs, laboratory tests, vital signs, and ECG measurements.

The analysis of safety results will follow a tiered approach (Table 11). The tiers differ with respect to the analyses that will be performed. Adverse events are either pre-specified as Tier 1 events or will be classified as belonging to Tier 2 or Tier 3 based on the number of events observed.

Tier 1 Events

Safety parameters or AEOSIs that are identified a priori constitute Tier 1 safety events that will be subject to inferential testing for statistical significance. Based on a review of historic chemotherapy data in CRC and data from ongoing olaparib clinical studies, there are no AEs that warrant inferential testing between treatment groups; therefore, there are no Tier 1 events for this protocol.

Tier 2 Events

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

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

Tier 3 Events

Safety events that are not Tier 1 or Tier 2 events will be considered Tier 3 events. Only point estimates by treatment arm will be provided for Tier 3 safety parameters.

Continuous Safety Measures

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

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Specific AEs (incidence ≥10% in at least 1 treatment group)	X	X
	Specific Grade 3 to 5 AEs (incidence ≥5% in at least 1 treatment group)	X	X
	Specific Serious AEs (incidence ≥5% in at least 1 treatment group)	X	X
Tier 3	Safety events that are not (Tier 1 or Tier 2)		X
	Change from baseline results (laboratory tests, vital signs, ECGs)		X
Abbreviations: AE = adverse event; CI = confidence interval; ECG = electrocardiogram; X = results will be provided.			

9.6.3 Statistical Methods for Patient-reported Outcomes

Details of PRO analyses will be included in the sSAP.

9.6.4 Summaries of Baseline Characteristics

The comparability of the treatment groups for each relevant demographic and baseline characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants randomized and the primary reason for discontinuation will be displayed. Demographic variables (such as age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables. The reasons for exclusion from the ITT population (if any) will be summarized.

9.7 Interim Analyses

Note: As of Amendment 05, the prespecified interim analyses 2, 3, 4, and final analysis of the study described in the SAP will not be performed. This section is retained for reference.

An eDMC will serve as the primary reviewer of the unblinded results of the IAs and will make recommendations for discontinuation of the study or protocol modifications to an EOC of the Sponsor. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC (and potentially other limited additional Sponsor personnel) may be unblinded to results at the study intervention level in order to act on these recommendations. Additional logistical details will be provided in the eDMC Charter.

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

9.7.1 Efficacy Interim Analyses

The study includes a non-binding futility analysis (IA1) to determine whether there is sufficient evidence to continue the experimental arms. The analysis will occur approximately 19 months after study initiation at 40% information fraction for the PFS analysis. This analysis will compare PFS between Arm 1 and the control arm (Arm 3a/Arm 3b) as well as Arm 2 and the control arm (Arm 3a/Arm 3b). The study may be stopped if both arms are deemed futile; otherwise, the study may continue as planned. The operating characteristics of the futility interim analysis for each comparison are shown in Table 12.

Table 12 Operating Characteristics of the Futility Interim Analysis (IA1)

Futility HR Boundary	IA1 Information Fraction (%)	Prob arm is futile based on HR=1.0	Prob arm is futile based on HR=0.65	IA1 Timing (Month)
0.85	40	81.2%	7.2%	19
Abbreviations: HR = hazard ratio; IA1 = Interim Analysis 1.				

Three IAs beyond IA1 are planned in addition to the final analysis. The timing and purpose of analyses are summarized in Table 13.

Table 13 Summary of Interim and Final Analyses

Analyses	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
IA1	~ 119 PFS events have been observed for both treatment comparisons (119 events in Arm 1 plus Control; and 119 events in Arm 2 plus Control).	~ 19 months	PFS futility analysis
IA2	~ 238 PFS events have been observed for at least 1 treatment comparison (238 events in Arm 1 plus Control or 238 events in Arm 2 plus Control). ~ 117 deaths are expected in these 2 arms (Arm 1 plus Control or Arm 2 plus Control) where ~ 238 PFS events are observed.	~ 30 months	Interim PFS and OS analysis
IA3	~ 297 PFS events have been observed for both treatment comparisons (297 events in Arm 1 plus Control; and 297 events in Arm 2 plus Control). ~ 174 deaths are expected for both treatment comparisons.	~ 42 months	Final PFS analysis Interim OS analysis
IA4	~ 228 deaths have occurred for at least one treatment comparison (228 deaths in Arm 1 plus Control or 228 deaths in Arm 2 plus Control).	~ 58 months	Interim OS analysis
Final Analysis	~ 268 deaths have occurred for both treatment comparisons (268 deaths in Arm 1 plus Control; and 268 deaths in Arm 2 plus Control).	~ 78 months	Final OS analysis
Abbreviations: IA = Interim Analysis; OS = overall survival; PFS = progression-free survival.			

9.7.2 Safety Interim Analyses

Note: As of Amendment 05, no further analysis to the eDMC is warranted as the eDMC has recommended at IA1 that study participants randomized to one of the two experimental arms (olaparib plus bevacizumab [Arm1] or olaparib monotherapy [Arm2]) must discontinue study intervention.

The eDMC conducted regular safety monitoring. The timing of the safety monitoring was specified in the DMC charter. No further analysis is warranted.

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

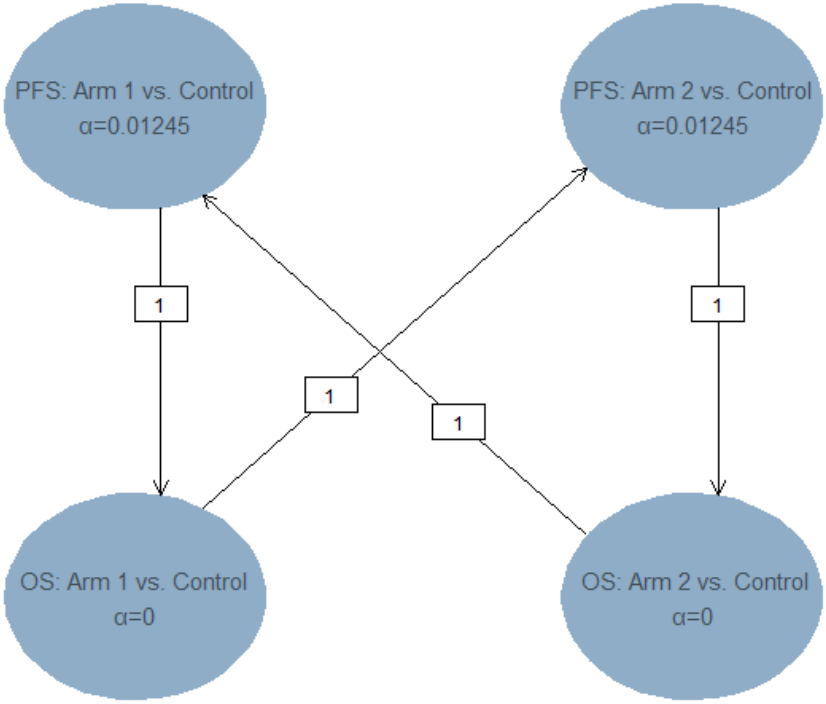
9.8 Multiplicity

Note: As of Amendment 05, the prespecified interim analyses 2, 3, 4, and final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The Type-I error rate over the multiple treatment comparisons and primary and key secondary efficacy endpoints will be controlled at 2.5% (1-sided). A small alpha penalty of 0.01% will be paid for the futility analysis. The study will use the graphic method of Maurer and Bretz to control multiplicity for multiple hypotheses as well as IAs [Bretz, F., et al 2009]. According to this approach, study hypotheses may be tested more than once, and, when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests.

Figure 2 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

Figure 2 Multiplicity Diagram for Type-I Error Control



Abbreviations: OS = overall survival; PFS = progression-free survival.

9.8.1 Progression-free Survival

PFS will be tested at IA2 and IA3. The study allocates α=0.0249, 1-sided, to test PFS for Arm 1 versus Control and Arm 2 versus Control (α=0.01245 for each comparison). If the null hypothesis for PFS in 1 comparison is rejected, Figure 2 shows that its α=0.01245 is essentially fully reallocated to the OS hypothesis in the same treatment comparison. If the null hypotheses for OS is rejected, the alpha will be reallocated to the PFS in the other treatment comparison. Thus, each PFS comparison may be tested at α=0.01245 (initial α), or at α=0.0249 (if the null hypotheses for the other PFS comparison and OS comparison are rejected) (Table 14). For each comparison, the actual boundaries will be calculated based on the observed number of PFS events at the interim and final PFS analyses using the Lan-DeMets O'Brien-Fleming spending function accordingly. For PFS interim analysis, the same alpha spend will be used for both comparisons (Arm 1 vs. Control and Arm 2 vs. Control), based on the lower number of observed PFS events from both comparisons.

Table 14 Efficacy Boundaries and Properties for PFS Analyses

Analyses	Value	α=0.01245	α=0.0249
IA2: 80%[a] N:350 Events: 238 Months: 30	Z	2.5594	2.2500
	p (1-sided)[b]	0.0052	0.0122
	HR at bound[c]	0.7176	0.7470
	P(Cross) if HR = 1[d]	0.0052	0.0122
	P(Cross) if HR = 0.65[e]	0.7616	0.8324
IA3:100%[a] N:350 Events: 297 Months: 42	Z	2.2943	2.0270
	p (1-sided)[b]	0.0109	0.0213
	HR at bound[c]	0.7662	0.7904
	P(Cross) if HR = 1[d]	0.01245	0.0249
	P(Cross) if HR = 0.65[e]	0.8817	0.9047

Abbreviations: HR = hazard ratio; IA = Interim Analysis; PFS = progression-free survival.
a. Percentage of total number of required events needed at each interim analysis.
b. The nominal α for testing.
c. The approximate HR required to reach an efficacy bound.
d. The probability of crossing a bound under the null hypothesis.
e. The probability of crossing a bound under the alternative hypothesis.

Note that if the α-reallocation from OS hypothesis testing occurs at the final analysis after hypothesis testing for PFS has been completed, the previously computed PFS test statistic for the PFS analysis may be re-evaluated versus the updated bounds.

9.8.2 Overall Survival

No initial alpha is allocated to the OS hypothesis. The OS hypothesis will only be tested if the test for PFS for the same treatment comparison is significant. If the test for PFS is not significant at the final analysis for PFS, the study may not continue for test of OS.

If the study continues based upon the IA1 futility criterion, OS will be tested at IA2 only if the test for PFS for the same treatment comparison is significant at IA2; and tested at IA3, IA4 and final analysis only if the final analysis of PFS (IA3) for the same treatment comparison is significant. Each OS comparison (Arm 1 vs. Control and Arm 2 vs. Control) may be tested at α=0.01245 (if the null hypothesis for the PFS in the same treatment comparison is rejected), or at α=0.0249 (if the null hypotheses for both PFS comparisons and OS for the other comparison are rejected). Table 15 shows the boundary properties for OS interim analyses and final analysis for each treatment comparison, which were derived using a Lan-DeMets O'Brien-Fleming spending function.

Table 15 Efficacy Boundaries and Properties for OS Analyses

Analyses	Value	α=0.01245	α=0.0249
IA2: 44%[a] N:350 Events: 117 Months: 30	Z	3.6062	3.2000
	p (1-sided)[b]	0.0002	0.0007
	HR at bound[c]	0.5134	0.5534
	P(Cross) if HR = 1[d]	0.0002	0.0007
	P(Cross) if HR = 0.75[e]	0.0202	0.0501
IA3: 65%[a] N:350 Events: 174 Months: 42	Z	2.8988	2.5655
	p (1-sided)[b]	0.0019	0.0052
	HR at bound[c]	0.6443	0.6778
	P(Cross) if HR = 1[d]	0.0019	0.0054
	P(Cross) if HR = 0.75[e]	0.1595	0.2547
IA4: 85%[a] N:350 Events: 228 Months: 58	Z	2.5046	2.2160
	p (1-sided)[b]	0.0061	0.0133
	HR at bound[c]	0.7177	0.7456
	P(Cross) if HR = 1[d]	0.0067	0.0150
	P(Cross) if HR = 0.75[e]	0.3770	0.4931
Final:100%[a] N:350 Events: 268 Months: 78	Z	2.3145	2.0511
	p (1-sided)[b]	0.0103	0.0201
	HR at bound[c]	0.7537	0.7784
	P(Cross) if HR = 1[d]	0.01245	0.0249
	P(Cross) if HR = 0.75[e]	0.5332	0.6396

Abbreviations: HR = hazard ratio; IA = Interim Analysis; OS = overall survival.

a. Percentage of total number of required events needed at each interim analysis.
b. The nominal α for testing.
c. The approximate HR required to reach an efficacy bound.
d. The probability of crossing a bound under the null hypothesis.
e. The probability of crossing a bound under the alternative hypothesis.

Alpha spending for OS at IA2 and IA3 is provided for regulatory purposes since it will be summarized in conjunction with PFS analyses.

9.9 Sample Size and Power Calculations

Note: As of Amendment 05, the prespecified interim analyses 2, 3, 4, and final analysis of the study described in the SAP will not be performed. This section is retained for reference.

The study will randomize approximately 525 participants in a 1:1:1 ratio into Arm 1 olaparib + bevacizumab, Arm 2 olaparib, and Arm 3 bevacizumab + fluoropyrimidine (5-FU in Arm 3a or capecitabine in Arm 3b). PFS is the primary endpoint for the study, with OS as the key secondary endpoint. For PFS, based on a target number of 297 events at IA3, the study has 88% power to detect a HR of 0.65 at α=1.245% (1-sided) for each treatment comparison (Arm 1 vs. Control, or Arm 2 vs. Control). If PFS is positive for the same treatment

comparison, then for OS, based on a target number of 268 events, the study has 53% (73%) power to detect an HR of 0.75 (0.70) at α=1.245% (1-sided) for each treatment comparison (Arm 1 vs. Control, or Arm 2 vs. Control). The above sample size and power calculations for PFS and OS assume the following. CCI

[redacted]

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect (Arm 1 vs. Control, and Arm 2 vs. Control) for PFS and OS (with a nominal 95% CI) will be estimated and plotted by treatment group within each category of the following classification variables:

- Stratification factors
  - SD versus PR/CR to prior FOLFOX (or CAPOX) + bevacizumab induction
  - $BRAF_{mut}$ and/or Ras_{mut} versus $BRAF_{wt}$ + Ras_{wt}
  - Number of induction cycles
    - For FOLFOX-based induction, 6 to 8 cycles versus >8 cycles
    - For CAPOX-based induction, 4 to 6 cycles versus >6 cycles
- Age category (<70 years; ≥70 years)
- Sex (female; male)
- Geographic region (Asia vs. Western Europe/North America vs. Rest of World)
- Hepatic or pulmonary metastases versus other metastases
- ECOG performance status (0, 1)

- Site (colon, rectum)
- Number of metastatic sites (1, >1)
- Induction regimen
  - FOLFOX + bevacizumab
  - CAPOX + bevacizumab

For subgroup analysis to take place, a given subgroup must include ≥10% of the total sample size in the 2 treatment arms to be compared.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of exposure for a participant is defined as the number of days in which the participant receives olaparib, and the number of cycles in which the participant receives the study treatment infusion for bevacizumab and/or 5-FU (or capecitabine). Summary statistics will be provided on the extent of exposure for the APaT population.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Clinical Trials

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

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

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

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

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

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

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

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

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

10.1.2 Financial Disclosure

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

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

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

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

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

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

10.1.4.1 Executive Oversight Committee

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

10.1.4.2 External Data Monitoring Committee

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

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

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

10.1.5 Publication Policy

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

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

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

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

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 16 will be performed by the local laboratory.
- Results of predose laboratory procedures must be reviewed by the investigator or qualified designee and found acceptable prior to study intervention administration at study visits.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 16 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes[a]	WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	Blood Urea Nitrogen (BUN) or urea	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	Bicarbonate or CO_2 [a]	Chloride	Phosphorous
	Creatinine or creatinine clearance	Sodium	Alanine Aminotransferase (ALT)/ Serum Glutamic Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (nonfasting)	Calcium	Alkaline phosphatase	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)			

Laboratory Assessments	Parameters
Other Tests	• Urine (or serum) β-human chorionic gonadotropin (β-hCG) pregnancy test (as needed for WOCBP) • Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) if required by local regulations • Prothrombin time (PT)/International normalized ratio (INR) and activated partial thromboplastin time (aPTT) • Carcinoembryonic antigen (CEA) levels
a. Performed only if considered local standard of care.	

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

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, or are considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology “accidental or intentional overdose without adverse effect.”

- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not considered a reportable event unless it results in hospitalization or death.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

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

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- In offspring of participant taking the product regardless of time to diagnosis.

f. Other important medical events

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

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

10.3.4 Additional Events Reported in the Same Manner as SAE

Additional events that require reporting in the same manner as SAE

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

- Is a new cancer (that is not a condition of the study)
- Is associated with an overdose

10.3.5 Recording AE and SAE

AE and SAE recording

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

Assessment of intensity/toxicity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.
- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) according to the NCI CTCAE, version 5.0. Any AE that changes CTCAE grade over the course of a given episode will have each change of grade recorded on the AE CRFs/worksheets.

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

- Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

- Grade 4: Life threatening consequences; urgent intervention indicated.

- Grade 5: Death related to AE.

Assessment of causality

- Did the Sponsor's product cause the AE?

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

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

- If yes, this is a positive dechallenge.
- If no, this is a negative dechallenge.

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

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

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

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

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

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).
  - Yes, there is a reasonable possibility of Sponsor's product relationship:
    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
  - No, there is not a reasonable possibility of Sponsor's product relationship:

  - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

- For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each AE causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the AE to the single agent.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

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

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

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.

- Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).

- If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.

    - Reference Section 8.4.1 for reporting time requirements.

- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.

- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Male Participants

Male participants with female partners of childbearing potential are eligible to participate if they agree to 1 of the following for the minimum protocol-defined time frame in Section 5.1 or the time frame detailed in the approved product label per local requirements:

- Be abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.
  - The following are not acceptable methods of contraception:
    - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM).
    - Male condom with cap, diaphragm, or sponge with spermicide.
    - Male and female condom cannot be used together.

Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration.

Female Participants

Female participants of childbearing potential are eligible to participate if they agree to consistent and correct use of a highly effective method of contraception as described in Table 17 during the protocol-defined time frame in Section 5.1.

Table 17 Highly Effective Contraception Methods

• **Contraceptives allowed during the study include[a]:**
• **Highly Effective Contraceptive Methods That Have Low User Dependency** *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • IUS[c] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
• **Sexual Abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c Male condoms must be used in addition to female participant hormonal contraception. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

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

The specimens consented and/or collected in this study as outlined in Section 8.9 will be used in various experiments to understand:

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

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

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

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

a. Participants for Enrollment

All participants enrolled in the clinical study will be considered for enrollment in the future biomedical research

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

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

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

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

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

5. Biorepository Specimen Usage[3,4]

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

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

Participants may withdraw their consent for future biomedical research and ask that their biospecimens not be used for future biomedical research. Participants may withdraw consent at any time by contacting the investigator for the main study. If medical records for the main study are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@msd.com). Subsequently, the participant's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for future biomedical research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the participant of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses would be generated after the request is received.

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

7. Retention of Specimens[3,4]

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

Specimens from the study site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular study, the study site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which

operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security[3,4]

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

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

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

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

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

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

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

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

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

12. Questions

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

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3. Industry Pharmacogenomics Working Group [Internet]: Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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10.7 Appendix 7: Country-specific Requirements

10.7.1 France

Section 1.3 Schedule of Activities

Pregnancy testing must be performed prior to study intervention administration at each cycle during the treatment period as well as before the last dose of study intervention, and 180 days after the last dose of olaparib, at the end of study intervention.

Section 5.2 Exclusion Criteria

Dihydropyrimidine dehydrogenase deficient participants who are treatment-naïve to 5-FU and 5-Fluoropyrimidin containing drugs

Received the last dose of brivudine within the past 4 weeks or is currently receiving brivudine

Section 8.11.1 Screening

All participants at study sites in France must be tested for hepatitis B and hepatitis C at Screening prior to randomization.

10.7.2 Japan

Section 6.1 Study Intervention(s) Administered

Bevacizumab in combination with other anti-cancer agents for CRC has been approved in Japan with the same dosage and administration as in this study, and authorization application/submission of bevacizumab is not planned based on the results of this study.

Bevacizumab used in Arm1 in this study is categorized as “product(s) used in the clinical trial other than test product(s)” in Japan local regulation.

10.7.3 Germany

Section 1.3 Schedule of Activities (SoA)

Dihydropyrimidine dehydrogenase deficiency testing is required at screening for participants.

Section 5.2 Exclusion Criteria

- Dihydropyrimidine dehydrogenase deficient participants who are treatment-naïve to 5-FU and 5-Fluoropyrimidin containing drugs
- Received the last dose of brivudine within the past 4 weeks or is currently receiving brivudine

6.5.3 Rescue Medications and Supportive Care

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

Legally Acceptable Representative protocol sections

For a participant to be eligible to participate in Germany, they must be capable of providing documented informed consent; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
5-FU	fluorouracil
AML	acute myeloid leukemia
APaT	All Participants as Treated
BICR	blinded independent central review
BID	twice daily
CAPOX	capecitabine and oxaliplatin
CEA	carcinoembryonic antigen
CFI	chemotherapy-free interval
CI	confidence interval
CRC	colorectal cancer
CRO	contract research organization
CT	computed tomography
ctDNA	circulating tumor DNA
DBP	diastolic blood pressure
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DPD	dihydropyrimidine dehydrogenase
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
eDMC	external data monitoring committee
EMA	European Medicines Agency
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FAS	full analysis set
FDAAA	Food and Drug Administration Amendments Act
FOLFIRI	fluorouracil/leucovorin/irinotecan
FOLFOX	folinic acid/fluorouracil/oxaliplatin
FSH	follicle stimulating hormone
gBRCA	germline breast cancer susceptibility gene
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HER2-	human epidermal growth factor receptor 2 negative
HGSOC	high-grade serous ovarian cancer
HIV	human immunodeficiency virus
HR	hazard ratio
HRCT	high-resolution computed tomography
HRD	homologous recombination deficiency
HRQoL	health-related quality of life
HRR	homologous recombination repair
HRRm	homologous recombination repair mutation
HRT	hormone replacement therapy
IA	interim analysis
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

Abbreviation	Expanded Term
iCRO	imaging contract research organization
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IRT	interactive response technology
ITT	intention-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LAM	lactational amenorrhea method
LOH	loss of heterozygosity
mCRPC	metastatic castrate-resistant prostate cancer
MDS	myelodysplastic syndrome
mPFS	median PFS
MRI	magnetic resonance imaging
mut	mutant
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHEJ	non-homologous end-joining
ORR	objective response rate
OS	overall survival
OTC	over-the-counter
PARP	polyadenosine 5′-diphosphoribose polymerase
PD	progressive disease
PFS	progression-free survival
PFS2	second progression-free survival
PK	pharmacokinetic
po	by mouth/orally
PR	partial response
PRO	patient-reported outcomes
PSA	prostate-specific antigen
Q2W	every 2 weeks
Q3W	every 3 weeks
QLQ	Quality of Life Questionnaire
RECIST 1.1	Response Evaluation Criteria In Solid Tumors version 1.1
RNA	ribonucleic acid
RPLS	reversible posterior leukoencephalopathy syndrome
RR	response rate
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCLC	small cell lung cancer
SD	stable disease
SIM	Site Imaging Manual
SLAB	supplemental laboratory test(s)
SoA	Schedule of Activities
sSAP	supplemental statistical analysis plan
SSB	single-strand break
SUSAR	suspected unexpected serious adverse reaction
TCD	tumor control duration
TDT	time from randomization to discontinuation or death

Abbreviation	Expanded Term
TFST	time from randomization to first subsequent therapy or death
TNBC	triple-negative breast cancer
TPC	treatment of physician's choice
TSST	time from randomization to second subsequent therapy or death
VEGF	vascular endothelial growth factor
WOCBP	woman/women of childbearing potential
wt	wild type

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