Official Protocol Title:	A Multicenter, Open-label, Phase 2 Basket Study of MK-7684A, a Co-formation of Vibostolimab (MK-7684) With Pembrolizumab (MK-3475), With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors
NCT Number:	NCT05007106
Document Date:	22-Jan-2025

TITLE PAGE

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Protocol Title: A Multicenter, Open-label, Phase 2 Basket Study of MK-7684A, a Co-formation of Vibostolimab (MK-7684) With Pembrolizumab (MK-3475), With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors (KEYVIBE-005)

Protocol Number: 005-12

Compound Number: MK-7684A

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

Legal Registered Address:

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Regulatory Agency Identifying Number(s):

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IND	155349

Approval Date: 22 January 2025

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 12	22-JAN-2025	The Sponsor has decided to discontinue treatment with MK-7684A based on lack of efficacy observed in other studies.
Amendment 11	03-OCT-2024	To remove unnecessary visits and to adjust other visits to standard of care on all cohorts that have completed primary and secondary endpoint analyses.
Amendment 10	19-APR-2024	To add a maximum number of 45 cycles to lenvatinib for initial treatment/first course in Arm 3 (Cohort B2) and Arm 4 (Cohort G).
Amendment 09	16-AUG-2023	New data on the PFS event rate in the study supports a need to add flexible language to the timing of the final analysis of Cohort A1.
Amendment 08	01-MAY-2023	Incorrect non-standard text.
Amendment 07	05-APR-2023	To provide updates to reflect the evolving SOC, improve clarity of text, and correct inconsistencies.
Amendment 06	27-OCT-2022	To incorporate revisions based on health authority feedback.
Amendment 05	05-APR-2022	To add 4 new cohorts (Bladder, Ovarian, Gastric and Biliary) and an interim analysis to the ongoing randomized cervical cohort.
Amendment 04	30-NOV-2021	To correct errors in the numbering of the exclusion criteria specific for France.
Amendment 03	08-NOV-2021	To incorporate changes based on feedback from Health Authorities.
Amendment 02	04-JUN-2021	The chemotherapy study interventions fit the description of background treatment in the European Commission guidance and should have been listed as NIMP rather than IMP in the protocol.
Amendment 01	06-MAY-2021	To incorporate revisions based on health authority feedback.
Original Protocol	30-MAR-2021	Not applicable

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Amendment: 12

Overall Rationale for the Amendment:

The Sponsor has decided to discontinue treatment with MK-7684A based on lack of efficacy observed in other studies.

Summary of Changes Table

Section Number and Name	Description of Change	Brief Rationale
Primary Reason for Amendment		
Section 1, Protocol Summary	Participants receiving MK-7684A will be transitioned to pembrolizumab monotherapy or in combination with another protocol-specified therapy.	The Sponsor has decided to discontinue treatment with MK-7684A based on lack of efficacy observed in other studies.

Section Number and Name	Description of Change	Brief Rationale
Additional Changes		
Section 1, Protocol Summary	A brief summary of new data from MK-7684A studies was added.	To provide context for the discontinuation of the MK-7684A clinical program.
	A list of changes implemented in Amendment 11 was added for reference.	To emphasize that Amendment 12 is adding to the updates implemented in Amendment 11.
Section 1.1, Synopsis	Updated the pembrolizumab row in the study interventions table to apply to all participants.	Refer to rationale for Section 1 for the discontinuation of the MK-7684A clinical program.
Section 4, Study Design	The list of changes implemented in Amendment 11 was moved to this section from the subsequent section.	Refer to Section 1 rationale for including Amendment 11 information.
Section 4, Study Design Section 6, Study Intervention Section 7, Discontinuation of Study Intervention and Participant Withdrawal Section 8, Study Assessments and Procedures	•All cohorts are closed to enrollment. This study has enrolled 613 participants. •Participants receiving MK-7684A will be transitioned to pembrolizumab monotherapy or in combination with another protocol-specified therapy. •Pembrolizumab 200 mg will be administered IV q3w for all cohorts. •Pembrolizumab can be sourced locally or centrally. •Participants with access to approved SOC (eg, pembrolizumab alone or in combination with another protocol-defined therapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab alone or in combination with another protocol-defined therapy, but unable to access it as SOC outside the study, may continue on study and receive treatment until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.	Refer to rationale for Section 1 for the discontinuation of the MK-7684A clinical program.

Section Number and Name	Description of Change	Brief Rationale
Section 9, Statistical Analysis Plan	•All assessments in the SoA will be done per local standard of care. •Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit. If currently receiving protocol-specified therapy that does not include pembrolizumab, the participants will be discontinued from the study. •There will be no follow-up for survival status. Participants currently in imaging follow up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable. •Those participants remaining on study at the time of Amendment 12, should continue to be monitored in the study through the AE reporting period (Section 8.4). •Participants may enroll in an extension study, if available. -Participation in this study is ended when the participant is consented for an extension study. -The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study. -For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention allocation up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.	
Section 6.1, Study Intervention(s) Administered	Table 6: updated the pembrolizumab row to apply to all participants.	Refer to rationale for Section 1 for the discontinuation of the MK-7684A clinical program.
	Pembrolizumab can be sourced locally or centrally.	Refer to rationale for Section 1 for the discontinuation of the MK-7684A clinical program.
Section 8.11.5.2, Efficacy Follow-up Visits	Follow-up visits for efficacy will be discontinued for all participants. Exceptions for Cohort B1 and Cohort I were removed.	Refer to rationale for Section 1 for the discontinuation of the MK-7684A clinical program.

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1 PROTOCOL SUMMARY

Four Phase 3 studies met prespecified futility criteria for OS or RFS: MK-7684A-003 in metastatic NSCLC with PD-L1 TPS ≥50% [redacted], MK-7684A-007 in metastatic NSCLC with PD-L1 TPS ≥1% [redacted], MK-7684A-008 in ES-SCLC (OS HR, 1.26; 95% CI, 1.00-1.59; presented at Society for Immunotherapy of Cancer 2024), and MK-7684A-010 in adjuvant melanoma (RFS HR, 1.25; 95% CI, 0.87-1.80; presented at Society for Melanoma Research 2024) (data on file). Overall, the lack of efficacy observed with MK-7684A rendered the risk-benefit balance unfavorable, so treatment with this investigational therapy was stopped in all studies.

At implementation of Amendment 12 or upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments. Amendment 12 is adding to the updates implemented in Amendment 11.

- All cohorts are closed to enrollment. This study has enrolled 613 participants.
- Participants receiving MK-7684A will be transitioned to pembrolizumab monotherapy or in combination with another protocol-specified therapy.
- Pembrolizumab 200 mg will be administered IV q3w for all cohorts.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab alone or in combination with another protocol-defined therapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab alone or in combination with another protocol-defined therapy, but unable to access it as SOC outside the study, may continue on study and receive treatment until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- All assessments in the SoA will be done per local standard of care.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit. If currently receiving protocol-specified therapy that does not include pembrolizumab, the participants will be discontinued from the study.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 12, should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.

- The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.
- For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention allocation up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

Existing protocol content is retained for historical reference.

NOTE: As of Amendment 11, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, assessments of tumor response by imaging should continue as per local institutional guidelines.

In addition:

- Vital status (ie, OS) data will no longer be collected.
- PRO assessments (EORTC QLQ-C30, EORTC QLQ-CX24, EQ-5D-5L) will no longer be performed.
- Blood for ctDNA analysis and PBMC analysis will no longer be collected.
- Blood for PK and ADA will no longer be collected.
- Participants still on treatment with MK-7684A or pembrolizumab who are benefiting may continue treatment.
- Participants who are only receiving treatment with chemotherapy will continue treatment as part of the standard of care off-study.
- Second Course will no longer be offered. However, any participant receiving Second Course treatment prior to implementation of Amendment 11 will be able to complete treatment as planned.
- Treatment beyond progression, unless previously approved, will no longer be available.

1.1 Synopsis

Protocol Title: A Multicenter, Open-label, Phase 2 Basket Study of MK-7684A, a Co-formation of Vibostolimab (MK-7684) With Pembrolizumab (MK-3475), With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors (KEYVIBE-005)

Short Title: MK-7684A With or Without Other Anticancer Therapies in Participants With Selected Solid Tumors

Acronym: KEYVIBE-005

Hypotheses, Objectives, and Endpoints:

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

As of Amendment 11, OS data will no longer be collected.

In male and female participants with selected solid tumors:

Primary Objective	Primary Endpoint
- Objective: To compare MK-7684A to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1. - Hypothesis (H1): MK-7684A is superior to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- Objective response: A confirmed CR or PR.
- Objective: To compare MK-7684A to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1. - Hypothesis (H2): MK-7684A is superior to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- PFS: The time from randomization to first documented disease progression or death due to any cause, whichever occurs first.

- Objective: To evaluate MK-7684A alone or in combination with other anticancer therapies with respect to ORR per RECIST 1.1 as assessed by the investigator in participants with selected solid tumors, excluding 1) those with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1, 2) those enrolled in Cohort I.	- Objective response: A confirmed CR or PR.
- Objective: To evaluate MK-7684A in combination with other anticancer therapies with respect to PFS per RECIST 1.1 at 9 months (PFS-9) and 12 months (PFS-12) as assessed by the investigator in participants with previously untreated BRCA1/2 nonmutated and HRD-negative advanced epithelial ovarian cancer enrolled in Cohort I.	- PFS: The time from first dose of study intervention to first documented disease progression or death due to any cause, whichever occurs first.
Secondary Objectives	**Secondary Endpoints**
- Objective: To evaluate MK-7684A alone or in combination with other anticancer therapies with respect to OS in participants with selected solid tumors.	- OS: The time from randomization/treatment allocation to death due to any cause.
- Objective: To evaluate MK-7684A alone or in combination with other anticancer therapies with respect to PFS per RECIST 1.1 as assessed by the investigator in participants with selected solid tumors, excluding those with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- PFS: The time from first dose of study intervention to first documented disease progression or death due to any cause, whichever occurs first.
- Objective: To evaluate MK-7684A alone with respect to DOR per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- DOR: For participants with a confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

- Objective: To evaluate MK-7684A alone or in combination with other anticancer therapies with respect to DOR per RECIST 1.1 as assessed by the investigator in participants with selected solid tumors, excluding those with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- DOR: For participants with a confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
- Objective: To compare MK-7684A to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by investigator in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- Objective response: A confirmed CR or PR.
- Objective: To compare MK-7684A to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by investigator in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1	- PFS: The time from randomization to first documented disease progression or death due to any cause, whichever occurs first.
- Objective: To evaluate change from baseline in HRQoL using the EORTC QLQ-C30 in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- Mean change from baseline in the following scales/items: - Global health status/QoL score (EORTC QLQ-C30 items 29 and 30) - Physical functioning score (EORTC QLQ-C30 items 1-5)
- To evaluate the safety and tolerability of MK-7684A alone or in combination with other anticancer therapies.	- AEs - Discontinuations of study intervention due to AEs.

Overall Design:

Study Phase	Phase 2
Primary Purpose	Treatment
Indication	Advanced solid tumor
Population	Adult participants with selected solid tumors
Study Type	Interventional
Intervention Model	Parallel This is a multi site study.
Type of Control	Active-control for the randomized cohort (Cohort A1) No treatment control (Cohorts A2 to J)
Study Blinding	Unblinded open-label
Blinding Roles	No blinding
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 5.5 years from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 604 participants will be allocated to the study as described in Section 4.1. Enrollment may be expanded in the event intermediate dose levels are explored during the safety lead-in to identify the RP2D for lenvatinib, gemcitabine/cisplatin, 5-FU/cisplatin, paclitaxel, bevacizumab, and capecitabine/oxaliplatin to be used in combination with MK-7684A.

Intervention Groups and Duration:

At the time of implementation of Amendment 11, all cohorts are closed to enrollment.

Eligible participants will be randomly assigned/allocated to one of the following study intervention arms depending on selected cancer type:

- Arm 1: MK-7684A (Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, and Cohort H)
- Arm 2: Pembrolizumab (Cohort A1)
- Arm 3: MK-7684A + lenvatinib (Cohort B2)
- Arm 4: MK-7684A + lenvatinib (Cohort G)
- Arm 5: MK-7684A + 5-FU/cisplatin (Cohort E)
- Arm 6: MK-7684A + paclitaxel (Cohort F)
- Arm 7: MK-7684A + gemcitabine/cisplatin (Cohort D2)
- Arm 8: MK-7684A + carboplatin/ paclitaxel/bevacizumab (Cohort I)
- Arm 9: MK-7684A + capecitabine/oxaliplatin (Cohort J)

A safety lead-in will be performed to determine the tolerability and RP2D of lenvatinib (Cohort B2 and Cohort G), gemcitabine/cisplatin (Cohort D2), 5-FU/cisplatin (Cohort E), paclitaxel (Cohort F), bevacizumab (Cohort I), and capecitabine/oxaliplatin (Cohort J) to be used in combination with MK-7684A. Continued allocation into these cohorts will only occur if the starting dose (ie, Dose Level 0) is determined to be the RP2D (Section 4.3.5).

Arm Name	**Intervention Name**	**Unit Dose Strength(s)**	**Dosage Level(s)**	**Route of Administration**	**Regimen/ Treatment Period/ Vaccination Regimen**	**Use**
Arm 1	MK-7684A	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 mg/200 mg	IV Infusion	Q3W up to 35 cycles	Test Product
ALL PARTICIPANTS	Pembrolizumab	25 mg/mL	200 MG	IV Infusion	Q3W up to 35 cycles	Comparator
Arm 3	MK-7684A	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W up to 35 cycles	Test Product
Arm 3	Lenvatinib	10 mg; 4 mg	20 MG	Oral	Once daily up to 45 cycles	Test Product
Arm 4	MK-7684A	vibostolimab 200 mg + pembrolizumab 200 mg/20 mL	200 MG/200 MG	IV Infusion	Q3W up to 35 cycles	Test Product
Arm 4	Lenvatinib	10 mg/ 4 mg	12 mg/ 8 mg	Oral	Once daily up to 45 cycles	Test Product

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 5	MK-7684A	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W up to 35 cycles	Test Product
Arm 5	Cisplatin	1 mg/mL	80 MG/M^2	IV Infusion	Q3W up to 6 cycles	Background Treatment
Arm 5	5-FU	50 mg/mL	800 mg/m^2/day	IV Infusion	Continuous iv infusion on each of days 1 to 5 Q3W for up to 35 cycles	Background Treatment
Arm 6	MK-7684A	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W for up to 35 cycles	Test Product
Arm 6	paclitaxel	6 mg/mL	90 MG/M^2	IV Infusion	QW; Days 1, 8, and 15 of every 4-week cycle	Background Treatment
Arm 7	MK-7684A	vibostolimab 200 mg + pembrolizumab 200 mg/20 mL	200 MG/200 MG	IV Infusion	Q3W for up to 35 cycles	Test Product
Arm 7	Cisplatin	1 mg/mL vial, 20 mg vial, or 50 mg vial	25 MG/M²	IV Infusion	Day 1 and Day 8 of each 3-week cycle, up to 8 cycles	Background Treatment
Arm 7	Gemcitabine	1 g/ vial	1000 MG/M^2	IV Infusion	day 1 and day 8 of each 3-week cycle, until pd or unacceptable toxicity	Background Treatment
Arm 8	MK-7684A	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W for up to 35 cycles	Test Product
Arm 8	Carboplatin	10 mg/mL (60 mL)	AUC5 – AUC6	IV Infusion	Q3W; Day 1 of each 3-week cycle for up to 5 cycles	Background Treatment
Arm 8	Carboplatin	10 mg/mL (60 mL)	AUC2-AUC2.7	IV Infusion	QW; Day 1, 8, and 15 of each 3-week cycle for up to 5 cycles	Background Treatment
Arm 8	Paclitaxel	6 mg/mL (16.7 mL)	175 MG/M^2	IV Infusion	Q3W; Day 1 of each cycle for up to 5 cycles	Background Treatment

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Arm 8	Paclitaxel	6 mg/mL (16.7 mL)	80 MG/M^2	IV Infusion	QW; Day 1, 8, and 15 of each 3-week cycle for up to 5 cycles	Background Treatment
Arm 8	Paclitaxel	6 mg/mL (16.7 mL)	60 MG/M^2	IV Infusion	QW; Day 1, 8, and 15 of each 3-week cycle for up to 5 cycles	Background Treatment
Arm 8	Docetaxel	20 mg/mL	75 MG/M^2	IV Infusion	Q3W, Day 1 of each cycle for up to 5 cycles	Background Treatment
Arm 8	Bevacizumab (or biosimilars: MVASI®, Zirabev®, Aybintio®, ALYMSYS®, Abevmy®, Onbevezy®, Vegzelma®, CTNK®, Daiichi Sankyo®)	25 mg/mL (4 mL)	Variable	IV Infusion	Q3W; Day 1 of each 3-week cycle for up to 15 cycles or as local soc	Background Treatment
Arm 9	MK-7684A	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W for up to 35 cycles	Test Product
Arm 9	Capecitabine	150 mg tablet 500 mg tablet	1000 MG/M²	Oral	Twice daily on Days 1 to 14 of each cycle (q3w) for up to 35 cycles	Background Treatment
Arm 9	Oxaliplatin	5 mg/mL vial 50 mg vial or 100 mg vial	130 mg/m² on Day 1 of each cycle	IV Infusion	Q3W for up to 35 cycles	Background Treatment

5-FU=5-fluorouracil; Bkg=background; BW=body weight; Comp=comparator; DC=discontinuation; IV=intravenous; PD=disease progression; QW=once weekly; Q3W=every 3 weeks; qd=once daily; Test Prod=test product.
MK-7684A is a coformulation of vibostolimab (MK-7684) and pembrolizumab.
Starting dose for participants with HCC is based on actual body weight: 12 mg qd for participants ≥60 kg; 8 mg qd for participants <60 kg.
Formulation and unit dose strength may vary by region depending on market availability.
Administered as a continuous infusion on each of Days 1 to 5 Q3W; a total of 4000 mg/m^2 per 21-day cycle).
Administered as a 28-day cycle.
Investigator's choice of:

- Carboplatin AUC5 or AUC6 Q3W plus paclitaxel 175 mg/m2 Q3W
- Carboplatin AUC5 or AUC6 Q3W plus paclitaxel 80 mg/m2 QW
- Carboplatin AUC2 or AUC2.7 QW plus paclitaxel 60 mg/m^2 QW

For participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor. Docetaxel 75 mg/m^2 Q3W plus carboplatin AUC 5 Q3W.
Following consultation with the Sponsor, bevacizumab may be administered for up to 21 cycles on a case-by-case basis.
Duration of oxaliplatin treatment may be capped at 6 cycles as per local country guidelines.

Other current or former name(s) or alias(es) for study intervention(s) are as follows: MK-3475 (pembrolizumab); vibostolimab (MK-7684).

Total Number of Intervention Groups/Arms	9
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 (Cohorts A to H and J) or 56 days (Cohort I), each participant will be assigned to receive study intervention until one of the conditions for discontinuation of study intervention is met. Participants who complete study intervention after receiving 35 administrations of either MK-7684A or pembrolizumab, and participants who attain a complete response and stop study intervention may be eligible for up to 17 additional administrations of either MK-7684A or pembrolizumab (approximately 1 year) upon experiencing disease progression. After the end-of-treatment, each participant will be followed for the occurrence of AEs, SAEs, and other reportable safety events. Participants who discontinue for reasons other than radiographic disease progression will have posttreatment follow-up imaging for disease status until any of the conditions for discontinuation of imaging are met. All participants will be followed for overall survival until death, withdrawal of consent, or the end of the study.

Study Governance Committees:

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

Study governance considerations are outlined in Appendix 1.

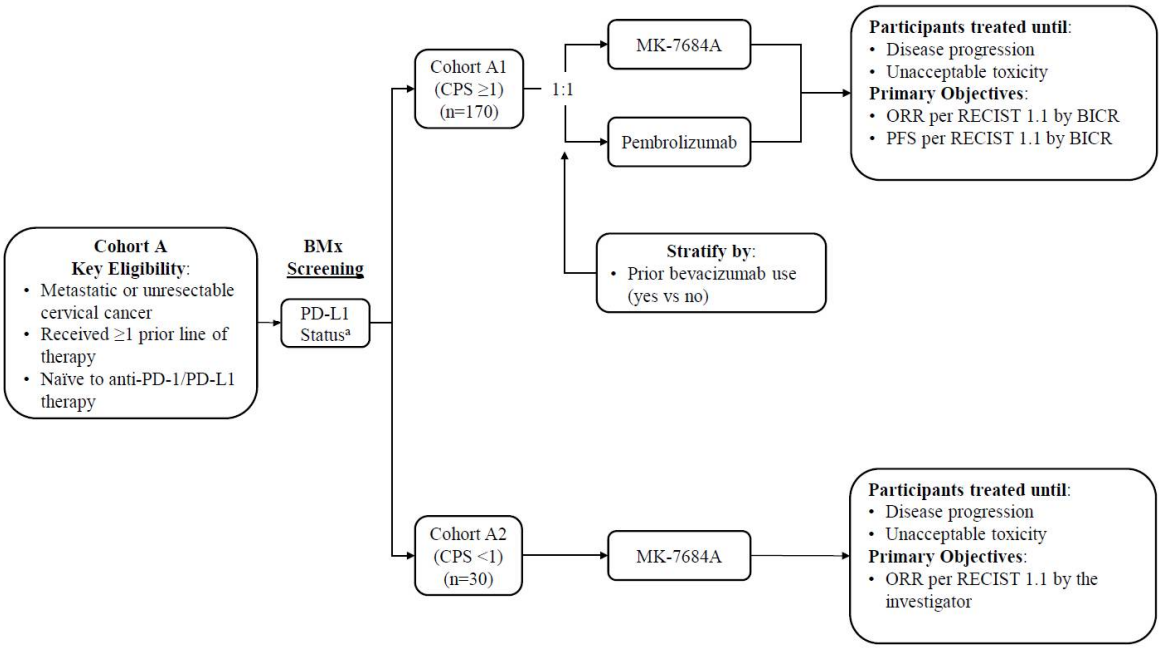
Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1, Figure 2, and Figure 3.

Figure 1 Study Design – Cohort A

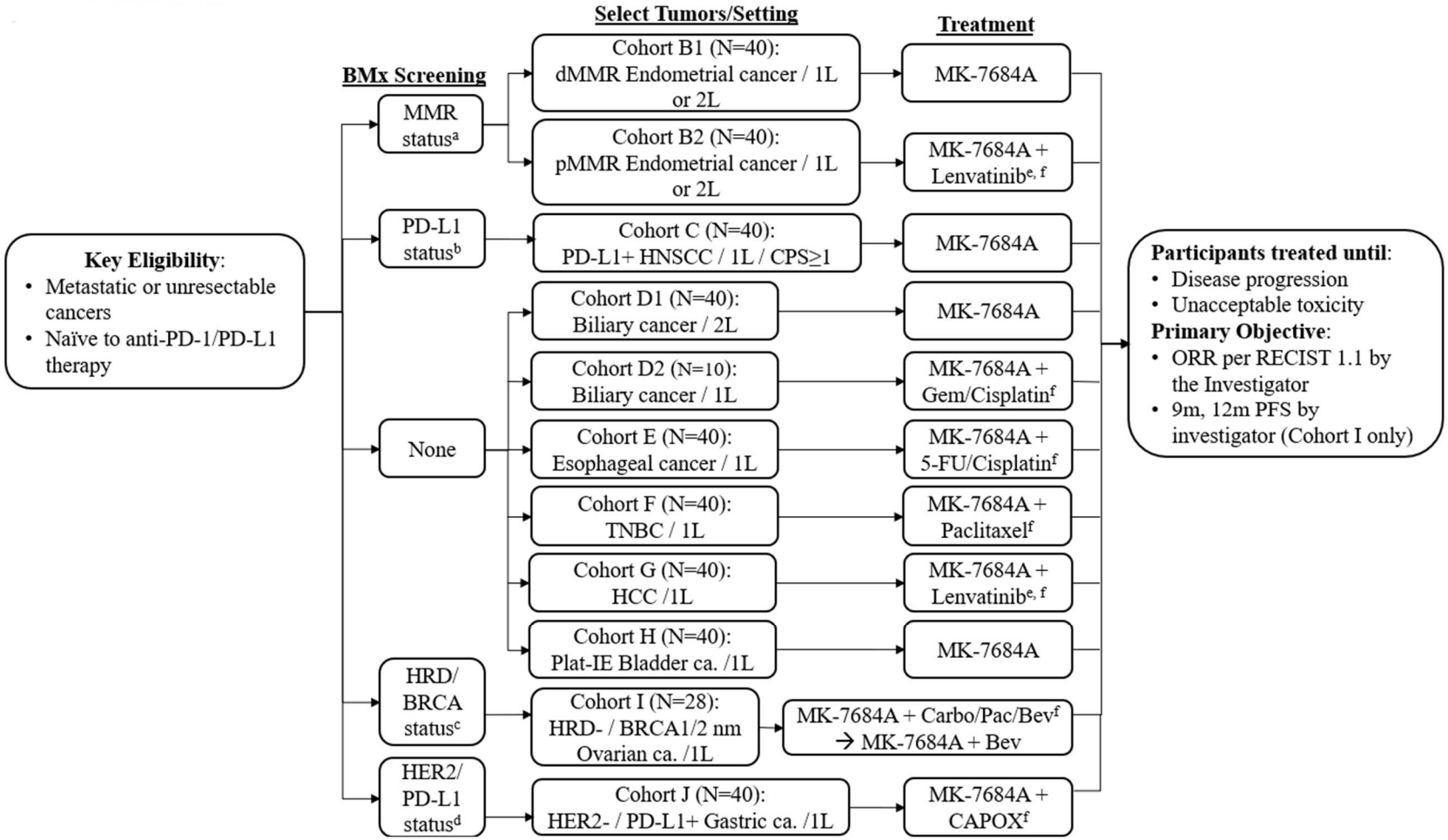


BICR=blinded independent central review; BMx=biomarker; CPS=combined positive score; ORR=objective response rate; PD-1=programmed cell death 1; PD-L1=programmed cell death 1 ligand 1; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

NOTE: MK-7684A – coformulation 200 mg vibostolimab and 200 mg pembrolizumab.

[a] PD-L1 testing to be performed by the central laboratory. Results are needed before randomization to study intervention.

Figure 2 Study Design – Cohort B to Cohort J



1L=first-line; 2L=second-line; 5-FU=5-fluorouracil; Bev=bevacizumab; BMx=biomarker; BRCA=breast cancer susceptibility gene; BW=body weight ca.=cancer; CAPOX=capecitabine and oxaliplatin; Carbo=carboplatin; CPS=combined positive score; dMMR=mismatch repair deficient; Gem=gemcitabine; HCC=hepatocellular carcinoma; HER2=human epidermal growth factor receptor-2; HNSCC=head and neck squamous cell carcinoma; HRD=homologous recombination repair deficient; IE=ineligible; m=months; MMR=mismatch repair; nm=nonmutated; ORR=objective response rate; Pac=paclitaxel; PD-1=programmed cell death 1; PD-L1=programmed cell death 1 ligand 1; PFS=progression-free survival; plat=platinum; pMMR=mismatch repair proficient; qd=once daily; RESIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; RP2D=recommended Phase 2 dose; TNBC=triple-negative breast cancer.

Note: MK-7684A – coformulation 200 mg vibostolimab and 200 mg pembrolizumab.

[a] MMR testing to be performed by the central laboratory. Results are needed before allocation to study intervention.

[b] PD-L1 testing will be performed by the local laboratory using the PD-L1 IHC 22C3 pharmDx assay. Data from the local PD-L1 testing are needed before allocation to study intervention. A sample must be submitted to the central laboratory for retrospective determination of PD-L1 status.

[c] HRD testing to be performed by the central laboratory. Results are needed before allocation to study intervention.

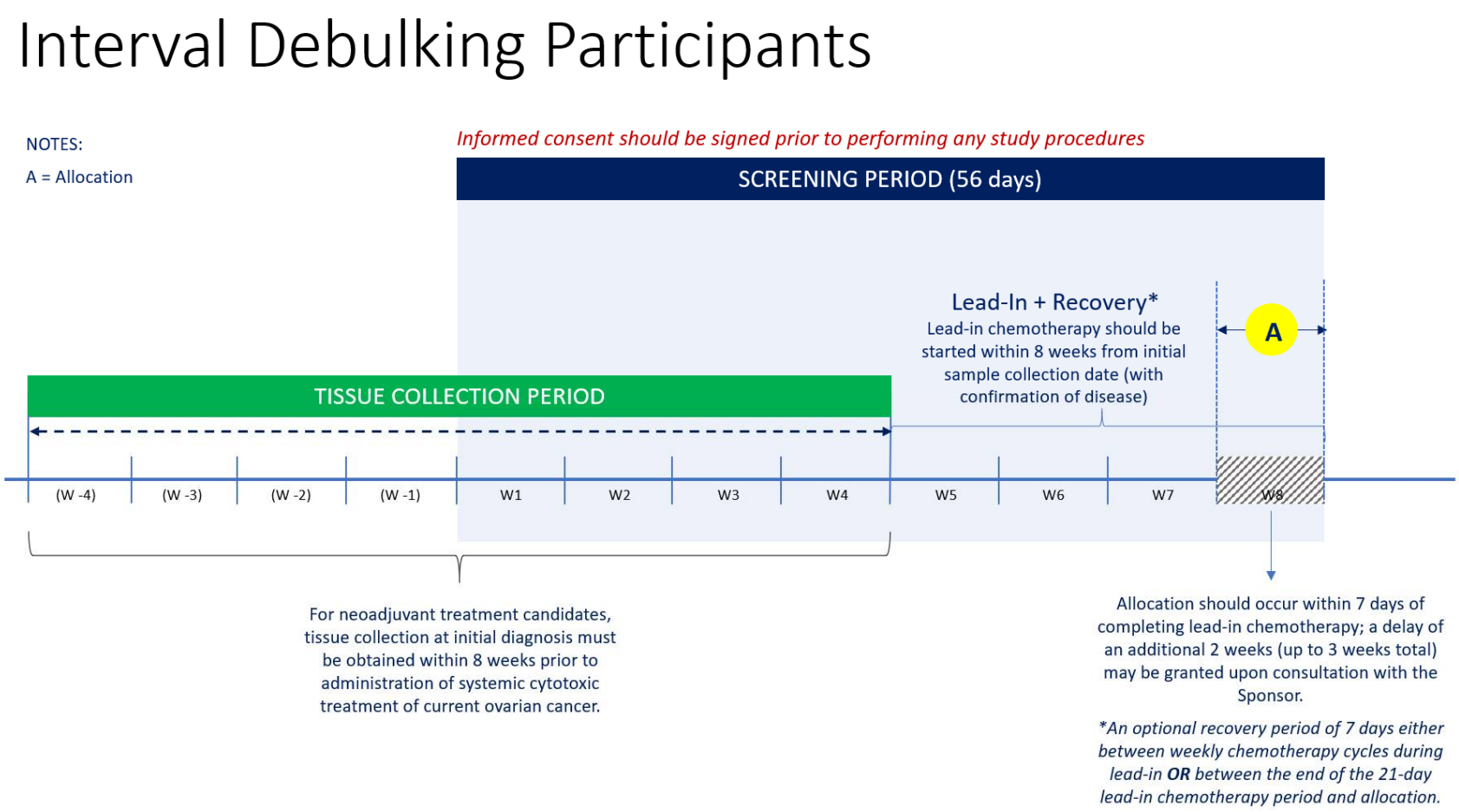
[d] HER2 testing to be performed by the local laboratory. Results are needed before allocation to study intervention. PD-L1 testing to be performed by the central laboratory. Results are needed before allocation to study intervention.

[e] Lenvatinib starting doses: endometrial cancer = 20 mg qd; HCC = 12 mg qd (BW ≥60 kg) or 8 mg qd (BW <60 kg). Lenvatinib is to be administered for up to 45 cycles.

[f] A safety lead-in will be performed to determine the tolerability and RP2D of lenvatinib, gemcitabine/cisplatin, 5-FU/cisplatin, paclitaxel, bevacizumab, and capecitabine/oxaliplatin to be used in combination with MK-7684A. Continued allocation into these cohorts will only occur if the starting dose (ie, Dose Level 0) is determined to be the RP2D.

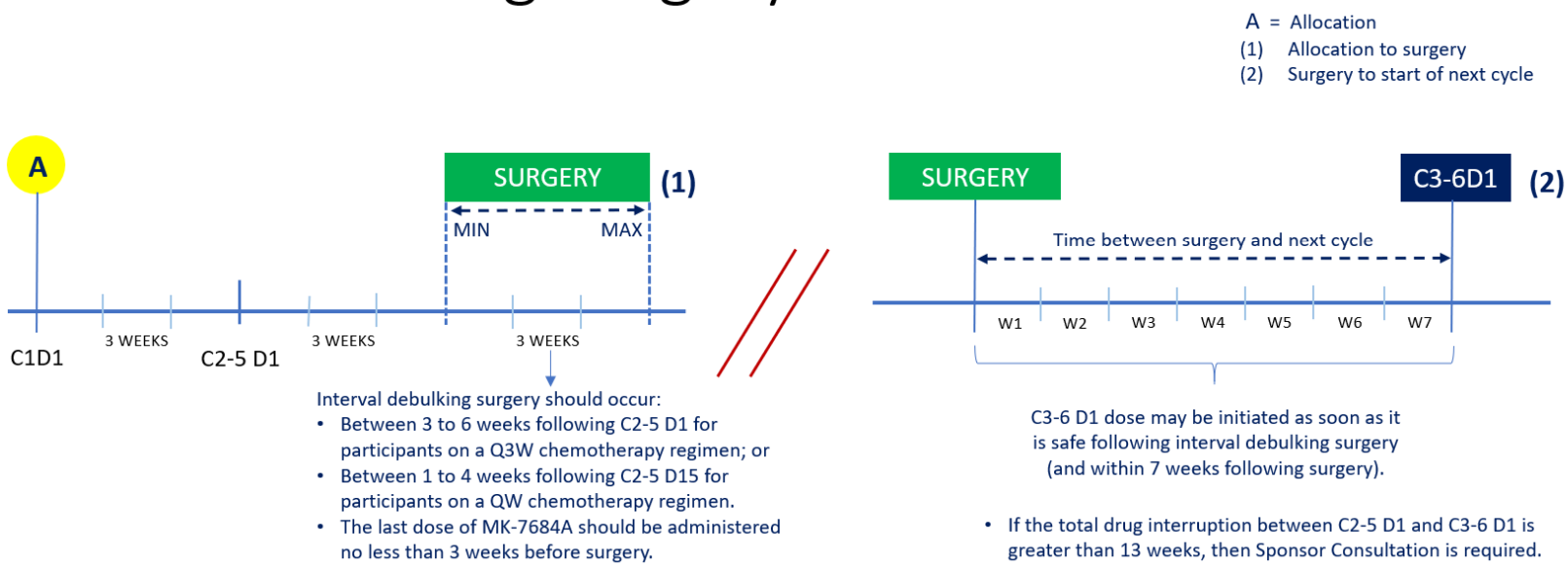
Figure 3 Study Intervals for Participants Eligible for Interval Debulking – Cohort I (Ovarian Cancer)

A) Screening / Lead-In



B) Interval Debulking Surgery

Interval Debulking Surgery



C1D1=Cycle 1 Day 1; C2D1=Cycle 2 Day 1, C2D15=Cycle 2 Day 15; C3D1=Cycle 3 Day 1; QW=once weekly; Q3W=every 3 weeks.

1.3 Schedule of Activities

1.3.1 Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J

NOTE: As of Amendment 11, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, assessments of tumor response by imaging should continue as per local institutional guidelines.

In addition:

- Vital status (ie, OS) data will no longer be collected.
- PRO assessments (EORTC QLQ-C30, EORTC QLQ-CX24, EQ-5D-5L) will no longer be performed.
- Blood for ctDNA analysis and PBMC analysis will no longer be collected.
- Blood for PK and ADA will no longer be collected.
- Participants still on treatment with MK-7684A or pembrolizumab who are benefiting can continue treatment.
- Participants who are only receiving treatment with chemotherapy will continue treatment as part of the standard of care off-study.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Administrative Procedures												
Authorization for Release of Tumor Tissue (**optional, Cohort A1, Cohort A2, Cohort B1, and Cohort J**)	X											Optional for participants who agree to provide a previously obtained tumor tissue sample for central determination of biomarker status prior to providing main ICF. Participants may provide documented Authorization for Release of Tumor Tissue before the start of the 28-day Screening Period and while on prior treatment.
Informed consent	X											Documented informed consent must be obtained before any protocol-specific screening procedures are performed. If the investigator plans to treat beyond disease progression, additional consent is required.
Inclusion/exclusion criteria	X											Refer to Appendix 7 for country-specific requirements.
Participant identification card	X	X										Update with randomization/allocation number at C1D1.
Demographic	X											
Medical history	X											
Cancer history	X											Review prior surgery, radiation, and oncologic therapy
FIGO stage at diagnosis (**Cohorts A1/A2 and B1 only**)	X											

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Prior and concomitant medications review	X	X	X*	X	X*	X	X*	X	X			Prior concomitant medications received within 28 days before the first dose of study intervention through 30 days after the last dose of study intervention. All concomitant medications administered during SAEs or ECIs (Section 8.4) are to be recorded. *Cohort D2 only. Note: CM review on Day 8 is not required after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.
Treatment randomization/allocation		X										Dose within 3 days of randomization/allocation.
Anticancer therapy status									X	X	X	Any changes in new treatment will be collected.
Vital status		X						X	X	X	X	Updated survival status may be requested by the Sponsor at any time during the course of the study.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Interventions												
MK-7684A (**All cohorts**)		X		X		X						Coformulation: 200 mg vibostolimab + 200 mg pembrolizumab Q3W MK-7684A should be administered before gemcitabine and cisplatin (**Cohort D2 only**), or 5-FU and cisplatin (**Cohort E only**).
Pembrolizumab (**Cohort A1 only**)		X		X		X						200 mg Q3W
Gemcitabine/Cisplatin (**Cohort D2 only**)		X	X	X	X	X	X					Gemcitabine: 1000 mg/m^2 IV on Day 1 and Day 8 Q3W until PD or unacceptable toxicity or maximum of 35 cycles. Refer to Section (8.1.8.1.3) for timing and order of dose administration. Cisplatin: 25 mg/m^2 IV on Day 1 and Day 8 Q3W for up to 8 cycles. Refer to Section (8.1.8.1.3) for timing and order of dose administration.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
5-FU/cisplatin (**Cohort E only**)		X		X		X						5-FU: 800 mg/m2/day (continuous IV on D1 through D5 of every 21-day cycle) Q3W × 35 cycles Cisplatin: 80 mg/m^2 Q3W × 6 cycles. Cisplatin will be capped at a total of 6 doses; cisplatin dosing may occur after Cycle 6 if cisplatin was withheld for 1 or more cycles during Cycles 2 to 6. Treatment with cisplatin and/or 5-FU may follow 1 to 2 days after MK-7684A (ie, Day 2 or Day 3) as needed per local standard of care.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Capecitabine/Oxaliplatin Administration (**Cohort J only**)		X		X		X						Oxaliplatin: 130 mg/m^2 IV administered as a 60 to 120 minute infusion or per the site's standard practice on D1 of each treatment cycle. Capecitabine: administered orally as a 1000 mg/m^2 dose twice daily from D1 to D14 of each treatment cycle. The evening dose of capecitabine should be taken approximately 12 hours after the morning dose. Capecitabine should be taken with food, or within 30 minutes after food/meal, with approximately 200 mL of water.
Efficacy Assessments												
Brain imaging (MRI; CT imaging will be acceptable if MRI is contraindicated)	X	X										Only required at Screening for participants with brain metastases (to demonstrate stability) or who are clinically symptomatic. On study imaging as clinically indicated. Perform at CR to confirm response for participants with brain metastases at baseline or at any other point during the study.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J								**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Bone imaging	X	X										Only required at Screening for participants with a history of bone metastases or who are clinically symptomatic. On study imaging as clinically indicated. Perform at CR to confirm response for participants with bone metastases at baseline or at any other point during the study.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J								**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**					**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Tumor imaging and response assessment (chest, abdomen, and pelvis)	X	X						X		X		Schedule should be followed regardless of treatment delays. **For Cohort C**: imaging must also include the head and neck. Perform imaging at Screening, then Q9W (63 ±7 days) from either randomization (Cohort A1) or C1D1 (all other cohorts) through Week 54, and Q12W (±7 days) thereafter: ▪ For Cohort A1, imaging will be performed until BICR confirmed PD or as detailed in Section 8.2.1.2. ▪ For Cohorts B1, C, D1, D2, E, H, and J, imaging will be performed until PD is identified by the investigator or as detailed in Section 8.2.1.2. If imaging was obtained within 4 weeks before treatment DC, scan at DC is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Clinical Procedures/Assessments												
AE/SAE monitoring	X	X	X*	X	X*	X	X*	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier. *Cohort D2 only. Note: AE review on Day 8 is not required after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J								**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**					**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**			
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Full physical examination	X							X			To be performed within 7 days before start of study intervention. **Cohorts D2 and E**: Refer to local regulations or local standard of practice for patient management regarding 5-FU and cisplatin treatment (eg, requirements for baseline and periodic audiograms for cisplatin). **Cohort J**: Include additional monitoring, as necessary, for participants receiving capecitabine. Refer to Appendix 7 for country-specific requirements.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Directed physical examination		X	X*	X	X*	X	X*		X			**Cohorts D2 and E**: Refer to local regulations or local standard of practice for patient management regarding 5-FU and cisplatin treatment (eg, requirements for baseline and periodic audiograms for cisplatin). **Cohort J**: Include additional monitoring, as necessary, for participants receiving capecitabine Refer to Appendix 7 for country-specific requirements. *Cohort D2 only. Note: Day 8 directed physical examination is not required after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.
Height	X											
Vital sign measurements, weight	X	X	X*	X	X*	X	X*	X	X			Predose and as clinically indicated. *Cohort D2 only. Note: Day 8 vital signs and weight are not required after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
12-lead ECG	X											Additional ECGs can be performed as clinically indicated. 6-lead ECGs may be allowed per institutional standard. Refer to Section 8.3.3.1.
ECOG performance status	X	X	X*	X	X*	X	X*	X	X			Performed within 7 days before starting study intervention and before each treatment administration. *Cohort D2 only. Note: Day 8 ECOG PS will not be performed after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.
Laboratory Assessments – Local Laboratory												
Pregnancy test for WOCBP (**Cohorts A1, A2, B1, C, D1, and H**)	X							X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before starting MK-7684A or pembrolizumab. Additional pregnancy testing to be conducted as clinically indicated. Refer to Appendix 7 for country-specific requirements.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Pregnancy test for WOCBP (**Cohorts D2, E, and J**)	X	X		X		X		X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before each dose of study intervention. Additional pregnancy testing to be conducted as clinically indicated.
HBV / HCV / HIV	X											Testing is only required if mandated by local regulations. Refer to Appendix 7 for country-specific requirements.
HPV (**Cohorts A1, A2, and C only**)	X											**Cohorts A1/A2**: If available, collect history of HPV status at baseline. **Cohort C**: history of HPV status is only to be collected for participants with oropharyngeal cancer. HPV status for Cohorts A and C should be determined locally by P16 IHC, PCR, or FISH.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
CBC with differential	X		X*	X	X*	X	X*	X	X			Performed within 10 days before first dose. After C1, collect within 3 days before dosing. Urinalysis should be performed every 4 cycles (C5, C9, etc.). *Cohort D2 only. Note: Day 8 CBC and chemistry panel blood samples will not be collected after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.
Chemistry Panel	X		X*	X	X*	X	X*	X	X			
Urinalysis	X			X		X		X	X			
PT/INR and aPTT/PTT	X											Screening samples collected within 10 days before first dose of study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
Thyroid function (T3, T4, and TSH)	X			X		X		X	X			Should be performed at Screening and predose of every other cycle starting from C2 (ie, C4, C6, C8, etc.). Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
PD-L1 status (**Cohort C only**)	X											PD-L1 status will be determined locally using the PD-L1 IHC 22C3 pharmDx assay for participants with HNSCC for eligibility purposes (ie, CPS ≥1); the results are needed before allocation to study intervention. A sample must be submitted to the central laboratory for retrospective determination of PD-L1.
HER2/neu status (**Cohort E and Cohort J only**)	X											Results from the local laboratory for HER2/neu status are needed before allocation to study treatment. **For Cohort E**: only for participants with Siewert type 1 adenocarcinoma of the GEJ. If HER-2/neu status is unknown, site should follow local standards for HER-2/neu testing.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Laboratory Assessments – Central Laboratory												
PD-L1 status	X											**Cohorts A1 and A2**: Results from the central determination of PD-L1 status are needed before randomization to study treatment. **Cohorts B1, C, D1, D2, E, and H**: PD-L1 status can be retrospectively determined. Central PD-L1 status from screening can be used for rescreening. **Cohort J**: Submit only for participants that are HER2 negative. Results from the central determination of PD-L1 status are needed before allocation to study treatment.
MMR status (**Cohort B1 only**)	X											Results from the central determination of MMR status are needed before allocation to study treatment. Central MMR status from screening can be used for rescreening.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J									**Posttreatment Visits**			**Notes**
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Blood for serum vibostolimab and pembrolizumab PK		X		X		X						PK and ADA samples should be drawn within 24 hours before study intervention administration in Cycles 1, 2, 4 and every 4 cycles thereafter (ie, C8, C12, C16, etc.) through C32. Additional postdose (end of infusion) PK only samples will be drawn within 10 minutes after end of infusion at C1 and C8. Note: PK and ADA sampling is not required for participants receiving pembrolizumab monotherapy in Cohort A1.
Blood for ADA of vibostolimab and pembrolizumab		X		X		X						
Blood for genetic analysis		X										Collect before study intervention. If broad genetic analysis is not approved, the sample will only be collected and tested for MSI (Cohort J).
Blood for PBMC analysis		X		X				X				Collect at predose on D1 of C1, C2, C3, and at EOT.
Blood for ctDNA Analysis		X		X		X		X				Collect at predose on D1 of C1, C2, C3, C5, C7, C10, C13, C16, C19, then on D1 of every 4 cycles (ie, C23, C27, etc.).
Tumor Tissue Collection												
Newly obtained/archival tissue sample for PD-L1 analysis and other biomarkers	X											May use archival tissue sample obtained before Screening as part of the participant's SOC.

Initial Treatment/First Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J								Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**						**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**		**2 to 8**		**9 to 35**		**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**1**	**8**	**1**	**8**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Patient-reported Outcomes												**Perform PRO assessments in the order as listed.**
EORTC QLQ-C30 (**Cohort A only**)		X*		X*		X*		X	X			*Perform up to -3 days before every cycle through C17, then every other cycle through C35 (ie, C19, C21, C23, etc.). If the EOT visit occurs 30 days (+7 days) from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, ePROs do not need to be repeated. If the participant does not complete the HRQoL survey(s), the MISS_MODE form must be completed to capture the reason the assessment(s) was not performed.
EORTC QLQ-CX24 (**Cohort A only**)		X*		X*		X*		X	X			
EQ-5D-5L (**Cohort A only**)		X*		X*		X*		X	X			

5-FU=5-fluorouracil; ADA=antidrug antibody(ies); AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; BW=body weight; C#=cycle number; CBC=complete blood count; CM=concomitant medication; CR=complete response; CT=computed tomography; ctDNA=circulating tumor DNA; D#=day number; DC=discontinuation; dMMR=mismatch repair deficient; ECG=electrocardiogram; ECHO=echocardiogram; ECI=event(s) of clinical interest; ECOG=Eastern Cooperative Oncology Group; EDTA=ethylenediaminetetraacetic acid; EORTC=European Organisation for Research and Treatment of Cancer; EOT=end-of-treatment; EQ-5D-5L=EuroQol 5-dimension 5-level; FIGO=International Federation of Gynecology and Obstetrics; FISH=fluorescent in situ hybridization; FU=follow-up; HBV=hepatitis B virus; HCV=hepatitis C virus; HER2=human epidermal growth factor receptor 2; HIV=human immunodeficiency virus; HPV=human papilloma virus; HRQoL=health-related quality-of-life; INR=international normalized ratio; IV=intravenous(ly); LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MSI=microsatellite instability; MUGA=multiple-gated acquisition; PBMC=peripheral blood mononuclear cell; PCR=polymerase chain reaction; PD=progressive disease; PD-L1=programmed cell death 1 ligand 1; PK=pharmacokinetic; pMMR=mismatch repair proficient; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; qd=once daily; QLQ-C30=quality-of-life questionnaire core 30; QLQ-CX24=cervical cancer-specific quality-of-life questionnaire; SAE=serious adverse event; SOC=standard of care; TNBC=triple-negative breast cancer; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; UPCR=urine protein-to-creatinine ratio; WOCBP=women of childbearing potential.

1.3.2 Initial Treatment/First Course – Cohort B2 and Cohort G

NOTE: As of Amendment 11, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, assessments of tumor response by imaging should continue as per local institutional guidelines.

In addition:

- Vital status (ie, OS) data will no longer be collected.
- Blood for ctDNA analysis and PBMC analysis will no longer be collected.
- Blood for PK and ADA will no longer be collected.
- Participants still on treatment with MK-7684A and/or lenvatinib who are benefiting can continue treatment.

The section below is retained for reference.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Administrative Procedures																
Authorization for Release of Tumor Tissue (**optional, Cohort B2 only**)	X															Optional for participants who agree to provide a previously obtained tumor tissue sample for central determination of MMR status prior to providing main ICF. Participants may provide documented Authorization for Release of Tumor Tissue before the start of the 28-day Screening Period and while on prior treatment.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Informed consent	X															Documented informed consent must be obtained before any protocol-specific screening procedures are performed. **Cohort B2 only**: If MMR results are unavailable within 28 days from the date of original consent, an extension may be granted after consultation with the Sponsor as long as all other screening procedures are performed within the protocol-specified timeframe. If the investigator plans to treat beyond disease progression, additional consent is required.
Inclusion/ exclusion criteria	X															
Participant identification card	X	X														Update with allocation number at C1D1.
Demographic	X															
Medical history	X															
Cancer history	X															Review prior surgery, radiation and oncologic therapy

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
FIGO stage at diagnosis (**Cohort B2 only**)	X															
Prior and concomitant medications review	X	X	X	X	X	X	X	X	X	X	X	X	X			Prior concomitant medications received within 28 days before the first dose of study intervention through 30 days after the last dose of study intervention. All concomitant medications administered during SAEs or ECIs (Section 8.4) are to be recorded.
Treatment allocation		X														Dose within 3 days of allocation.
Anticancer therapy status													X	X	X	Any changes in new treatment will be collected.
Vital status		X										X	X	X	X	Updated survival status may be requested by the Sponsor at any time during the study.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Home virtual visit			X													Participants will be contacted to report BP and record AEs. Blood pressure will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee.
Interventions																
MK-7684A		X			X		X	X	X	X						Coformulation: 200 mg vibostolimab + 200 mg pembrolizumab Q3W. MK-7684A should be administered prior lenvatinib on C1D1 and C2D1.
Lenvatinib dispensing		X			X		X	X	X	X	X					Lenvatinib to be self-administered daily for up to 45 cycles: – 20 mg qd (Cohort B2) – 12 mg qd (Cohort G; BW ≥60 kg); – 8 mg qd (Cohort G; BW <60 kg).
Lenvatinib bottle collection					X		X	X	X	X	X	X				

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Efficacy Assessments																
Brain imaging (MRI; CT imaging will be acceptable if MRI is contraindicated)	X	X														Only required at Screening for participants with brain metastases (to demonstrate stability) or who are clinically symptomatic. On study imaging as clinically indicated. Perform at CR to confirm response for participants with brain metastases at baseline or at any other point during the study.
Bone imaging	X	X														Only required at Screening for participants with a history of bone metastases or who are clinically symptomatic. On study imaging as clinically indicated. Perform at CR to confirm response for participants with bone metastases at baseline or at any other point during the study.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Tumor imaging and response assessment (chest, abdomen, and pelvis)	X	X										X		X		Schedule should be followed regardless of treatment delays. **For Cohort G**: imaging must also include triphasic abdomen CT/MRI for liver evaluation. Perform imaging at Screening, then Q9W (63 ±7 days) from C1D1 through Week 54, and Q12W (±7 days) thereafter until PD is identified by the investigator or as detailed in Section 8.2.1.2. If imaging was obtained within 4 weeks before treatment DC, scan at DC is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Clinical Procedures/Assessments																
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.
Full physical examination	X											X				To be performed within 7 days before start of study intervention. An oral examination must be included.
Directed physical examination		X	X*	X	X	X*	X	X	X	X	X		X			*C1D8 and C2D15 are mandatory visits in the Safety lead-in. C1D8 can be omitted during the expansion phase if a home virtual visit is performed. C2D15 is not mandatory during the expansion phase. An oral examination must be included.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Child-Pugh score (**Cohort G only**)	X															If any hepatic ECI criteria are met, document the Child-Pugh score with each visit until the hepatic ECIs resolve.
Height	X															
Vital sign measurements (including BP), weight	X	X	X*	X	X	X*	X	X	X	X	X	X	X			Predose and as clinically indicated. Participants with initial or recurrent systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored until systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg for 2 consecutive treatment cycles. *C1D8 and C2D15 are mandatory visits in the Safety lead-in. During the expansion phase, a home virtual visit can be scheduled at C1D8 to report BP and AEs. C2D15 is not mandatory during the expansion phase.
NYHA	X															See Appendix 9

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
12-lead ECG	X	X			X					X	X	X	X			After C2D1, ECG to be performed D1 of every fourth cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.). ECG at C1D1 and C2D1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk participants (Section 8.3.3.2), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.
LVEF assessment by MUGA or ECHO	X												X			Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study. Refer to Appendix 7 for country-specific requirements.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
ECOG performance status	X	X			X		X	X	X	X	X	X	X			Performed within 7 days before starting study intervention and before each treatment administration.
Gastroenterological endoscopy (Cohort G only)	X															Gastroenterological upper endoscopy at Screening Period is necessary unless such screening has been performed in the past 3 months before the first dose of treatment.
Laboratory Assessments – Local Laboratory																
Pregnancy test for WOCBP	X				X		X	X	X	X	X	X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before each dose of study intervention. Additional testing to be performed as clinically indicated. Refer to Appendix 7 for country-specific requirements.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
HBV / HCV / HIV	X															Testing is only required if mandated by local regulations. Refer to Appendix 7 for country-specific requirements.
CBC with differential	X			X	X		X	X	X	X	X	X	X			Performed within 10 days before first dose. After C1, collect within 3 days before dosing. Urinalysis should be performed every 4 cycles (C5, C9, etc.).
Chemistry Panel	X			X	X		X	X	X	X	X	X	X			
Urinalysis	X								X	X	X	X	X			
Urine dipstick testing for protein	X	X			X		X	X	X	X	X	X	X			Perform at Screening and within 7 days before the first dose of study intervention. After C1D1, urine dipstick testing will be performed within 3 days before D1 of each subsequent cycle while participants are taking lenvatinib. Note: urinalysis may be used if the urine dipstick is not feasible. Refer to Section 6.6.3.2 for management of proteinuria by dipstick, UPCR and/or 24-hour urinalysis.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
PT/INR and aPTT/PTT	X															Screening samples collected within 10 days before the first dose of study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
Thyroid function (T3, T4, and TSH)	X				X			X		X	X	X	X			Should be performed at Screening and predose of every other cycle starting from C2 (ie, C4, C6, C8, etc.). Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.
Laboratory Assessments – Central Laboratory																
PD-L1 status	X															PD-L1 status will be retrospectively determined.

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
MMR status (**Cohort B2 only**)	X															Results from the central determination of MMR status are needed before allocation to study treatment. Central MMR status from screening can be used for rescreening.
Blood for serum vibostolimab and pembrolizumab PK		X			X			X		X*	X*					PK and ADA samples should be drawn within 24 hours before study intervention administration. Additional postdose (end of infusion) PK only samples will be drawn within 10 minutes after end of infusion at C1 and C8. *After C4, PK and ADA samples to be collected every 4 cycles (ie, C8, C12, C16, etc.) through C32.
Blood for ADA of vibostolimab and pembrolizumab		X			X			X		X*	X*					

Initial Treatment/First Course – Cohort B2 and Cohort G												Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Blood for plasma lenvatinib PK		X		X	X											Lenvatinib PK samples will be drawn: • Day 1 of Cycle 1 (between 0.5 to 4 hours and 6 to 10 hours postdose) • Day 15 of Cycle 1 (predose and between 2 to 12 hours postdose) • Day 1 of Cycle 2 (predose and between 0.5 to 4 hours and 6 to 10 hours postdose). All predose samples should be collected within 2 hours of lenvatinib dosing. Postdose samples are not needed if lenvatinib administration is skipped.
Blood for genetic analysis		X														Collect before study intervention.
Blood for PBMC analysis		X			X		X					X				Collect at predose on D1 of C1, C2, C3, and EOT.
Blood for ctDNA Analysis		X			X		X		X	X	X	X				Collect at predose on D1 of C1, C2, C3, C5, C7, C10, C13, C16, C19, then on D1 of every 4 cycles (ie, C23, C27, etc.).

Initial Treatment/First Course – Cohort B2 and Cohort G													Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**										**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**-28 to -1**	**1**			**2**		**3**	**4**	**5**	**6 to 35**	**36-45**	**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day		**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Tumor Tissue Collection																
Newly obtained/archival tissue sample for PD-L1 analysis and other biomarkers	X															May use archival tissue sample obtained before Screening as part of the participant's SOC.

ADA=antidrug antibody(ies); AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; BW=body weight; C#=cycle number; CBC=complete blood count; CR=complete response; CT=computed tomography; ctDNA=circulating tumor DNA; D#=day number; DC=discontinuation; dMMR=mismatch repair deficient; ECG=electrocardiogram; ECHO=echocardiogram; ECI=event(s) of clinical interest; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; FIGO=International Federation of Gynecology and Obstetrics; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; IV=intravenous(ly); LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; NYHA=New York Heart Association; PBMC=peripheral blood mononuclear cell; PD=progressive disease; PD-L1=programmed cell death 1 ligand 1; PK=pharmacokinetic; pMMR=mismatch repair proficient; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; qd=once daily; SAE=serious adverse event; SOC=standard of care; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; UPCR=urine protein-to-creatinine ratio; WOCBP=women of childbearing potential.

1.3.3 Initial Treatment/First Course – Cohort F

NOTE: As of Amendment 11, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, assessments of tumor response by imaging should continue as per local institutional guidelines.

In addition:

- Vital status (ie, OS) data will no longer be collected.
- Blood for ctDNA analysis and PBMC analysis will no longer be collected.
- Blood for PK and ADA will no longer be collected.
- Participants still on treatment with MK-7684A who are benefiting can continue treatment.
- Participants who are only receiving treatment with chemotherapy will continue treatment as part of the standard of care off study.

The section below is retained for reference.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Administrative Procedures																		
Informed consent	X																	Documented informed consent must be obtained before any protocol-specific screening procedures are performed. If the investigator plans to treat beyond disease progression, additional consent is required.
Inclusion/exclusion criteria	X																	
Participant identification card	X	X																Update with allocation number at C1D1.
Demographic	X																	
Medical history	X																	
Cancer history	X																	Review prior surgery, radiation and oncologic therapy.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Prior and concomitant medications review	X	X	X	X	X	X	X	X		X	X	X		X	X			Prior concomitant medications received within 28 days before the first dose of study intervention through 30 days after the last dose of study intervention. All concomitant medications administered during SAEs or ECIs (Section 8.4) are to be recorded.
Treatment allocation		X																Dose within 3 days of allocation.
Anticancer therapy status															X	X	X	Any changes in new treatment will be collected.

Initial Treatment/First Course – Cohort F															Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Vital status		X												X	X	X	X	Updated survival status may be requested by the Sponsor at any time during the course of the study.
Interventions																		
MK-7684A		X			X			X			X							Coformulation: 200 mg vibostolimab + 200 mg pembrolizumab Q3W. MK-7684A should be administered prior to paclitaxel.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Paclitaxel		X	X	X		X	X	X		X	X	X						90 mg/m^2 on D1, D8, and D15 of every 28-day cycle. Should an investigator discontinue treatment with paclitaxel but continue treatment with MK-7684A, the participant does not need to come to the clinic on dates when only paclitaxel would have been administered. The participant should still follow the treatment and procedure schedule for MK-7684A visits.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Efficacy Assessments																		
Brain imaging (MRI; CT imaging will be acceptable if MRI is contraindicated)	X	X																Only required at Screening for participants with brain metastases at (to demonstrate stability) or who are clinically symptomatic. On study imaging as clinically indicated. Perform at CR to confirm response for participants with brain metastases at baseline or at any other point during the study.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**											**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Bone imaging	X	X															Only required at Screening for participants with a history of bone metastases or who are clinically symptomatic. On study imaging as clinically indicated. Perform at CR to confirm response for participants with bone metastases at baseline or at any other point during the study.	

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Tumor imaging and response assessment (chest, abdomen, and pelvis)	X	X												X		X		Schedule should be followed regardless of treatment delays. Perform imaging at Screening, then Q9W (63 ±7 days) from C1D1 through Week 54, and
																		Q12W (±7 days) thereafter until PD is identified by the investigator or as detailed in Section 8.2.1.2. If imaging was obtained within 4 weeks before treatment DC, scan at DC is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Clinical Procedures/Assessments																		
AE/SAE monitoring	X	X	X	X	X	X	X	X		X	X	X		X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.
Full physical examination	X													X				To be performed within 7 days before start of study intervention.
Directed physical examination		X			X			X			X				X			

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Height	X																	
Vital sign measurements, weight	X	X	X	X	X	X	X	X		X	X	X		X	X			Predose and as clinically indicated.
12-lead ECG	X																	Additional ECGs can be performed as clinically indicated. 6-lead ECGs may be allowed per institutional standard. Refer to Section 8.3.3.1.
ECOG performance status	X	X			X			X			X			X	X			Performed within 7 days before starting study intervention and before each treatment administration.

Initial Treatment/First Course – Cohort F															Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Laboratory Assessments – Local Laboratory																		
Pregnancy test for WOCBP	X	X			X			X			X			X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before C1 of each 21-day treatment cycle. Additional testing to be performed as clinically indicated. Refer to Appendix 7 for country-specific requirements.
HBV / HCV / HIV	X																	Testing is only required if mandated by local regulations. Refer to Appendix 7 for country-specific requirements.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
CBC with differential	X	X*	X	X	X	X	X	X		X	X	X		X	X			Performed within 10 days before first dose. After C1, collect within 3 days before dosing. *Not required for C1D1; assessments on D1 are required in subsequent cycles starting with Cycle 5. §Urinalysis should be performed every 4 cycles (C5, C9 etc.).
Chemistry Panel	X	X*			X			X			X			X	X			
Urinalysis	X	X*									X§			X	X			

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
PT/INR and aPTT/PTT	X																	Screening samples collected within 10 days before first dose of study intervention. Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.

Initial Treatment/First Course – Cohort F															Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Thyroid function (T3, T4, and TSH)	X				X						X			X	X			Should be performed at Screening and predose of every other cycle starting from C2 (ie, C4, C6, C8, etc.). Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.
ER/PgR status	X																	Results from the local determination of ER/PgR status are needed before allocation to study treatment.
BRCA1/2 status	X																	BRCA1/2 status can be determined retrospectively.

Initial Treatment/First Course – Cohort F															Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
HER2/neu status	X																	Results from the local testing of HER2/neu status are needed before allocation to study treatment.
Laboratory Assessments – Central Laboratory																		
PD-L1 status	X																	PD-L1 status will be retrospectively determined.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Blood for serum vibostolimab and pembrolizumab PK		X			X						X*							PK and ADA samples should be drawn within 24 hours before study intervention administration. Additional postdose (end of infusion) PK only samples will be drawn within 10 minutes after end of infusion at C1 and C8. *After C4, PK and ADA samples to be collected every 4 cycles (ie, C8, C12, C16, etc.) through C32.
Blood for ADA of vibostolimab and pembrolizumab		X			X						X*							
Blood for genetic analysis		X																Collect before study intervention.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** ***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Blood for PBMC analysis		X			X			X						X				Collect at predose on D1 of C1, C2, C3, and at EOT.
Blood for ctDNA Analysis		X			X			X			X*			X				Collect at predose on D1 of C1, C2, C3. *After C3, collect predose on D1 of C5, C7, C10, C13, C16, C19, then on D1 of every 4 cycles (ie, C23, C27, etc.).
Tumor Tissue Collection																		
Newly obtained/archival tissue sample for PD-L1 analysis and other biomarkers	X																	May use archival tissue sample obtained before Screening as part of the participant's SOC.

Initial Treatment/First Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Screening**	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number		**1**			**2**			**3**			**4 to 35***			**At DC**	**30 Days post last dose**	**Q9W or Q12W**	**Q12W**	***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Cycle Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)		**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	

ADA=antidrug antibody(ies); AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; BP=blood pressure; BRCA=breast cancer susceptibility gene 1/2; BW=body weight; C#=cycle number; CBC=complete blood count; CR=complete response; CT=computed tomography; ctDNA=circulating tumor DNA; D#=day number; DC=discontinuation; ECG=electrocardiogram; ECHO=echocardiogram; ECI=event(s) of clinical interest; ECOG=Eastern Cooperative Oncology Group; HBV=hepatitis B virus; HCV=hepatitis C virus; HER2=human epidermal growth factor receptor 2; HIV=human immunodeficiency virus; INR=international normalized ratio; IV=intravenous(ly); MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cell; PD=progressive disease; PD-L1=programmed cell death 1 ligand 1; PK=pharmacokinetic; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; SAE=serious adverse event; SOC=standard of care; TNBC=triple-negative breast cancer; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.4 Second Course Treatment – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J

Note: As of implementation of Amendment 11, Second Course will no longer be offered. Any participant receiving Second Course treatment prior to implementation of Amendment 11 will be able to complete treatment as planned.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Administrative Procedures																	
Informed consent	X																
Inclusion/exclusion criteria	X																
Concomitant Medication Review	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X			Concomitant medications received within 28 days before the first dose of study intervention in Second Course through 30 days after the last dose of study intervention. All concomitant medications administered during SAEs or ECIs (Section 8.4) are to be recorded. *Cohort D2 only. Note: CM review on Day 8 is not required after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Anticancer therapy status														X	X	X	Any changes in new treatment will be collected.
Vital Status	X												X	X	X	X	Updated survival status may be requested by the Sponsor at any time during the course of the study.
Interventions																	
MK-7684A	X		X		X		X		X		X						Coformulation: 200 mg vibostolimab + 200 mg pembrolizumab Q3W. MK-7684A should be administered before 5-FU and cisplatin (**Cohort E only**).
Pembrolizumab (**Cohort A1 only**)	X		X		X		X		X		X						200 mg Q3W

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Gemcitabine (**Cohort D2 only**)	X	X	X	X	X	X	X	X	X	X	X	X					The decision of whether to continue gemcitabine during second course will be at the discretion of the investigator. If continued, the dose of gemcitabine will be given in clinic on Day 1 and Day 8 of each SC cycle. Refer to Section 8.1.8.1.3 for timing and order of dose administration. Treatment with gemcitabine will continue until unacceptable toxicity or PD.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
5-FU/cisplatin (**Cohort E only**)	X		X		X		X		X		X						Continuation or resumption of 5-FU/cisplatin is allowed during Second Course at the discretion of the investigator. Chemotherapy different from 5-FU/cisplatin is not permitted. 5-FU: 800 mg/m^2/day (continuous IV on D1 through D5 of every 21-day cycle) Q3W × 17 cycles Cisplatin: 80 mg/m^2 Q3W × 6 cycles Treatment with cisplatin and/or 5-FU may follow 1 to 2 days after MK-7684A (ie, Day 2 or Day 3) as needed per local standard of care.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Imaging																	**Schedule should be followed regardless of treatment delays.**
Tumor imaging and response assessment (Chest, Abdomen, and Pelvis)	X												X		X		Second course imaging should not be sent to the iCRO. If tumor image documenting PD is older than 28 days before entry into Second Course, a new image must be obtained and reviewed by the site before treatment. Perform imaging Q9W (63 days ±7 days) through EOT and Q12W (84 days ±7 days) thereafter, until PD is identified by the investigator or as outlined in Section 8.2.1.4. If imaging was obtained within 4 weeks before DC, scan at DC is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Clinical Procedures/Assessments																	
AE/SAE monitoring	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier. *Cohort D2 only. Note: AE review on Day 8 is not required after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Full Physical Examination	X												X				**Cohort E**: Refer to local regulations or local standard of practice for patient management regarding 5-FU and cisplatin treatment (eg, requirements for baseline and periodic audiograms for cisplatin). Refer to Appendix 7 for country-specific requirements. *Cohort D2 only. Note: Day 8 directed physical examination is not required after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.
Directed Physical Examination		X*	X	X*	X	X*	X	X*	X	X*	X	X*		X			

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Vital Sign measurements and Weight	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X			Predose and as clinically indicated. *Cohort D2 only. Note: Day 8 vital signs and weight are not required after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.
12-lead ECG	X																Additional ECGs can be performed as clinically indicated.
ECOG performance status	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X				Performed within 7 days of beginning of C1 and before each treatment administration. *Cohort D2 only. Note: Day 8 ECOG PS will not be performed after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Laboratory Procedures/Assessments																	
Pregnancy Test for WOCBP (**Cohorts A, B1, C, D1, and H**)	X												X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before restarting MK-7684A or pembrolizumab. Additional pregnancy testing to be conducted as clinically indicated. Refer to Appendix 7 for country-specific requirements.
Pregnancy test for WOCBP (**Cohorts D2, E and J**)	X		X		X		X		X		X		X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before each dose of study intervention. Additional pregnancy testing to be conducted as clinically indicated. Refer to Appendix 7 for country-specific requirements.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
CBC with Differential	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X			Performed locally within 10 days before first dose. After C1, collect within 3 days before dosing. Urinalysis should be performed every 4 cycles (C1, C5, etc.). *Cohort D2 only. Note: Day 8 CBC and chemistry panel blood samples will not be collected after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.
Chemistry Panel	X	X*	X	X*	X	X*	X	X*	X	X*	X	X*	X	X			
Urinalysis	X								X		X		X	X			
PT/INR and aPTT/PTT	X																Required at C1. Additional testing as needed for participants on anticoagulation therapy.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Thyroid function (T3, T4, and TSH)	X		X				X				X			X			Should be performed at C1 and predose of every other cycle starting from C2 (ie, C4, C6, C8, etc.). Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.

Study Period:	**Second Course – Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, Cohort D2, Cohort E, Cohort H, and Cohort J Treatment Cycle = 21 days**												**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**		**2**		**3**		**4**		**5**		**6 to 17**		**At DC**	**Safety Follow-up**	**Efficacy Follow-up**	**Survival Follow-up**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
														30 days post last dose	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**					
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Patient-reported Outcomes																	**Perform PRO assessments in the order as listed**
EORTC QLQ-C30 **(Cohort A only)**	X		X*		X*		X*		X*		X*		X	X			*Perform up to -3 days before every cycle through C17. If the EOT visit occurs 30 days (+7 days) from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, ePROs do not need to be repeated. If the participant does not complete the HRQoL survey(s), the MISS_MODE form must be completed to capture the reason the assessment(s) was not performed.
EORTC QLQ-CX24 **(Cohort A only)**	X		X*		X*		X*		X*		X*		X	X			
EQ-5D-5L **(Cohort A only)**	X		X*		X*		X*		X*		X*		X	X			

AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; C#=cycle number; CBC=complete blood count; CR=complete response; D#=day number; DC=discontinuation; ECG=electrocardiogram; EORTC=European Organisation for Research and Treatment of Cancer; EOT=end-of-treatment; EQ-5D-5L=EuroQol 5-dimension 5-level; iCRO=imaging CRO; INR=international normalized ratio; IV=intravenous(ly); PD=progressive disease; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; QLQ-C30=quality-of-life questionnaire core 30; QLQ-CX24=cervical cancer-specific quality-of-life questionnaire; SAE=serious adverse event; SOC=standard of care; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.5 Second Course Treatment – Cohort B2 and Cohort G

Note: As of implementation of Amendment 11, Second Course will no longer be offered. Any participant receiving Second Course treatment prior to implementation of Amendment 11 will be able to complete treatment as planned.

Second Course – Cohort B2 and Cohort G											**Posttreatment Visits**			**Notes**
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** **All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Administrative Procedures														
Informed consent	X													
Inclusion/exclusion criteria	X													
Prior and concomitant medications review	X	X	X	X	X	X	X	X	X	X	X			Prior concomitant medications received within 28 days before the first dose of study intervention in Second Course through 30 days after the last dose of study intervention. All concomitant medications administered during SAEs or ECIs (Section 8.4) are to be recorded.

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** **All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Anticancer therapy status											X	X	X	Any changes in new treatment will be collected.
Vital status	X									X	X	X	X	Participants may be contacted for survival status at any time during the study.
Home virtual visit		X												Participants will be contacted to report BP and record AEs. Blood pressure will be taken, for example, at home or at a local pharmacy, and will be reviewed with the investigator or designee.
Interventions														
MK-7684A	X			X		X	X	X	X					Coformulation: 200 mg vibostolimab + 200 mg pembrolizumab Q3W.

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** **All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Lenvatinib dispensing	X			X		X	X	X	X					Continuation of lenvatinib is allowed during Second Course at the discretion of the investigator for up to 17 cycles. Antineoplastic therapy different from lenvatinib is not permitted. Lenvatinib to be self-administered daily: – 20 mg qd (Cohort B2) – 12 mg qd (Cohort G; BW ≥60 kg); – 8 mg qd (Cohort G; BW <60 kg).
Lenvatinib bottle collection				X		X	X	X	X	X				

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	**All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Imaging														**Schedule should be followed regardless of treatment delays.**
Tumor imaging and response assessment (chest, abdomen, and pelvis)	X									X		X		**For Cohort G**: imaging must also include triphasic abdomen CT/MRI for liver evaluation. Second course imaging should not be sent to the iCRO. If tumor image documenting PD is older than 28 days before entry into Second Course, a new image must be obtained and reviewed by the site before treatment. Perform imaging Q9W (63 days ±7 days) through EOT, and Q12W (84 days ±7 days) thereafter until PD is identified by the investigator or as detailed in Section 8.2.1.4.

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	**All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
														If imaging was obtained within 4 weeks before treatment DC, scan at DC is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule.
Clinical Procedures/Assessments														**If lenvatinib is discontinued, lenvatinib-specific procedures and assessments are only required at the EOT and Safety FU visits.**
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** **All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Full physical examination	X									X				An oral examination must be included. *Not required if a home virtual visit is performed.
Directed physical examination		X*	X	X		X	X	X	X		X			
Vital sign measurements (including BP), weight	X	X*	X	X		X	X	X	X	X	X			Predose and as clinically indicated. Participants with initial or recurrent systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored until systolic BP is ≤150 mm Hg and diastolic BP is ≤95 mm Hg for 2 consecutive treatment cycles. *A home virtual visit can be scheduled to report BP and AEs.

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** **All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
12-lead ECG	X			X					X	X	X			After C2D1, ECG to be performed D1 of every fourth cycle (12 weeks) thereafter (eg, C6, C10, C14, etc.). ECG at C1D1 and C2D1 should be performed approximately 2 hours post- lenvatinib dose. For high-risk participants (Section 8.3.3.2), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the EOT and Safety Follow-up visits.

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** **All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
LVEF assessment by MUGA or ECHO	X										X			Additional assessments as clinically indicated. Assessments should use the same method (MUGA or ECHO) throughout the study. Refer to Appendix 7 for country-specific requirements.
ECOG performance status	X			X		X	X	X	X	X	X			Performed within 7 days of beginning of C1 and before each treatment administration.

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** **All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Laboratory Procedures/Assessment														
Pregnancy test for WOCBP	X			X		X	X	X	X	X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before each dose of study intervention. Additional testing to be performed as clinically indicated. Refer to Appendix 7 for country-specific requirements.
CBC with differential	X		X	X		X	X	X	X	X	X			After C1, collect within 3 days before dosing. Urinalysis should be performed every 4 cycles (C5, C9, etc.).
Chemistry Panel	X		X	X		X	X	X	X	X	X			
Urinalysis	X							X	X	X	X			

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	**All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Urine dipstick testing for protein	X			X		X	X	X	X	X	X			Note: urinalysis may be used if the urine dipstick is not feasible. Refer to Section 6.6.3.2 for management of proteinuria by dipstick, UPCR and/or 24-hour urinalysis.
PT/INR and aPTT/PTT	X													Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.

Second Course – Cohort B2 and Cohort G											Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**									**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.** **All lenvatinib-specific procedures are only to be performed if lenvatinib is administered during Second Course.**
Visit Timing / Cycle Number	**1**			**2**		**3**	**4**	**5**	**6 to 17**	**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Thyroid function (T3, T4, and TSH)	X			X			X		X	X	X			Should be performed at C1 and predose of every other cycle starting from C2 (ie, C4, C6, C8, etc.). Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.

AE=adverse event; aPTT=activated partial thromboplastin time; BP=blood pressure; BW=body weight; C#=cycle number; CBC=complete blood count; CR=complete response; CT=computed tomography; D#=day number; DC=discontinuation; ECG=electrocardiogram; ECHO=echocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; INR=international normalized ratio; iCRO= imaging CRO; IV=intravenous(ly); LVEF=left ventricular ejection fraction; MRI=magnetic resonance imaging; MUGA=multiple-gated acquisition; PD=progressive disease; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; qd=once daily; SAE=serious adverse event; SOC=standard of care; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; UPCR=urine protein-to-creatinine ratio; WOCBP=women of childbearing potential.

1.3.6 Second Course Treatment – Cohort F

Note: As of implementation of Amendment 11, Second Course will no longer be offered. Any participant receiving Second Course treatment prior to implementation of Amendment 11 will be able to complete treatment as planned.

Second Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**			**3**			**4 to 17***			**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Cycle Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Administrative Procedures																	
Informed consent	X																
Inclusion/exclusion criteria	X																
Prior and concomitant medications review	X	X	X	X	X	X	X		X	X	X		X	X			Prior concomitant medications received within 28 days before the first dose of study intervention in Second Course through 30 days after the last dose of study intervention. All concomitant medications administered during SAEs or ECIs (Section 8.4) are to be recorded.

Second Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**			**3**			**4 to 17***			**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Cycle Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Anticancer therapy status														X	X	X	Any changes in new treatment will be collected.
Vital status	X												X	X	X	X	Updated survival status may be requested by the Sponsor at any time during the course of the study.
Interventions																	
MK-7684A	X			X			X			X							Coformulation: 200 mg vibostolimab + 200 mg pembrolizumab Q3W.

Second Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**			**3**			**4 to 17***			**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Cycle Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Paclitaxel	X	X	X		X	X	X		X	X	X						Continuation or resumption of paclitaxel is allowed during Second Course at the discretion of the investigator. Chemotherapy different from paclitaxel is not permitted. 90 mg/m^2 on D1, D8, and D15 of every 28-day cycle. Should an investigator discontinue treatment with paclitaxel but continue treatment with MK-7684A, the participant does not need to come to the clinic on dates when only paclitaxel would have been administered. The participant should still follow the treatment and procedure schedule for MK-7684A visits.

Second Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**			**3**			**4 to 17***			**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Cycle Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Imaging																	
Tumor imaging and response assessment (chest, abdomen, and pelvis)	X												X		X		Schedule should be followed regardless of treatment delays. Second course imaging should not be sent to the iCRO. If tumor image documenting PD is older than 28 days before entry into Second Course, a new image must be obtained and reviewed by the site before treatment. Perform imaging Q9W (63 days ±7 days) through EOT, and Q12W (84 days ±7 days) thereafter until PD is identified by the investigator or as detailed in Section 8.2.1.4. If imaging was obtained within 4 weeks before treatment DC, scan at DC is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule.

Second Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**			**3**			**4 to 17***			**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Cycle Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Clinical Procedures/Assessments																	
AE/SAE monitoring	X	X	X	X	X	X	X		X	X	X		X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.
Full physical examination	X												X				To be performed within 7 days before start of study intervention.
Directed physical examination	X			X			X			X				X			
Vital sign measurements, weight	X	X	X	X	X	X	X		X	X	X		X	X			Predose and as clinically indicated.
12-lead ECG	X																Additional ECGs can be performed as clinically indicated.

Second Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**			**3**			**4 to 17***			**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	
Cycle Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
ECOG performance status	X			X			X			X			X	X			Performed within 7 days of beginning of C1 and before each treatment administration.
Laboratory Procedures/Assessments																	
Pregnancy test for WOCBP	X			X			X			X			X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before C1 of each 21-day treatment cycle. Additional testing to be performed as clinically indicated.
CBC with differential	X	X	X	X	X	X	X		X	X	X		X	X			Performed within 10 days before first dose. After C1, collect within 3 days before dosing. Urinalysis should be performed every 4 cycles (C5, C9, etc.).
Chemistry Panel	X			X			X			X			X	X			
Urinalysis	X									X			X	X			

Second Course – Cohort F														Posttreatment Visits			Notes
Study Period	**Treatment Cycle = 21 Days**												**EOT**	**Safety FU**	**Efficacy FU**	**Survival FU**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Visit Timing / Cycle Number	**1**			**2**			**3**			**4 to 17***			**At DC**	**30 Days post last dose**	**Q12W**	**Q12W**	***Starting with C5, the pattern of study intervention administration, assessments, and procedures will be repeated (ie, Cycle 5 is the same as Cycle 1; Cycle 6 is the same as Cycle 2, Cycle 7 is the same as Cycle 3 and Cycle 8 is the same as Cycle 4) unless otherwise stated.**
Cycle Day	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**–**				
Scheduling Window (Days)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
PT/INR and aPTT/PTT	X																Additional testing to be conducted as clinically indicated for participants taking anticoagulant therapy.
Thyroid function (T3, T4, and TSH)	X			X						X			X	X			Should be performed at C1 and predose of every other cycle starting from C2 (ie, C4, C6, C8 etc.). Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.

AE=adverse event; aPTT=activated partial thromboplastin time; C#=cycle number; CBC=complete blood count; CR=complete response; CT=computed tomography; ctDNA=circulating tumor DNA; D#=day number; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT=end-of-treatment; iCRO=imaging CRO; INR=international normalized ratio; IV=intravenous(ly); MRI=magnetic resonance imaging; PD=progressive disease; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; qd=once daily; SAE=serious adverse event; SOC=standard of care; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.7 Neoadjuvant/Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I

NOTE: As of Amendment 11, Blood for ctDNA analysis, PBMC analysis, PK, and ADA will no longer be collected.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Administrative Procedures														
Authorization for Release of Tumor Tissue	X													Optional for participants who agree to provide a previously obtained tumor tissue sample for central determination of biomarker status prior to providing main ICF. Participants may provide documented Authorization for Release of Tumor Tissue before the start of the 56-day Screening Period.
Informed consent	X													Consent must be obtained prior to performing any protocol-specific procedures. If the signature falls outside of the 56-day screening window, the participant does not need to be reconsented. Participant must be reconsented prior to continuing study treatment after initial disease progression.
Inclusion /Exclusion	◄--------►													

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Participant ID Card	X		X											Distribute at screening and add allocation number at C1D1.
Demographics and Medical History	X													
FIGO stage at diagnosis (**Cohort I only**)	X													
Ovarian Cancer History	X													Assess and record tumor burden per imaging.
History of Blood Transfusion	X													Include history of blood transfusion within previous 120 days from start of study intervention and the reasons, eg, bleeding or myelosuppression
Prior/Concomitant Medication Review	◄- - - - - - - - ►		X	X	X	X	X	X	X	X	X			Record medications taken within 56 days prior to randomization. Concomitant medications will be recorded for 30 days after last dose (or for up to 90 days after last dose for SAEs). Include blood transfusions during review of concomitant medications.
Treatment Allocation			X											Allocation via IRT may occur up to 3 days prior to C1D1.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Interval Debulking Surgery					◄- - - -

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Study Treatment Administration[g]														
Lead-in Carboplatin/ Paclitaxel		X												Investigator's choice of 3 regimens: 1) Carboplatin AUC5 or AUC6 + paclitaxel 175 mg/m^2 Q3W, or 2) Carboplatin AUC5 or AUC6 Q3W + paclitaxel 80 mg/m^2 QW, or 3) Carboplatin AUC2 or AUC2.7 QW + paclitaxel 60 mg/m^2 QW Q3W dosing on Day 1 and QW dosing on Days 1, 8 and 15 of each cycle. Docetaxel (75 mg/m^2 Q3W) may be considered for participants who either experience a severe hypersensitivity reaction or an AE that requires discontinuation of paclitaxel only after Sponsor consultation.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Carboplatin / Paclitaxel			X	◄- - - - - - - - ►										Investigator's choice of 3 regimens: 1) Carboplatin AUC5 or AUC6 + paclitaxel 175 mg/m^2 Q3W, or 2) Carboplatin AUC5 or AUC6 Q3W + paclitaxel 80 mg/m^2 QW, or 3) Carboplatin AUC2 or AUC2.7 QW + paclitaxel 60 mg/m^2 QW Q3W dosing on Day 1 and QW dosing on Days 1, 8 and 15 of each cycle. Day 1 of Cycle 1 must be at least 20 days after the first dose of lead-in chemotherapy. Docetaxel (75 mg/m^2 Q3W) may be considered for participants who either experience a severe hypersensitivity reaction or an AE that requires discontinuation of paclitaxel only after Sponsor consultation.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Bevacizumab		X	X	◄--------►				X	X*					For Safety Lead in participants, bevacizumab must be administered during the lead-in period. For all other participants, Day 1 of Cycle 1 must be at least 20 days after the first dose of lead-in chemotherapy. The investigator may wait to administer the first dose of bevacizumab, as long as the first dose is administered by the second cycle following surgery (but it may be started with lead-in). *Bevacizumab continued for up to 15 infusions or as per local SOC (see Section 4.1.9).
MK-7684A			X	◄--------►				X	X					Coformulation: 200 mg vibostolimab + 200 mg pembrolizumab Q3W MK-7684A should be administered before carboplatin/paclitaxel and bevacizumab. See Section 8.1.8.1.7 for treatment sequence. Participant may receive up to 35 infusions. Day 1 of Cycle 1 must be at least 20 days after the first dose of lead-in chemotherapy.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Efficacy Procedures														
Pathological Tumor Assessment				◄- - - - - - - - ►										Detailed pathological assessment of all tumor tissue collected during interval debulking for determination of pCR.
Tumor Imaging	X		X							X		X		Refer to Section 1.3.9
Bone imaging	X		X							X		X		Refer to Section 1.3.9
Brain Imaging	X		X							X		X		Refer to Section 1.3.9
Safety Procedures (during treatment visits safety assessments and procedures must be done prior to treatment administration)[e, f]														
AE Monitoring	◄- - - - - - - - ►		X	X	X	X	X	X	X	X	X	X		Report all AEs through 30 days following last dose of study treatment. Report SAEs through 90 days following last dose of study treatment (or 30 days following last dose if participant initiates new anticancer therapy, whichever is earlier).
Full physical examination	X									X				
Directed physical examination		X	X	X	X	X	X	X	X		X			Perform as clinically indicated.
Weight		X	X	X	X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Vital Signs		X	X	X	X	X	X	X	X	X	X			Assess BP, heart rate, RR, temperature. Height only assessed once prior to starting lead-in chemotherapy. Perform within 7 days prior to starting lead-in chemotherapy.
12-lead ECG		X												Additional ECGs may be performed as clinically indicated. Perform within 7 days prior to starting lead-in chemotherapy. 6-lead ECGs may be allowed per institutional standard. Refer to Section 8.3.3.1
PT or INR and aPTT/PTT		X												Perform within 7 days prior to starting lead-in chemotherapy. PT or INR and aPTT/PTT should be monitored more closely in participants receiving anticoagulant therapy during treatment and Safety Follow-up Period.
Chemistry Panel		X	X	X	X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment.
CBC with differential		X	X	X	X	X	X	X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Urinalysis (dipstick or laboratory analysis)		X	X				X		X	X	X			Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment. Urinalysis should be performed every 4 cycles (C5, C9, etc.). Perform at every dosing cycle while receiving bevacizumab.
T3 or free T3 / FT4 / TSH		X		X		X		X	X	X	X			Perform within 7 days prior to starting lead-in chemotherapy. Perform at every other cycle (C2, C4, C6, C8, etc.).
Cortisol Levels	X				◄- - - -

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
CA-125	X		◄----------	----------	----------	----------	----------	----------	----------►	X		X		Perform within 7 days prior to starting lead-in chemotherapy. Sample to be collected at the time of each tumor imaging assessment (±14 days of scheduled imaging assessment) (Section 1.3.9). An optional sample may be collected at the time of unscheduled imaging at the investigator's discretion. All CA-125 testing will be performed locally.
CEA	X													Perform within 7 days prior to starting lead-in chemotherapy.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Urine or serum pregnancy test – WOCBP only		X	X	X	X	X	X	X	X	X	X			WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to starting lead-in chemotherapy and again within either 24 hours (urine) or 72 hours (serum) before each dose of study intervention. A pregnancy test must be performed at the cycle the participant enters maintenance. Additional pregnancy testing to be conducted as clinically indicated. Refer to Appendix 7 for country-specific requirements.
Serum Follicle-Stimulating Hormone (FSH) – WOCBP only	◄- - - - - - - - ►													Only to be determined once for women <45 years old with no menses for ≥1 year (12 months) prior to screening and not currently on HRT or hormonal contraception
HIV / HBV / HCV	◄- - - - - - - - ►													Testing is only required once at screening if mandated by local health authority. Refer to Appendix 7 for country-specific requirements.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
ECOG Performance Status		X	X	X	X	X	X	X	X	X				Perform within 7 days prior to starting lead-in chemotherapy and again within 3 days prior to C1D1 treatment.
Laboratory Assessment – Central Laboratory														
Blood for serum vibostolimab and pembrolizumab PK			X	X		X			X*					PK and ADA samples should be drawn within 24 hours before study intervention administration. Additional postdose (end of infusion) PK only samples will be drawn within 10 minutes after end of infusion at C1 and C8. *After C4, PK and ADA samples to be collected every 4 cycles (ie, C8, C12, C16, etc.) through C32. PK and ADA sample collections should be interrupted for IDS. Collection pre and post IDS should follow SoA.
Blood for ADA of vibostolimab and pembrolizumab			X	X		X			X*					
Biomarker Sample Collection														**Biomarker samples may be collected up to 3 days prior to C1D1.**
Blood for Genetic Analysis			X											Collect prior to administration of study treatment. Refer to Section 8.8 for additional collection information.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
Blood for PBMC Analysis			X	X	X			X*	X	X				Collect at predose on D1 of C1, C2, C3, and at EOT. *A sample needs to be collected at the cycle the participant enters maintenance (C6 or earlier); during maintenance, a sample to be collected every second regularly scheduled imaging assessment (±14 days). A sample may be collected at the time of unscheduled imaging (±14 days) at the investigator's discretion. Refer to imaging timing outlined in Section 1.3.9.
Blood for ctDNA Analysis			X	X			X	X*	X	X		X		Collect prior to administration of study treatment. *A sample needs to be collected at the cycle the participant enters maintenance (C6 or earlier); during maintenance, a sample to be collected every second regularly scheduled imaging assessment (±14 days). A sample may be collected at the time of unscheduled imaging (±14 days) at the investigator's discretion. Refer to imaging timing outlined in Section 1.3.9.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	
PD-L1 Status	X													PD-L1 status will be retrospectively determined by the central laboratory.
BRCA1/2 Status	X													Results must be available prior to allocation and must be BRCA1/2 nonmutated. Sponsor consultation is required to delay allocation if the results are not available at the planned time of allocation.
HRD Status	X													Tumor biopsy is required to determine HRD status. Results must be available prior to allocation and must be HRD-negative.
Submission of Newly obtained (preferred) or Archival Tissue Collection	X													
Tumor tissue at surgery				◄- - - - - - - - ►										Tumor tissue is required and should be obtained at the following time points and submitted to the central laboratory: 1) Tumor tissue removed during interval debulking 2) Not required if participant is unable to undergo interval debulking.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I														
Study Period	**Screening +Lead-in**		**Treatment (C1 – C5) Maintenance (C6+)[a] (3-Week Cycles)**							**EOT**	**Posttreatment Visits**			**Notes**
Treatment Cycle	**Screen[b]**	**Lead -in**	**1**	**2**	**3**	**4**	**5**	**6**	**7 to 35**	**DC**	**Safety FU[c]**	**Efficacy FU[d]**	**Survival FU**	**The Screening Period is a total of 56 days, which includes the 21-day Lead-in Period and an optional 7-day recovery period during or following lead-in chemotherapy. Maintenance is for participants without radiographic disease progression; participants must have SD, PR or CR, or non-PD.**
Scheduling Window (Days):	**-28 to start of Lead-in**	**Start of Lead -in to -1**	**+3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**At DC**	**30 Days After Last Dose (-3 to + 7)**	**Q9W, Q12W, or post DC (± 7)**	**Q12W (± 14)**	

AE=adverse event; aPTT=activated partial thromboplastin time; AUC=area under the concentration-time curve; BICR=blinded independent central review; BID=twice daily; BRCA1/2=breast cancer susceptibility gene 1/2; C1D1=Cycle 1, Day 1; C2=Cycle 2; C5D1=Cycle 5, Day 1; C7=Cycle 7; CA-125=cancer antigen-125; CEA=cancer embryonic antigen; ctDNA=circulating tumor DNA; DBP=diastolic blood pressure; DC=discontinuation; ECG=electrocardiogram; ECOG=Eastern Cooperative Cancer Group; EOT=end of therapy; FIGO=International Federation of Gynecology and Obstetrics; FT3=free triiodothyronine; FT4=free thyroxine; HRD=homologous recombination deficiency; HRT=hormone replacement therapy; ICF=informed consent form; ID=identification; IDS=interval debulking surgery; INR=International Normalized Ratio; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; IRT=interactive response technology; NED=no evidence of disease; PBMC=peripheral blood mononuclear cell; pCR=pathological complete response; PD=progressive disease; PD-L1=programmed cell death ligand 1; PR=partial response; PRO=patient-reported outcome; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; QW=once weekly; RECIST=Response Evaluation Criteria in Solid Tumors; RR=respiratory rate; SBP=systolic blood pressure; SD=stable disease; SOC=standard of care; T3=triiodothyronine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

[a] Following consultation with the Sponsor, participants who are unable to complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity, may be eligible to start the Maintenance Period earlier.

[b] All screening procedures should be performed prior to starting lead-in chemotherapy unless otherwise noted. The Lead-in Period occurs within the 56-day window. The optional recovery period, if needed, should not exceed 7 days between cycles (weekly chemotherapy regimen) or at the end of lead-in chemotherapy. Allocation should occur within 7 days of completing lead-in chemotherapy; a delay of an additional 2 weeks (up to 3 weeks total) may be granted upon consultation with the Sponsor.

[c] If the DC visit occurs ≥30 days from last dose of study treatment, a Safety Follow-up Visit is not required.

[d] For participants who DC for reasons other than radiographic PD, imaging continues until radiographically documented PD by the investigator (and, when clinically appropriate, confirmed by iRECIST), initiation of a new anticancer therapy, withdrawal of consent, becoming lost to follow-up, pregnancy, or death, whichever occurs first. Efficacy follow-up visits may be scheduled to coincide with Follow-Up imaging. Refer to Section 1.3.9 for the imaging schedule during the treatment and posttreatment Efficacy Follow-up Period.

[e] All procedures and laboratory testing should be conducted on the day of, or within the specified window, but prior to dosing. Laboratory results must be assessed by a qualified investigator prior to dosing; thyroid function testing is an exception as outlined in Appendix 2.

[f] For participants receiving carboplatin/paclitaxel QW dosing, perform the following assessments on Days 1, 8 and 15 of each cycle: Prior/Concomitant Medication Review; AE monitoring; Directed PE; Weight; Vital Signs; Chemistry Panel; CBC with differential; ECOG Performance status.

[g] If a participant's study intervention administration is delayed more than 21 days (±3 days) from previous cycle due to IDS procedures, a Sponsor consultation form is required.

1.3.8 Second Course Treatment – Cohort I

Note: As of implementation of Amendment 11, Second Course will no longer be offered. Any participant receiving Second Course treatment prior to implementation of Amendment 11 will be able to complete treatment as planned.

Study Period:	**Second Course – Cohort I Treatment Cycle = 21 days**						**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At DC**	**Safety Follow-up** 30 days post last dose	**Efficacy Follow-up** Q12W	**Survival Follow-up** Q12W	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Administrative Procedures											
Informed consent	X										
Inclusion/exclusion criteria	X										
Concomitant Medication Review	X	X	X	X	X	X	X	X			Concomitant medications received within 28 days before the first dose of study intervention in Second Course through 30 days after the last dose of study intervention. All concomitant medications administered during SAEs or ECIs (Section 8.4) are to be recorded.
Anticancer therapy status								X	X	X	Any changes in new treatment will be collected.
Vital Status	X						X	X	X	X	Updated survival status may be requested by the Sponsor at any time during the course of the study.

Study Period:	**Second Course – Cohort I Treatment Cycle = 21 days**						**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At DC**	**Safety Follow-up** **30 days post last dose**	**Efficacy Follow-up** **Q12W**	**Survival Follow-up** **Q12W**	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Interventions											
MK-7684A	X	X	X	X	X	X					Coformulation: 200 mg vibostolimab + 200 mg pembrolizumab Q3W. MK-7684A should be administered before bevacizumab.
Bevacizumab	X	X	X	X	X	X					Optional during Second Course.
Imaging											**Schedule should be followed regardless of treatment delays.**
Tumor imaging and response assessment (Chest, Abdomen, and Pelvis)	X						X		X		Second course imaging should not be sent to the iCRO. If tumor image documenting PD is older than 28 days before entry into Second Course, a new image must be obtained and reviewed by the site before treatment. Perform imaging Q9W (63 days ±7 days) through EOT and Q12W (84 days ±7 days) thereafter, until PD is identified by the investigator or as outlined in Section 8.2.1.4. If imaging was obtained within 4 weeks before DC, scan at DC is not mandatory. Follow-up visits may be scheduled to coincide with the imaging schedule.

Study Period:	**Second Course – Cohort I Treatment Cycle = 21 days**						**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At DC**	**Safety Follow-up** 30 days post last dose	**Efficacy Follow-up** Q12W	**Survival Follow-up** Q12W	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Clinical Procedures/Assessments											
AE/SAE monitoring	X	X	X	X	X	X	X	X	X		Report AEs occurring within 30 days after the last dose of study intervention. Report SAEs occurring within 90 days after the last dose of study intervention, or 30 days after the last dose of study intervention if a new anticancer therapy is initiated, whichever is earlier.
Full Physical Examination	X						X				Refer to Appendix 7 for country-specific requirements.
Directed Physical Examination		X	X	X	X	X		X			
Vital Sign measurements and Weight	X	X	X	X	X	X	X	X			Predose and as clinically indicated.
12-lead ECG	X										Additional ECGs can be performed as clinically indicated.
ECOG performance status	X	X	X	X	X	X	X				Performed within 7 days of beginning of C1 and before each treatment administration.

Study Period:	**Second Course – Cohort I Treatment Cycle = 21 days**						**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At DC**	**Safety Follow-up** 30 days post last dose	**Efficacy Follow-up** Q12W	**Survival Follow-up** Q12W	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	
Laboratory Procedures/Assessments											
Pregnancy test for WOCBP	X	X	X	X	X	X	X	X			WOCBP require negative serum test within 72 hours or negative urine test within 24 hours before each dose of study intervention. Additional pregnancy testing to be conducted as clinically indicated. Refer to Appendix 7 for country-specific requirements.
CBC with Differential	X	X	X	X	X	X	X	X			Performed locally within 10 days before first dose. After C1, collect within 3 days before dosing. Urinalysis should be performed every 4 cycles (C1, C5, etc.).
Chemistry Panel	X	X	X	X	X	X	X	X			
Urinalysis	X				X	X	X	X			
PT/INR and aPTT/PTT	X										Required at C1. Additional testing as needed for participants on anticoagulation therapy.
Thyroid function (T3, T4, and TSH)	X	X		X		X		X			Should be performed at C1 and predose of every other cycle starting from C2 (ie, C4, C6, C8, etc.). Participants may be dosed in subsequent cycles after C1 while thyroid function tests are pending. Free T3 and free T4 are acceptable.

Study Period:	**Second Course – Cohort I Treatment Cycle = 21 days**						**End-of-Treatment**	**Posttreatment Visits**			**Notes**
Visit Timing / Cycle Number	**1**	**2**	**3**	**4**	**5**	**6 to 17**	**At DC**	**Safety Follow-up** 30 days post last dose	**Efficacy Follow-up** Q12W	**Survival Follow-up** Q12W	**All procedures are to be performed before study intervention administration unless otherwise indicated. Refer to Section 8.11 for visit details.**
Scheduling Window (Days):	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**		**-3 to +7**	**±7**	**±14**	

AE=adverse event; aPTT=activated partial thromboplastin time; BICR=blinded independent central review; C#=cycle number; CBC=complete blood count; CR=complete response; D#=day number; DC=discontinuation; ECG=electrocardiogram; EORTC=European Organisation for Research and Treatment of Cancer; EOT=end-of-treatment; iCRO=imaging CRO; INR=international normalized ratio; IV=intravenous(ly); PD=progressive disease; PT=prothrombin time; PTT=partial thromboplastin time; Q3W=every 3 weeks; Q9W=every 9 weeks; Q12W=every 12 weeks; SAE=serious adverse event; SOC=standard of care; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential.

1.3.9 Imaging Assessments for Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I	
Imaging Visit	**Description**
Baseline	Perform imaging within 28 days prior to starting lead-in chemotherapy.
Peri-surgery	• Presurgery: Imaging performed a minimum of 21 days after C2-C5D1 • Postsurgery: Imaging performed prior to resuming treatment Note: If surgery is attempted but not performed (with or without biopsy collection), continue imaging as specified here.
Maintenance Eligibility	To confirm SD, PR, CR, or non-PD, imaging must be performed: • A minimum of 21 days following C5D1 (for Q3W regimen) or a minimum of 7 days following C5D15 (for QW regimen) (for participants completing 6 cycles of chemotherapy [including lead-in dose]) **OR** • A minimum of 21 days after Day 1 of the last cycle of chemotherapy (if discontinued due to toxicity). Imaging obtained within 4 weeks (28 days) prior to the planned start of maintenance, including postsurgery imaging, may be used as the maintenance eligibility scan following Sponsor approval. Participants with radiographic evidence of PD (but clinically stable) can start the Maintenance Period (MK-7684A only) and must not have confirmed PD (ie, iCPD) as assessed by iRECIST at the next imaging (Section 8.2.1.6). The maintenance eligibility scan will be used to establish the new baseline for the purposes of future assessments during the maintenance period. Brain and bone imaging should be repeated if performed at baseline.
Maintenance	Imaging is to be performed Q9W (63 days ± 7) from the date of the maintenance eligibility assessment through Week 54, and Q12W (84 days ± 7 days) thereafter or until meeting discontinuation criteria. Week 54 is calculated from the date of allocation.
Posttreatment Efficacy Follow-up Imaging	Participants who discontinue study treatment without documented disease progression should continue monitoring disease status by tumor imaging Q9W (63 days ± 7) through Week 54, and Q12W (84 days ± 7 days) thereafter. Week 54 is calculated from the date of allocation.
End of Treatment	Imaging performed at the time of treatment discontinuation (±4 weeks) and prior to starting a new anticancer treatment. If previous imaging was obtained within 4 weeks (28 days) before the date of discontinuation, then imaging at treatment discontinuation is not mandatory. For participants who discontinue study treatment due to documented PD (Section 8.2.1.3), this is the final required tumor imaging if the investigator elects not to implement iRECIST.

Neoadjuvant / Adjuvant Treatment Period With Interval Debulking Followed by Maintenance – Cohort I	
Imaging Visit	**Description**
C2-5D1=Cycle 2-5 Day 1; C5D1=Cycle 5 Day 1; C5D15=Cycle 5 Day 15; CR=complete response; iRECIST=modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics; NED=no evidence of disease; PD=progressive disease; Q9W=every 9 weeks; Q12W=every 12 weeks; PR=partial response; SD=stable disease. NOTES: Chest, abdomen, and pelvis imaging – required at baseline and every timepoint according to the schedule above. Brain and bone imaging are required at baseline for participants with a history of brain and bone metastases or who are clinically symptomatic. Follow-up brain and bone imaging can be performed as clinically indicated if PD is suspected or to confirm CR. If the participant does not have surgery prior to 9 weeks on study, a scan will also have to be included to assess progression (by investigator). The presurgery scan can be used as the first 9 week scan with sponsor consultation. Unscheduled imaging may be performed as clinically indicated.	

2 INTRODUCTION

MK-7684A is being developed for treatment of solid tumors. This basket study of MK-7684A alone or in combination with other therapies is designed to assess the safety, tolerability, and preliminary efficacy of MK-7684A in selected advanced solid tumor indications.

2.1 Study Rationale

TIGIT is highly coexpressed with PD-1 on both CD4+ and CD8+ T-cells during chronic inflammatory states, including viral infections and cancer [Chauvin, J. M., et al 2015] [Johnston, R. J., et al 2014]. A high TIGIT/DNAM-1 ratio on tumor-infiltrating Tregs was shown to correlate with poor clinical outcome following immune checkpoint blockade targeting PD-1 and/or CTLA-4 [Fourcade, J., et al 2018]. Furthermore, enhanced antitumor efficacy is observed in preclinical models when an anti-TIGIT antibody is used with an anti-PD-1 antibody. Combining an anti-TIGIT antibody with an anti-PD-1 agent may result in enhanced tumor killing and/or an expansion of the number of cancer indications responsive to PD-1-containing therapy. In addition, TIGIT blockade may overcome some forms of PD-1/PD-L1 checkpoint resistance. In vitro PD-1 blockade causes up-regulation of TIGIT in tumor antigen-specific CD8+ T-cells, a potential mechanism of resistance. Dual blockade of TIGIT and PD-1 increased IFN-γ, TNF, and T-cell proliferation [Chauvin, J. M., et al 2015a].

TIGIT is overexpressed in a number of solid tumors. TIGIT and its receptor, CD155, were overexpressed in lung primary adenocarcinomas by immunohistochemistry ($p<0.01$, n=334). Moreover, patients expressing high CD155 and TIGIT simultaneously have shorter OS ($p<0.01$) and PFS ($p<0.01$). They are also more likely to have advanced TNM staging and lymphatic and distant metastases [Sun, Y., et al 2020].

As of 15-APR-2021, preliminary efficacy data were available for a total of 76 participants with advanced solid tumors who were treated in the dose escalation and confirmation portion (Part A) of Study MK-7684-001 with either vibostolimab at doses from 2.1 mg to 700 mg as monotherapy (n=34) or in combination with 200 mg pembrolizumab (n=42). In the monotherapy group, at all vibostolimab doses tested, the investigator-assessed confirmed ORR per RECIST 1.1 was 0% and the DCR was 32.4%. In the vibostolimab + pembrolizumab group, the investigator-assessed confirmed ORR per RECIST 1.1 was 7.1% and the DCR was 35.7%.

In addition to the analyses of the efficacy and safety data across all tumor types (provided above), the efficacy and safety has also been analyzed in participants with NSCLC from the dose-expansion phase (Part B) of MK-7684-001. As of 15-APR-2021, in participants with anti-PD-1/PD-L1-naïve NSCLC (n=41), who received treatment of vibostolimab + pembrolizumab, the confirmed ORR was 24.4% (95% CI: 12.4, 40.3) in all participants and 30.8% (95% CI: 9.1, 61.4) in participants with tumors with PD-L1 TPS ≥1% (n=13). Median PFS was 5.4 months (95% CI: 2.1, 8.2) in all participants and 8.4 months (95% CI: 3.9, 10.2) in participants with tumors with PD-L1 TPS ≥1% [Niu, J., et al 2020]. To put these data in context, the best historical comparator is pembrolizumab monotherapy data in previously

treated patients with TPS ≥1% NSCLC from KEYNOTE-010. In KEYNOTE-010, ORR was 18% and median PFS was 4.0 months (95% CI: 3.1, 4.1).

The MK-7684-001 study also showed that the combination of vibostolimab and pembrolizumab demonstrated a trend toward improved efficacy compared with pembrolizumab monotherapy in participants with previously treated advanced cervical cancer. In this study, 80 participants with advanced cervical cancer who were naïve to prior anti-PD-1 therapy were enrolled. Compared with pembrolizumab monotherapy in KEYNOTE-158 (ORR=12.2%), the confirmed ORR by RECIST 1.1 as assessed by the investigator was 18.8% following treatment with vibostolimab and pembrolizumab (data cutoff 15-APR-2021). In participants whose tumors expressed PD-L1 (CPS ≥1), vibostolimab and pembrolizumab treatment resulted in a confirmed ORR of 20.8% compared with the ORR of 14.6% observed for pembrolizumab monotherapy. Finally, in participants whose tumors were PD-L1 negative (CPS <1), the confirmed ORR was 14.3% following treatment with vibostolimab + pembrolizumab, whereas no responses were observed following pembrolizumab monotherapy. These initial data show promising efficacy with an improvement in ORR compared with pembrolizumab in all participants, regardless of PD-L1 expression.

Vibostolimab has been generally tolerable. As of 15-APR-2021, of the 413 participants for whom safety data were available from all treatment arms of Study MK-7684-001 combined, 97.6% experienced at least 1 AE. The incidence of AE in all treatment arms combined was generally similar to that in participants treated with pembrolizumab monotherapy in previous studies (97.4%). The most common AE in all participants in all treatment arms combined by PT were fatigue (31.7%), nausea (25.4%), pruritus (24.7%), anemia (23.7%), and rash (21.5%).

A total of 291 of the 413 participants (70.5%) in all treatment arms combined experienced at least 1 AE that was considered by the investigators to be related to study treatment; most were of Grade 1 or 2 severity. The incidence of drug-related AEs in the vibostolimab and pembrolizumab combination therapy arm (70.6%), the MK-7684A arm (77.5%), and in all treatment arms combined (70.5%) was similar to that in participants treated with pembrolizumab monotherapy in previous studies (73.7%). The most common drug-related AE in all participants in all treatment arms combined by PT were pruritus (20.8%), rash (18.4%), fatigue (17.9%), and nausea (10.4%) (refer to the vibostolimab IB).

Clinical data from the MK-7684-001 study suggests that vibostolimab demonstrates greatest activity in combination with pembrolizumab in participants with advanced solid tumors. Activity appears to enrich in tumors that are IO responsive, such as NSCLC, and in biomarker groups consistent with the mechanism of action, including tumors expressing PD-L1 and those with immune infiltrate based on presence of CD4/CD8 cells or expression of an IFN-γ signature [Ayers, M., et al 2017]. Based on these observations, tumor types for this solid tumor basket study were chosen based on responsiveness to immune checkpoints and biomarker expression of PD-L1, TIGIT and other markers of immune infiltration, and unmet medical need.

In 2020, there were approximately 1.7 million adults in newly diagnosed with solid tumors in the US [Siegel, R. L., et al 2020]. Of these, approximately 25% of patients had Stage IV disease at diagnosis. Despite recent advances for the treatment for most cancer types, disease progression typically leads to treatment with chemotherapies, which are generally associated with low response rates, short DOR, and significant toxicities. Furthermore, few patients with advanced cancer that has progressed will survive longer than 5 years. Thus, those patients without satisfactory alternative treatment options whose disease has progressed either following treatment with curative intent or following 1L therapies comprise a population of high unmet medical need.

2.2 Background

2.2.1 Pharmaceutical and Therapeutic Background

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

2.2.1.1 Vibostolimab Background

Vibostolimab is a humanized, antagonist mAb that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligands. This human IgG1 antibody is being developed as a cancer immunotherapeutic with the potential to be used as monotherapy or to be combined with pembrolizumab (a humanized anti-PD-1 receptor antibody) to increase benefit to patients with various tumor types.

TIGIT is an immunomodulatory receptor expressed primarily on activated CD4+ and CD8+ T-cells, NK cells, and NKT cells. Its structure reveals a single extracellular immunoglobulin domain, a transmembrane region, an immunoglobulin tail tyrosine-like phosphorylation motif, and an immunoreceptor tyrosine-based inhibitory motif.

TIGIT forms part of a costimulatory network that consists of a positive (CD226) and negative (TIGIT) immunomodulatory receptor on T-cells, and ligands (CD155 and CD112) expressed on tumor cells and antigen presenting cells [Levin, S. D., et al 2011]. Whereas CD226 is widely expressed on most immune cells, TIGIT is highly expressed on memory T cells, Tregs, NK cells, and NKT cells [Dardalhon, V., et al 2005] [Stanietsky, N., et al 2009]. CD155/PVR and CD112/PVRL-2 are 2 nectin family members that are widely expressed both on cells of the hematopoietic system and on fibroblasts and endothelial cells. Functionally, these receptor ligands are involved in cell adhesion and motility. CD155 is reported to be overexpressed in several tumor types and has been found to be induced by Ras

activation and genotoxic stress [Carlsten, M., et al 2007] [Hirota, T., et al 2005] [Soriani, A., et al 2009] [Stanietsky, N., et al 2009].

In addition, TIGIT is highly coexpressed with PD-1 on both CD4+ and CD8+ TILs including Tregs, in mouse and human tumors, and has been reported to be coexpressed with PD-1 and Tim-3 on the TILs with the most exhausted phenotype [Chauvin, J. M., et al 2015] [Johnston, R. J., et al 2014]. Furthermore, enhanced antitumor efficacy is observed in preclinical models when an anti-TIGIT antibody is used with an anti-PD-1 antibody. We hypothesize, therefore, that combining vibostolimab with pembrolizumab will offer substantially augmented antitumor efficacy.

2.2.1.2 Pembrolizumab Background

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

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

The structure of murine PD-1 has been resolved [Zhang, X., et al 2004]. PD-1 and its family members are type I transmembrane glycoproteins containing an IgV–type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [Okazaki, T., et al 2001] [Chemnitz, J. M., et al 2004] [Sheppard, K-A, et al 2004] [Riley, J. L. 2009]. The mechanism by which PD-1 down-modulates T-cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [Parry, R. V., et al 2005] [Francisco, L. M., et al 2010].

For more details on specific indications refer to the pembrolizumab IB.

2.2.1.3 Lenvatinib Background

Angiogenesis, the formation of new blood vessels from a preexisting vascular network, is essential for tumor growth and metastasis. VEGF and its family of receptors (VEGRs 1-3) play a major role in tumor angiogenesis [Ferrara, N., et al 2003] [Ellis, L. M. and Hicklin, D. J. 2008] [Tammela, T. and Alitalo, K. 2010]. Accumulated evidence suggests that FGF and its receptor tyrosine kinase, FGFR also play important roles for tumor angiogenesis [Cross, M. J. and Claesson-Welsh L. 2001] [Lieu, C., et al 2011] [Limaverde-Sousa, G., et al 2014].

Lenvatinib (also known as E7080 or MK-7902) inhibits the kinase activities of VEGF receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib inhibits other kinases that have been implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including FGF receptors FGFR1, 2, 3, and 4; PDGFRα, KIT, and RET. Lenvatinib also exhibited antiproliferative activity in cell lines dependent on activated FGFR signaling with a concurrent inhibition of FGF-receptor substrate 2α phosphorylation. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis.

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8 nmol/L to 22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of HUVEC with IC_{50} values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the MAPK pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [Yamamoto, Y., et al 2014]. In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), RCC, HCC, melanoma, gastric cancer, NSCLC, ovarian cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

In summary, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in HUVEC models. Antitumor activity of lenvatinib in vivo has been shown in numerous xenograft animals. These results suggest that lenvatinib may be a novel anticancer therapy through inhibition of angiogenesis and may be useful as either monotherapy or in combination with other anticancer drugs.

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

2.2.2 Background on Selected Tumor Types

2.2.2.1 Cervical Cancer

Cervical cancer is the fourth leading cause of cancer-related mortality in women worldwide [Ferlay, J., et al 2019]. In recent years, systematic screening has led to a reduced incidence of cervical cancer in developed countries, which may decline further if widespread vaccination against human papillomavirus is adopted. This improvement has not been achieved in the developing world, where 87% of all cervical cancer-related deaths occur [Bray, F., et al 2018]. In contrast to patients with early stage cervical cancer, the prognosis for patients with recurrent or metastatic disease is poor [Pfaendler, K. S. 2016] with limited treatment options in the 2L and later setting.

Cervical cancer is generally considered a chemotherapy-resistant disease. Cisplatin, with concurrent radiotherapy, is the recommended treatment option for patients with advanced cervical cancer. The ORR with single-agent cisplatin ranges from 13% to 23%; however, the responses are not durable [Boussios, S., et al 2016] [Bonomi, P., et al 1985]. In contrast to single-agent cisplatin, cisplatin plus paclitaxel has shown improved ORR and PFS, but there was no significant benefit in OS [Moore, D. H., et al 2004] [Omura, G. A., et al 1997]. In addition, the toxicity and eventual resistance associated with platinum-based chemotherapy [Zhu, H., et al 2016] limit its utility in cervical cancer.

Results from KEYNOTE-158 demonstrated that pembrolizumab has promising efficacy in patients with previously treated advanced cervical cancer. The ORR in the total population (n=98) was 12.2%, including 3 participants that achieved CR. For the 82 patients with PD-L1–positive tumors, the ORR was 14.6%, with an ORR of 14.3% in participants who had previously received 1 or more lines of chemotherapy for recurrent or metastatic disease [Chung, H. C., et al 2019]. There were no responses observed in participants with PD-L1–negative tumors. For those participants with responses, responses were durable (median DOR not reached) and 50.0% of responses ongoing at the time of data cutoff. The safety profile was consistent with that previously observed for pembrolizumab monotherapy, with no new safety signals observed [Chung, H. C., et al 2019]. These results show that pembrolizumab offers a clinically meaningful therapeutic option for a subset of patients with previously treated advanced cervical cancer. Based on these data from KEYNOTE-158, the US Food and Drug Administration granted accelerated approval of pembrolizumab for the treatment of patients with advanced PD-L1-positive cervical cancer with disease progression during or after chemotherapy.

In the MK-7684-001 study, the combination of vibostolimab + pembrolizumab has demonstrated a trend toward improved efficacy compared with pembrolizumab monotherapy in participants with previously treated advanced cervical cancer. In this study, 80 participants with advanced cervical cancer who were naïve to prior anti-PD-1 therapy were enrolled. Compared with pembrolizumab monotherapy in KEYNOTE-158 (ORR=12.2%), the ORR by RECIST 1.1 as assessed by the investigator was 22.5% following treatment with vibostolimab + pembrolizumab. In participants whose tumors expressed PD-L1 (CPS ≥1), vibostolimab + pembrolizumab treatment resulted in an ORR of 25.5% compared with the ORR of 14.6% observed for pembrolizumab monotherapy. Finally, in participants whose

tumors were PD-L1 negative (CPS <1) the ORR was 14.3% following treatment with vibostolimab + pembrolizumab, whereas no responses were observed following pembrolizumab monotherapy. These initial data show promising efficacy with an improvement in ORR compared with pembrolizumab in all participants, regardless of both PD-L1 expression.

To better characterize the effect of MK-7684A versus pembrolizumab monotherapy, the cervical cohort of this study is designed as a randomized cohort in the CPS ≥1 biomarker subgroup. As pembrolizumab did not demonstrate a benefit in the PD-L1 negative population previously, participants whose tumors are PD-L1 negative (CPS <1) will be nonrandomly allocated only to the MK-7684A arm. Participants will be stratified for prior bevacizumab use as this may affect responses to subsequent treatment.

2.2.2.2 Endometrial Cancer

Carcinoma of the uterine corpus, often referred to as endometrial cancer is the sixth most common cancer among women worldwide with an estimated 382,000 new cases diagnosed in 2018 [Ferlay, J., et al 2019]. Endometrial cancer is the fourteenth leading cause of cancer-related death among women worldwide with approximately 90,000 deaths in 2018 [Ferlay, J., et al 2019].

The incidence and disease-related mortality of endometrial cancer, which is the most common gynecologic cancer in the US, continues to increase [Siegel, R. L., et al 2020] [Rahib, L., et al 2014] [Constantine, G. D., et al 2019] [Cote, M. L., et al 2015]. Early stage endometrial carcinoma is associated with a favorable 5-year relative survival rate (95%). In contrast, the 5-year survival rate is only 16% in patients with distant metastases [Siegel, R. L., et al 2020].

Paclitaxel plus carboplatin is standard 1L treatment of advanced, recurrent, and metastatic endometrial carcinoma [National Comprehensive Cancer Network 2019] [Miller, D., et al 2012]. Until recently, only 2 other therapies were specifically approved in the metastatic setting, cytotoxic chemotherapy and megestrol acetate [Makker, V., et al 2017] [Lentz, S. S., et al 1996]. Cytotoxic chemotherapy is associated with low response rates (≤15%) and short PFS (4 months), resulting in poor OS and QoL [McMeekin, S., et al 2015]. Megestrol acetate is approved for the palliative treatment of advanced endometrial carcinoma, regardless of platinum use [Lentz, S. S., et al 1996].

MSI-H tumors, particularly those with high mutational burdens, are more susceptible to checkpoint inhibitors [Arora, E., et al 2018]. In MSI-H endometrial cancers, the mutational burden is particularly high [Kandoth, C., et al 2013]. In patients with previously treated advanced MSI-H/dMMR endometrial cancer (n=49), pembrolizumab monotherapy resulted in an ORR of 57.1% (95% CI: 42.2, 71.2), with a median PFS of 25.7 months (95% CI: 4.9 months to not reached) [Marabelle, A., et al 2019]. Based on the results of KEYNOTE-158, pembrolizumab received a tissue agnostic approval for MSI-H/dMMR solid tumors that have progressed after prior therapy and have no satisfactory alternative treatment options. Accordingly, pembrolizumab is used for metastatic MSI-H endometrial carcinoma after failing 1L chemotherapy; however, the prevalence of MSI-H/dMMR endometrial cancers is

only ~25%, suggesting most patients will have tumors that are not MSI-H or dMMR [Lorenzi, M., et al 2018].

While pembrolizumab monotherapy is effective for MSI-H disease (ORR 57%) [Marabelle, A., et al 2019], it is less effective for MSS disease (ORR 13%) [Ott, P. A., et al 2017]. The combination of immune checkpoint inhibitors with lenvatinib had more potent antitumor activity than either agent alone in preclinical mouse xenograft studies [Kato, Y., et al 2019] [Kimura, T., et al 2018]. Therefore, the combination of pembrolizumab and lenvatinib was studied in participants with advanced previously treated MSS endometrial cancer in Study 111/KEYNOTE-146. The study enrolled 108 participants with previously treated endometrial carcinoma (median follow-up of 18.7 months). The overall ORR_{Wk24} was 38.0% (95% CI: 28.8, 47.8). In participants with MSI-H/dMMR tumors (n=11), the ORR_{Wk24} was 63.6% (95% CI: 30.8, 89.1), which did not represent a substantial improvement over pembrolizumab monotherapy [Marabelle, A., et al 2019]. In participants with non-MSI-H/pMMR tumors (n=94), the ORR_{Wk24} was 36.2% (95% CI: 26.5, 46.7). For previously treated patients, regardless of tumor MSI status, the median DOR was 21.2 months (95% CI, 7.6 months to not estimable), median PFS was 7.4 months (95% CI, 5.3 to 8.7 months), and median OS was 16.7 months (15.0 months to not estimable). Based on these data, lenvatinib plus pembrolizumab was granted accelerated approval in the US for the treatment of patients with advanced endometrial carcinoma that is not MSI-H or dMMR, who have disease progression after prior systemic therapy, and who are not candidates for curative surgery or radiation.

The purpose of this cohort is to study the efficacy of MK-7684A in participants with previously treated endometrial cancer. dMMR tumors are characterized by a dense immune infiltrate and heavily coexpress TIGIT and PD-L1. Activity in the dMMR subset is intended to interrogate MK-7684A activity in these highly IO responsive tumors. For pMMR endometrial cancer, the combination of MK-7684A with lenvatinib is potentially appealing due to the possibility of enhanced efficacy without significant added toxicity compared with pembrolizumab alone. Though both dMMR and pMMR subgroups will be permitted to enroll into this signal finding cohort, treatment allocation will be aligned with the approved therapy for that particular subgroup. For participants with dMMR tumors, given the approval of pembrolizumab monotherapy, participants will be allocated to receive MK-7684A. For participants with pMMR tumors, MK-7684A will be given in combination with lenvatinib, consistent with the pembrolizumab plus lenvatinib approval in this indication. A safety lead-in of MK-7684A and lenvatinib will be performed for the initial participants enrolling in the pMMR cohort to confirm safety and RP2D of this treatment combination.

2.2.2.3 HNSCC

Head and neck cancer describes an anatomically heterogeneous group of cancers that arise most often from the oral cavity, the oropharynx, hypopharynx, and the larynx [Dorsey, K. 2013]. More than 90% of head and neck cancers are squamous cell carcinomas, originating from the epithelium of the mucosal lining of the upper aerodigestive tract [Gupta, B., et al 2016]. As the sixth most common cancer worldwide, head and neck cancer is diagnosed in approximately 630,000 new patients annually, accounting for 350,000 deaths every year [Vigneswaran, N. 2014].

More than 90% of patients with HNSCC initially present with localized disease [Machiels, J. P. 2011]. Surgery and radiation therapy are remarkably effective for patients with Stage I and II disease. However, despite intensive multimodal treatment, approximately 50% to 60% of patients with locally advanced Stage III or Stage IV HNSCC recur initially with locoregional disease. However, a significant proportion of these patients ultimately have incurable disease recurrence requiring palliative systemic treatment. The prognosis for patients with R/M HNSCC has been dismal with OS less than 1 year [Argiris, A., et al 2017].

Patients with recurrent/metastatic HNSCC present a therapeutic challenge. 1L treatment generally includes the combination of either cetuximab or docetaxel with a platinum-based chemotherapy with or without 5-FU. Patients who are asymptomatic usually are treated with monotherapy to balance the side-effects associated with combination regimens. Options for 1L single-agent treatment include platinum, 5-FU, paclitaxel, docetaxel, methotrexate, cetuximab, gemcitabine, or capecitabine [National Comprehensive Cancer Network 2020].

No Phase 3 randomized study had showed an improvement in OS for any regimen until the EXTREME study [Vermorken, J. B., et al 2008]. This study demonstrated that the addition of cetuximab to the combination of platinum + 5-FU improved median OS to 10.1 months compared with 7.4 months for platinum + 5-FU alone.

Data from the final analysis of KEYNOTE-048, which evaluated pembrolizumab monotherapy and pembrolizumab + chemotherapy versus chemotherapy alone, demonstrated a clinically meaningful difference in OS when comparing pembrolizumab + chemotherapy (platinum + 5-FU) with standard treatment (cetuximab + platinum + 5-FU [EXTREME regimen]). The pembrolizumab + chemotherapy group had a more durable DOR than the EXTREME regimen and the safety profile was comparable. In addition, in participants whose tumors expressed PD-L1 (CPS ≥1), pembrolizumab monotherapy resulted in a clinically meaningful improvement in OS compared with standard treatment (cetuximab + platinum + 5-FU). The pembrolizumab monotherapy group had more responders who achieved a CR and a more durable DOR. The safety profile for pembrolizumab monotherapy was favorable. Based on this data, pembrolizumab is approved globally as monotherapy and in combination with chemotherapy for 1L treatment of metastatic or recurrent HNSCC.

There is strong biologic rationale for the combination of vibostolimab and pembrolizumab in HNSCC. HNSCC tumors coexpress PD-L1 and TIGIT. TIGIT overexpression is also noted in CD4 and CD8+ TILs and Tregs isolated from human HNSCC tumors and mouse HNSCC models. The TIGIT ligand, CD155, is associated with inferior OS in HNSCC [Wu, L., et al 2019]. Finally, in mouse models of HNSCC, anti-TIGIT treatment delayed tumor growth and enhanced CD8 effector function by inhibiting Treg and myeloid-derived suppressor cell function [Wu, L., et al 2019]. This signal finding cohort will assess the preliminary efficacy of MK-7684A in untreated advanced HNSCC in tumors expressing PD-L1 CPS ≥1 to assess whether there is benefit to the combination compared to pembrolizumab monotherapy in the population which has shown benefit with pembrolizumab monotherapy on KEYNOTE-048.

2.2.2.4 Biliary Cancer

Biliary tract cancer arises from the epithelial lining of the biliary tree, and typically includes cancers of the gallbladder and CCA. CCA is classified as intrahepatic or extrahepatic. Ampullary cancers usually are not included because of different biology and prognosis. Biliary tract cancer subtypes differ in their cancer biology and clinical presentation, but all are often diagnosed in the advanced stage. Nonetheless, for advanced or metastatic BTC (CCA and gallbladder cancer), platinum-based chemotherapy is the SOC irrespective of subtype. Although several studies are evaluating potential cytotoxic and molecularly targeted therapy options, the limitation of increased toxicity with cytotoxic chemotherapy and small selected populations for molecularly targeted therapy highlights the need for a more effective therapy that can be used for the majority of BTC patients. Current data support PD-1/PD-L1 mediated inhibition of adaptive immune response to carcinogenesis and, hence the role of checkpoint inhibition as a therapeutic option.

Immune checkpoint blockade is an attractive strategy for therapeutic intervention in BTC, considering that inflammation plays a key role in the development of BTC worldwide. In a retrospective analysis of BTC, the presence of TILs was associated with improved outcome [Goeppert, B., et al 2013]. A total of 375 cases were analyzed, which included intra-/extrahepatic CCA and gallbladder cancer. Of note, the presence of intraepithelial tumor-infiltrating CD4+, CD8+ and FoxP3+ TILs were associated with longer survival. This study also reported a decline in adaptive immune response and an increase in innate immune response components during dysplasia to primary carcinoma to metastases progression. Additionally, a large meta-analysis of 12 studies and over 2000 patients showed similar results indicating association of improved clinical outcome with higher expression of TILs [Wang, Y., et al 2017]. These findings theorize evasion of immune surveillance and adaptive immune response in BTC and, hence, support the role of checkpoint inhibitor therapy in this patient population.

In KEYNOTE-158 [Ueno, M., et al 2018], a total of 104 participants with BTC were enrolled with 61 participants having tumors positive for PD-L1 expression (CPS ≥1). Approximately half (52%) of participants had 2 or more prior lines of therapy. The ORR following pembrolizumab monotherapy (200 mg Q3W) was 5.8% with a DOR of >15 months. The median DOR was not reached. The median PFS was 2.0 months (95% CI: 1.9, 2.1) and median OS was 9.1 months (95% CI: 5.6, 10.4). Among patients with PD-L1 CPS ≥1, the ORR was 6.6 %, the median PFS was 2.1 months and the median OS was 9.6 months. Participants with CPS <1 had an ORR of 2.9%, the median PFS was 1.9 months, and the median OS was 7.2 months. None of the patients were found to be MSI-H. The overall toxicity profile was manageable, and activity was seen regardless of PD-L1 status. These data support modest efficacy of pembrolizumab monotherapy in advanced BTC, which underscores the need for combination therapies in this indication of unmet need.

The combination of vibostolimab and pembrolizumab may improve efficacy compared with pembrolizumab alone in participants with advanced BTC. TIGIT was found to be overexpressed in BTC in a meta-analysis of 250 CCA cases compared with 16 normal intrahepatic duct samples (p=0.0003) [Ross, J. S., et al 2020]. Additionally, CD155 was found to be upregulated in 62% of samples in a separate analysis of CCA tumors (n=90)

[Huang, D. W., et al 2017]. Therefore, based on preclinical and clinical data showing enhancement of efficacy for vibostolimab and pembrolizumab given together compared with pembrolizumab alone in IO responsive tumors, we hypothesize that MK-7684A could provide benefit to BTC patients in the clinical setting. In this study, a signal finding cohort of participants with advanced biliary cancer that have progressed on standard therapies will receive MK-7684A (Cohort D1).

This study will also evaluate the combination of MK-7684A with chemotherapy in previously untreated participants (Cohort D2). In Cohort D2, gemcitabine at 1000 mg/m^2 and cisplatin at 25 mg/m^2 are administered on Day 1 and Day 8 of a 21-day cycle. This dose of gemcitabine/cisplatin was used in the ABC-02 study, which defined gemcitabine/cisplatin as the SOC for advanced BTC [Valle, J., et al 2010]. Based on global clinical practice patterns, gemcitabine will be administered until PD or unacceptable toxicity, cisplatin will be administered for a maximum of 8 cycles.

2.2.2.5 Esophageal Cancer

Esophageal cancer is the seventh most common cancer and the sixth most common cause of cancer-related death worldwide, with approximately 572,000 new cases and 509,000 deaths in 2018 [Ferlay, J., et al 2019]. There are limited treatment options for patients with unresectable, locally advanced, or metastatic esophageal cancer [Shah, M. A. 2015]. The prognosis for patients with metastatic esophageal cancer is poor, with 5-year survival rates of less than 5% [Noone, A. M., et al 2017].

While current treatment guidelines recommend platinum-based combinations with fluoropyrimidine for the 1L treatment of metastatic esophageal cancer [Ajani, J. A., et al 2019] [Muro, K., et al 2019] [Kitagawa, Y., et al 2019], anti-PD-1/PD-L1 therapies have shown promising antitumor activity in these patients [Doi, T., et al 2018] [Hong, Y. 2019] [Shah, M. A., et al 2018] [Kato, K., et al 2020]. In KEYNOTE-181, pembrolizumab provided a clinically meaningful OS benefit versus chemotherapy (investigator's choice of paclitaxel, docetaxel, or irinotecan) in participants with metastatic esophageal squamous cell carcinoma whose tumors expressed PD-L1 (CPS ≥10) and progressed after one prior therapy. Pembrolizumab resulted in more than a 2-fold increase in the 12-month survival rate compared with chemotherapy (43% vs 20%) and reduced the risk of death by 31% to 33% [Kojima, T., et al 2020]. A similar survival benefit was generally observed across key subgroups of participants whose tumors express PD-L1 (CPS ≥10), with the highest survival benefit observed in patients with squamous cell carcinoma (OS HR=0.64) [Kojima, T., et al 2020].

The KEYNOTE-590 study examined pembrolizumab in combination with chemotherapy (cisplatin + 5-FU), for the 1L treatment of patients with metastatic or locally advanced esophageal or GEJ carcinoma. The study demonstrated that the addition of pembrolizumab improved OS, PFS, and ORR in participants with advanced esophageal and GEJ cancer that had not been previously treated [Kato, K., et al 2020]. Pembrolizumab + chemotherapy significantly improved OS in all participants (OS HR=0.73 [95% CI: 0.62, 0.86; p<0.0001]). Similarly, pembrolizumab + chemotherapy significantly improved PFS in all participants (PFS HR=0.65 [95% CI: 0.55, 0.76; p<0.0001]). In all participants, the confirmed ORR for

pembrolizumab + chemotherapy was 45.0% compared with 29.3% for chemotherapy (p<0.0001) and the median DOR was 8.3 months compared with 6.0 months, respectively. These data showed that pembrolizumab + chemotherapy provided superior OS, PFS, and ORR versus chemotherapy, with a manageable safety profile in patients with metastatic or locally advanced esophageal or GEJ carcinoma. Based on this data, global marketing application to support approval are currently under review.

TIGIT and PD-L1 tightly are coexpressed in both adenocarcinoma and ESCC. Patients with PD-1+/TIGIT+ TILs and PD-L1- and/or PD-L2-positive tumor cells have been reported to have worse prognosis in primary ESCC [Zhao, J. J., et al 2018]. Therefore, the combination of TIGIT and PD-L1 blockade may provide added benefit over single-agent checkpoint blockade. The tolerability of vibostolimab is a potential added benefit for combination with chemotherapy and anti-PD-1. In this study, MK-7684A will be tested in combination with chemotherapy in participants with previously untreated esophageal cancer as a signal finding cohort. A safety lead-in will be performed to confirm the tolerability and RP2D of chemotherapy to be used in this combination.

2.2.2.6 Triple-negative Breast Cancer

Breast cancer is the most common cancer and the leading cause of cancer mortality in women. Worldwide, in 2018 there were an estimated 2,088,849 newly diagnosed cases of breast cancer and an estimated 626,679 deaths [Bray, F., et al 2018].

TNBC, which is phenotypically defined by a lack of ER and PgR expression and the absence of HER2 overexpression and/or amplification [Dent, R., et al 2007], represents 15% to 20% of all breast cancers [Bauer, K. R., et al 2007] [Arnedos, M., et al 2012]. TNBC is overlapping, but not synonymous, with the basal-like subtype defined by gene expression, as about 70% of TNBCs have basal-like characteristics [Badve, S., et al 2011] [Sorlie, T., et al 2001]. TNBC is associated with higher tumor grade at diagnosis, a higher risk of distant disease recurrence, and poorer OS compared with other breast cancer subtypes [Dent, R., et al 2007] [Bauer, K. R., et al 2007] [Arnedos, M., et al 2012].

As reported in a seminal study on TNBC, patients with TNBC experience distant recurrence more frequently (~34% vs ~20%) and earlier (mean time to distant recurrence 2.6 years vs 5.0 years) compared with patients with other types of breast cancer [Dent, R., et al 2007]. The peak of recurrence for TNBC is within 1 to 3 years after initial diagnosis and decreases significantly thereafter. Patients with TNBC also have shorter median OS compared with patients with non TNBC (4.2 years vs 6.0 years) [Dent, R., et al 2007]. Finally, patients with TNBC tend to relapse with distant metastases rather than local recurrences and are more likely to develop visceral metastases and CNS involvement [Lin, N. U., et al 2008].

Treatment of TNBC is challenging and represents an area of continued medical need, as these tumors lack therapeutic targets, such as ER and HER2, and become rapidly resistant to chemotherapy upon local recurrence and/or metastasis (even though they are often sensitive to cytotoxic drugs at initial presentation) [Arnedos, M., et al 2012]. The majority of patients with metastatic TNBC have experienced relapse after neoadjuvant or adjuvant therapy for early or locally advanced disease [Arnedos, M., et al 2012].

The potential synergistic effects of standard cytotoxic chemotherapy in combination with immunotherapies have been demonstrated in preclinical studies [Peng, J., et al 2015] [Anraku, M., et al 2010]. Chemotherapy potentially augments the antitumor immune response by inducing immunogenic cell death, enhancing the maturation and activation of dendritic cells, increasing T-cell penetrance and function in the tumor, improving the presentation of tumor antigens, and eliminating immunosuppressive cells (Tregs, myeloid-derived suppressor cells, and M2 macrophages) [Apetoh, L., et al 2015]. TNBC may be an immune-reactive disease amenable to immune modulation of the tumor microenvironment. Pembrolizumab has shown promising clinical activity when administered as monotherapy for advanced TNBC [Nanda, R., et al 2016] [Adams, S., et al 2019] [Cortes, J., et al 2019] and has demonstrated a clinical benefit when administered with chemotherapy in the metastatic TNBC setting.

Recently, KEYNOTE-355 demonstrated that pembrolizumab in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine/carboplatin) is an effective and generally well tolerated treatment for participants with locally recurrent inoperable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10). Treatment with pembrolizumab in combination with chemotherapy provided a statistically significant and clinically meaningful improvement in PFS compared with placebo + chemotherapy in participants with PD-L1 positive tumors (CPS ≥10). The PFS HR of 0.65 (95% CI: 0.49, 0.86, p=0.0012) represents a 35% reduction in the risk of progression or death for participants with PD-L1 positive tumors (CPS ≥10). The median PFS was 4.1 months longer for participants with PD-L1 positive tumors (CPS ≥10) in the pembrolizumab + chemotherapy group compared with the placebo + chemotherapy group (9.7 months vs 5.6 months). These PFS data are further supported by clinically meaningful improvements in ORR and DOR in participants receiving pembrolizumab + chemotherapy combination compared with placebo + chemotherapy. Responses were durable in participants with PD-L1 positive tumors (CPS ≥10) who responded to pembrolizumab + chemotherapy, suggesting a long-term benefit for the use of pembrolizumab in this population of participants with locally recurrent inoperable or metastatic TNBC. Based on the results of KEYNOTE-355, pembrolizumab + chemotherapy received accelerated approval in the US for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer whose tumors express PD-L1 (CPS ≥10).

TIGIT and PD-L1 are highly expressed in TNBC; therefore, the combination of TIGIT and PD-L1 blockade may provide added benefit in combination with chemotherapy over single-agent checkpoint blockade. The tolerability of vibostolimab is a potential added benefit for combination with chemotherapy and anti-PD-1. In this study, MK-7684A will be tested in combination with chemotherapy in patients with previously untreated locally recurrent unresectable or metastatic TNBC as a signal finding cohort. A safety lead-in will be performed to confirm the tolerability and RP2D of paclitaxel to be used in this combination.

2.2.2.7 HCC

HCC is responsible for more than 700,000 new cases and 600,000 deaths annually [Dhanasekaran, R., et al 2012]. Most HCC arises in the setting of liver cirrhosis from varied causes, including viral hepatitis, excessive alcohol consumption, and metabolic syndrome.

Additionally, HCC incidence varies by region, with the highest rates seen in Eastern Asia and sub-Saharan Africa (over 20 cases per 100,000 individuals). China accounts for approximately 50% (395,000 new cases annually) of all new HCC cases. The predominant risk factors for HCC vary in high- and low-rate regions. In most high-rate countries, particularly Asia and Africa, chronic HBV infection and aflatoxin exposure are the major risk factors [McGlynn, K. A., et al 2015]. In contrast, in lower-rate areas, such as the US, HCV infection, excessive alcohol consumption, and metabolic syndrome play more important roles. Exceptions to these regional patterns are seen in Japan and Egypt, where the predominant risk factor is HCV infection.

Surgical resection, transplantation, and ablation are potentially curative treatment options for patients with early stage disease; however, about 70% of patients present with advanced, unresectable disease. As HCC is resistant to most traditional chemotherapy agents, the median survival for patients with advanced disease is typically 6 to 9 months without therapy [Qin, S., et al 2013].

Standard options for 1L therapy include receptor tyrosine kinase inhibitors including sorafenib and lenvatinib. Lenvatinib was approved globally for 1L treatment of unresectable HCC based on results from the open-label Phase 3 study E7080-G000-304 (REFLECT) study. In data published from the REFLECT study, 954 patients with 1L HCC were randomly assigned to receive lenvatinib at 12 mg or 8 mg qd depending on BW (≥60 kg or <60 kg, respectively [n=478]) or sorafenib at 400 mg twice a day (n=476). Lenvatinib showed noninferior median OS compared with sorafenib (13.6 months vs 12.3 months; HR: 0.92; 95% CI: 0.79, 1.06). Lenvatinib treatment also showed improvements when compared with sorafenib treatment in the following: ORR (24.1% vs 9.2%), PFS (7.4 months vs 3.7 months), and median TTP (8.9 months vs 3.7 months). The most common any grade AEs for lenvatinib were hypertension (201 [42%]), diarrhea (184 [39%]), decreased appetite (162 [34%]), and decreased weight (147 [31%]). When comparing the AE profile to sorafenib, lenvatinib has a decreased frequency of palmar-plantar erythrodysesthesia (128 participants [27%] vs 249 participants [52%]), but an increased frequency of hypertension (201 participants [42%]) vs 144 participants [30%]).

Immune checkpoint blockade has also been a successful therapeutic strategy in HCC, likely in part to the fact that HCC often develops in the setting of inflammation caused by various sources. Phase 2 data from treatment of 104 participants with pembrolizumab in 2L HCC (KEYNOTE-224) demonstrated an ORR of 17%, with responses seen in different viral subtypes, and several participants with prolonged DOR [Zhu, A. X., et al 2018]. Of the responders, 12 (77%) responders showed a response for at least 9 months, as estimated by the KM method, and the median TTR was 2.1 months (range, 2.1 to 4.1 months). Treatment-related AEs occurred in 76 (73%) of 104 participants; 16 (15%) were serious.

The combination of anti-PD-1/PD-L1 agents and receptor tyrosine kinase inhibitors have also demonstrated promising activity in unresectable HCC. In a global open-label Phase 3 study, patients with unresectable HCC who were naïve to prior systemic therapy were randomized to atezolizumab and bevacizumab (n=336) or sorafenib (n=165). Atezolizumab + bevacizumab treatment was associated with improved OS compared with sorafenib (OS HR=0.58 [95% CI: 0.42, 0.79; p<0.001]). OS at 12 months was 67.2% (95% CI: 61.3, 73.1)

with atezolizumab + bevacizumab compared with 54.6% (95% CI: 45.2, 64.0) for sorafenib. Median PFS was 6.8 months (95% CI: 5.7 to 8.3) and 4.3 months (95% CI, 4.0 to 5.6), respectively, with a PFS HR of 0.59 (95% CI: 0.47, 0.76; $p<0.001$) [Finn, R. S., et al 2020].

Additionally, the combination of lenvatinib with PD-1 inhibitors in HCC appears to provide added benefit over either treatment alone. In a study of pembrolizumab and lenvatinib in unresectable HCC (N=104), patients received lenvatinib (12 mg [BW ≥60 kg] or 8 mg [BW <60 kg]) qd and pembrolizumab 200 mg Q3W. With a median duration of follow-up of 10.6 months (95% CI: 9.2 to 11.5 months), the confirmed ORR and median DOR by mRECIST based on IIR was 46.0% (95% CI: 36.0, 56.3) and 8.6 months (95% CI: 6.9 months to not estimable), respectively. Median PFS by mRECIST based on IIR was 9.3 months and 8.6 months per RECIST v1.1. Median OS was 22 months. Grade ≥3 treatment-related AEs occurred in 67% of participants with 3 deaths considered related. No new safety signals were identified [Finn, R. S., et al 2020a].

TIGIT and PD-L1 are coexpressed in HCC tumors. To test whether the addition of a TIGIT blocking antibody can improve upon the response rate observed for pembrolizumab and lenvatinib alone, a signal finding cohort of participants with previously untreated unresectable HCC will receive MK-7684A + lenvatinib at the approved lenvatinib dose and schedule for HCC. A safety lead-in will be performed to confirm the tolerability and RP2D of lenvatinib to be used in this combination.

2.2.2.8 Bladder Cancer

UC, also referred to as transitional cell carcinoma, is a range of tumors that arise from the urothelial endothelium, including the bladder, renal pelvis, ureter, and urethra. The worldwide incidence of bladder cancer exceeds 300,000 cases annually [Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D 2011]. UC is the predominant histologic type of bladder cancer in the United States and western Europe, where it accounts for approximately 90% of bladder cancers.

UC disproportionately affects the elderly, who often have coexisting, impactful illnesses such as cardiovascular disease and impaired renal function. Such coexisting illnesses are important factors limiting treatment options for these patients [Bamias, A., et al 2007]. Many patients with UC present with advanced disease [Siegel, R. L., et al 2016]. Inoperable, metastatic disease is typically incurable; prognosis is poor and treatment options are limited. Patients receive palliative treatment or best supportive care as the only options.

For nearly 30 years, the first-line standard of care treatment for patients with locally advanced or metastatic UC has been cisplatin-containing combination chemotherapy, including either gemcitabine or methotrexate/vinblastine/doxorubicin [Sternberg, C. N., et al 2006] [Logothetis, C. J., et al 1990] [von der Maase, H., et al 2000]. Median survival with cisplatin-based multiagent chemotherapy is approximately 14 to 15 months [von der Maase, H., et al 2005]. While this result is superior to the estimated 6-month survival with metastatic disease before the development of modern chemotherapy regimens, the 5-year survival rate with contemporary regimens remains poor.

Chemotherapy, particularly with cisplatin, is toxic, and it has been estimated that only approximately 21% of patients are treated with cisplatin-based chemotherapy [Sonpavde, G., et al 2014]. Cisplatin ineligibility is commonly due to renal dysfunction (CrCl <60 mL/min), ECOG PS 2, or both. Hearing loss, Grade 2 neuropathy, and heart failure may also confer cisplatin ineligibility [Galsky, M. D., et al 2011] [Galsky, M. D., et al 2011a] [Dash, A., et al 2006]. There is no SOC chemotherapy for patients unable to tolerate cisplatin. Consensus guidelines, such as those of the NCCN, recommend participation in clinical trials of new and more tolerable therapy for patients who cannot tolerate cisplatin-based chemotherapy. As an alternative chemotherapy to cisplatin and clinical study participation, NCCN recommends gemcitabine/carboplatin on the basis of category 2 evidence (https://www.nccn.org/professionals/physician_gls/default.aspx). The NCCN recommendation for gemcitabine/carboplatin is based on the EORTC 30986 study, one of the largest clinical trials evaluating carboplatin-based chemotherapy in the cisplatin-ineligible population [De Santis, M., et al 2012]. In this study, 238 cisplatin-ineligible participants with UC were randomized to receive either gemcitabine/carboplatin or methotrexate/carboplatin/vinblastine. Overall, chemotherapy was active; the ORR was 36.1%. However, median survival was poor (9.3 months with gemcitabine/carboplatin, the more effective and less toxic of the 2 regimens studied) for the overall study population. Participants with baseline ECOG PS 2 and GFR <60 mL/min demonstrated a worse ORR of 26.5% and a median OS of 5.5 months (95% CI: 4.1, 8.3). Participants with ECOG PS 2 and visceral metastatic disease (represented by Bajorin risk group 2 [below]) had an ORR of 26.5% and a median OS of 5.5 months (95% CI: 4.2, 7.3). The rate of severe acute toxicity, defined as death as a result of toxicity, renal toxicity (Grade 3 to 4), febrile neutropenia (Grade 3 to 4), hemorrhage/bleeding with thrombocytopenia (Grade 4), or mucositis (Grade 3 to 4) was 9.3% of the overall population in the gemcitabine/carboplatin arm of EORTC 30986. The rate of severe acute toxicity was 28% in participants with ECOG PS 2 and GFR <60 mL/min. Of the participants receiving gemcitabine/carboplatin, 72.9% required dose reduction and 21% discontinued therapy due to toxicities. In light of these results, the overall benefit derived from carboplatin is small.

Consistent with these recommendations, a risk categorization called the Bajorin risk model has been formulated and published [Bajorin, D. F., et al 1999]. The 2 risk factors in the Bajorin risk model are:

- Poor performance status (Karnofsky performance status <80%, equivalent to ECOG PS ≥2)
- Presence of visceral (lung, liver, or bone) metastasis

Patients are placed in 3 prognostic groups (Bajorin risk groups 0, 1, or 2) depending on their number of adverse prognostic factors. Because of these findings, the NCCN warns that ECOG PS ≥2 and visceral metastatic disease or ECOG PS ≥2 and GFR <60 mL/min strongly predict a poor outcome of chemotherapy and suggests that such patients might be better served with best supportive care or participation in a clinical study [National Comprehensive Cancer Network 2016]. The results of the EORTC 30986 clinical study demonstrate that ECOG PS 2 plus an additional prognostic factor (GFR <60 mL/min or visceral metastases) are key characteristics that define chemotherapy unfitness [De Santis, M., et al 2012] and

suggested that alternative non-cisplatin-containing treatment regimens should be investigated for these patients.

Indeed, because of the frailty of this population with advanced UC and the toxicity associated with chemotherapy, it has been estimated that 48% of UC patients cannot be treated with any platinum chemotherapy at all. In addition, it has been shown that patients not treated with chemotherapy do worse than those who are able to tolerate it [Small, A. C., et al 2012] [Sonpavde, G., et al 2014] [Sonpavde, G., et al 2012]. The critical implication is that there are many patients who die not having received anticancer treatment. There are no clear guidelines or definitions of clinical characteristics for platinum-based chemotherapy ineligibility [Sonpavde, G., et al 2014]. Despite the absence of a precise definition, practicing clinical oncologists are adept at identifying patients who are good candidates for chemotherapy and do not offer chemotherapy to patients who are not good candidates for it.

The most frequently listed characteristics of patients deemed unfit for chemotherapy, and therefore of platinum ineligibility, are the following [Apolo, A. B., et al 2013]:

- ECOG PS 2 plus 1 of the following:
  - Visceral metastases
  - GFR 30 to 60 mL/min
  - Grade ≥2 audiometric hearing loss
  - Grade ≥2 peripheral neuropathy
  - Other reason for the participant's being unable to receive carboplatin safely

Recently, pembrolizumab has shown efficacy in 1L and 2L treatment of metastatic bladder cancer [Powles, T., et al 2014]. Pembrolizumab is indicated for the treatment of patients who are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status. Data from KEYNOTE-052 [Balar, A. V., et al 2017], a large single-arm Phase 2 study investigating pembrolizumab for the first-line treatment of advanced UC in cisplatin-ineligible participants, were the basis of approval for this indication. KEYNOTE-052 enrolled 370 participants who were cisplatin-ineligible (ECOG PS 2, CrCl ≥30 to <60 mL/min, Grade ≥2 neuropathy/hearing loss, NYHA Class 3 heart failure), had advanced UC, and had received no prior chemotherapy for metastatic disease. Participants received pembrolizumab 200 mg IV Q3W for up to 24 months.

In KEYNOTE-052, 48% of participants (n = 179) were at least 75 years of age, and 10.8% (n = 40) were at least 85 years of age. Many participants had poor prognostic features at study entry: 41.9% (n = 155) had ECOG PS 2, 85.1% (n = 315) had visceral disease, and 20.8% (n = 77) had liver metastases. In addition, 35% of participants (n = 130) had ECOG PS 2 and visceral metastatic disease and were considered ineligible for any platinum-containing chemotherapy. In summary, these participants represented the full spectrum of cisplatin-ineligible patients, including those who likely would not have been treated with any platinum chemotherapy at all had they not been enrolled into this study.

The results of KEYNOTE-052 demonstrate compelling antitumor activity across the full spectrum of the cisplatin-ineligible population. Treatment resulted in a clinically meaningful ORR of 28.9% (95% CI: 24.3%, 33.8%). Responses were accompanied by unprecedented durability: median DOR was not reached, and DOR ranged from 1.4+ to 27.9+ months (+ denotes ongoing response). The median OS in the overall population was 11.5 months (95% CI: 10.0, 13.3). In comparison to the overall population, median OS was longer in the PD-L1 CPS ≥10 subgroup (18.5 months [95% CI: 12.2, not reached]) and shorter in the PD-L1 CPS <10 subgroup (10.0 months [95% CI: 7.8, 11.6]). This included participants considered cisplatin-ineligible as well as those who were ineligible for any platinum-based combination chemotherapy. The median OS in the platinum-ineligible population was 8.3 months (95% CI: 5.2, 10.8). Due to the results of KEYNOTE-052, the NCCN recommends pembrolizumab as the SOC for all platinum-ineligible patients.

Pembrolizumab is also indicated for use in patients with locally advanced or metastatic UC and disease progression during or after platinum-containing chemotherapy. KEYNOTE-045 was the basis of approval for this indication and was a multicenter, randomized, active-controlled study in which participants had previously received platinum-based chemotherapy and were randomized to receive either pembrolizumab 200 mg Q3W (n = 270) or the investigator's choice of paclitaxel, docetaxel, or vinflunine (n = 272) [U.S. Prescribing Information. 2021].

In KEYNOTE-045 [Bellmunt, J., et al 2017], the median age of participants was 67 years in the pembrolizumab arm and 65 years in the chemotherapy arm. The majority of participants had ECOG PS 0 (44.1% for pembrolizumab and 39.0% for chemotherapy) or 1 (53.0% for pembrolizumab and 58.1% for chemotherapy). In addition, 89.2% of participants in the pembrolizumab arm and 86.0% of those in the chemotherapy arm had visceral metastases. The results of KEYNOTE-045 showed significantly superior OS with pembrolizumab (HR 0.73; 95% CI: 0.59, 0.91; p=0.002) compared with chemotherapy. The median OS with pembrolizumab was 10.3 months (95% CI: 8.0, 11.8), versus 7.4 months with chemotherapy (95% CI: 6.1, 8.3). KEYNOTE-045 also demonstrated higher response rates and longer response duration with pembrolizumab, compared with chemotherapy. The results in the pembrolizumab arm have led to pembrolizumab's becoming SOC in this disease setting [Bellmunt, J., et al 2017].

The criteria for defining platinum ineligibility for patients with metastatic bladder cancer are evolving. Gupta and colleagues surveyed genitourinary medical oncologists in the United States. Based on their responses it was recommended that 1 of the following 5 criteria be met to determine that a patient is platinum-ineligible: ECOG PS >3; Cr Cl <30 mL/min; peripheral neuropathy >Grade 3; NYHA Heart Failure >3; or ECOG PS 2 and Cr Cl <30 mL/min [Gupta, S., et al 2019]. However, this study did not consider other factors that often contribute to platinum ineligibility, including advanced age (≥80 years) and comorbid conditions that can worsen with chemotherapy, such as poorly controlled diabetes, progressive peripheral neuropathy, gastroesophageal reflux disease, and low bone marrow reserve. In real-world practice, many patients are not eligible for platinum chemotherapy based on these factors. Therefore, the current study will evaluate the safety and efficacy of treatment with MK-7684A in participants ineligible for any platinum chemotherapy as determined by the investigator.

2.2.2.9 Ovarian Cancer

OC is the most lethal gynecologic cancer and one of the top-leading causes of cancer death among women. In 2017, the estimated number of new cases and deaths from OC in the US was 22,440 and 14,080, respectively [Siegel, R. L., et al 2017]. Worldwide, OC represents one of the 10 most common cancer diagnoses and leading causes of cancer-related deaths in women [Torre, L. A., et al 2015]. Due to lack of tumor-specific signs and symptoms and effective screening tests for early detection, over 75% of OC patients are first diagnosed at advanced stages. Based on the US data from 2006 to 2012, at initial diagnosis, 60% had distant metastasis, 19% had regional disease and only 15% had localized disease. The overall 5-year survival rate of OC is approximately 46% counting all stages; the 5-year survival rate in patients with distant metastasis is only 29% [Siegel, R. L., et al 2017].

OC is a heterogeneous disease, with distinct histopathologic features, genetic alterations, and clinical behaviors. Epithelial OC is the most common (>90% of OCs) and most lethal of the gynecologic malignancies [Gilks, C. B. and Prat, J. 2009]. Currently, EOCs are classified into 5 main subtypes based on histopathology, immunohistochemistry, and molecular-genetic characteristics: HGSC (~ 70% of EOCs), endometrioid carcinoma (~ 10% of EOCs), clear cell carcinoma (~ 10% of EOCs), mucinous carcinoma (~ 3% of EOCs), and low-grade serous carcinoma (5% EOC) [Gilks, C. B. and Prat, J. 2009] [Prat, J. and FIGO Committee on Gynecologic Oncology 2014]. The distinction of EOC subtype at diagnosis/staging is a critical factor that will guide treatment, as each tumor type responds differently to chemotherapy [Gilks, C. B. and Prat, J. 2009]. Primary peritoneal carcinoma and fallopian tube carcinoma, while rare and distinct tumor types, have typically been managed and studied together with EOC as they share similar clinical and pathological characteristics with HGSC [Cannistra, S. A., et al 2011].

The current SOC for advanced EOC (FIGO Stage II to Stage IV) includes primary debulking surgery followed by postoperative front-line (ie, adjuvant) systemic treatment with IV carboplatin and paclitaxel administered Q3W for 6 cycles. However, weekly paclitaxel has also been frequently used to replace Q3W paclitaxel. In addition, where locally approved for front-line treatment, IV bevacizumab can be added to IV carboplatin and paclitaxel for up to 6 cycles and then continued as a single agent. In suitable cases, postoperative chemotherapy, usually cisplatin plus paclitaxel, can be delivered via the intraperitoneal route. Finally, in cases with bulky disease that is initially inoperable, 3 or more cycles of standard platinum/taxane-based chemotherapy can be administered as neoadjuvant therapy prior to debulking surgery (ie, interval debulking surgery) followed by additional cycles of adjuvant platinum/taxane-based chemotherapy for a total of 6 cycles. In these cases, bevacizumab can also be added to the chemotherapy regimen [Morgan, R. J ., et al 2016] [Ledermann, J. A., et al 2013].

The goal of debulking surgery is to achieve resection of all macroscopically visible tumors, while the goals of postoperative 1L chemotherapy are: 1) to help achieve complete remission in those with residual disease, and 2) to prevent disease recurrence for those with complete tumor resection. However, after these primary treatments, only a small proportion of patients will achieve long-term disease-free and survival status. A meta-analysis on data from 3 randomized studies following the standard primary treatment with surgery and

platinum/taxane-based chemotherapy (N = 3126), showed that only 24% of patients were recurrence-free after a median follow-up time of 53.9 months. The remaining 76% had recurrent disease (17.2%) or had died (58.8%) [du Bois, A., et al 2009].

The approval of PARP inhibitors for ovarian cancer ushered in a new SOC with improved clinical outcomes. On 19-DEC-2018, olaparib monotherapy was approved by the US FDA for first-line maintenance treatment of BRCAm advanced ovarian cancer based on the Phase 3 study SOLO-1. On 08-MAY-2020, the indication for olaparib was expanded to include its use in combination with bevacizumab for 1L maintenance treatment of HRD-positive advanced ovarian cancer based on the Phase 3 study PAOLA-1. On 29-APR-2020, niraparib monotherapy was approved by the FDA for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or PR to 1L platinum-based chemotherapy based on the Phase 3 study PRIMA [Gonzalez-Martin, A., et al 2019].

Despite the approval of PARP inhibitors for ovarian cancer, vulnerable populations of ovarian cancer patients remain, who have poorer outcomes and more unmet medical need. These underserved populations include interval debulking surgery patients, who experience a 4-year shorter median overall survival compared to primary debulking surgery patients, whose tumors are amenable to complete surgical resection prior to systemic therapy [Kraus, F., et al 2021]. In addition, PARP inhibitors have lower efficacy in BRCA1/2 nonmutated, HRD-negative patients, leading to a 2-year shorter median overall survival in this group of patients compared to their counterparts with BRCA1/2-mutated and/or HRD-positive tumors [Sims, T. T., et al 2021]. Therefore, the ovarian cancer cohort in this study was designed to investigate whether vibostolimab can improve clinical outcomes in the poor prognosis group of patients, who require interval debulking surgery and who have BRCA1/2 nonmutated, HRD-negative tumors.

The dosing regimens of carboplatin and paclitaxel that will be used in Cohort I are reflective of current clinical practice. The dose of docetaxel, if approved by the Sponsor, reflects the recommended dose for OC as determined by the SGCTG [Vasey, P. A., et al 2004]. The dosing regimen of bevacizumab will reflect the local SOC and approved product label.

2.2.2.10 Gastric Cancer

Gastric cancer is the fifth most common cancer in the world and is a major cause of cancer-related death [Ferlay, J., et al 2014]. In 2012, there were approximately 952,000 new cases of gastric cancer worldwide (631,000 men and 320,000 women) with 723,000 deaths (469,000 men and 254,000 women), making it the third-leading cause of cancer death globally in both sexes [Ferlay, J., et al 2014]. Gastric cancer incidence varies markedly by geographic region. More than 70% of cases occur in developing countries, and half the world total occurs in Eastern Asia. In the EU, approximately 82,000 new cases of gastric cancer were diagnosed in 2012, with approximately 58,000 deaths attributed to this disease. Corresponding numbers in the US showed an estimated 21,000 new cases of gastric cancer with nearly 12,000 deaths from this disease.

Until recently, there was no globally accepted standard 1L regimen in HER2 negative, advanced, unresectable and/or metastatic gastric and GEJ adenocarcinoma. In general, combination chemotherapy regimens provide higher response rates than do single agents. Many patients were recommended to receive a fluoropyrimidine-platinum doublet over more toxic triplet chemotherapeutic regimens.

The fluoropyrimidine/platinum doublet combination was a common 1L therapy for metastatic gastric cancer and it was considered "preferred" by the NCCN Gastric Cancer Guideline committee [National Comprehensive Cancer Network 2016a]. Fluoropyrimidine/platinum doublet regimens containing 5-FU or capecitabine and cisplatin or oxaliplatin are recognized worldwide as standard 1L chemotherapy regimens for patients with metastatic gastric and GEJ adenocarcinoma.

The ML17032 study was a randomized, Phase 3 study that compared the combination of cisplatin and capecitabine to the combination of cisplatin and 5-FU as 1L treatment in patients with previously untreated advanced gastric cancer [Ryu, M. H. and Kang, Y. K. 2009]. No difference was seen in median PFS and the results of this study suggest that capecitabine is at least as effective as 5-FU in the treatment of patients with advanced gastric cancers.

The REAL-2 study was a randomized, multicenter, Phase 3 study comparing capecitabine with 5-FU and oxaliplatin with cisplatin in 1002 patients with advanced esophagogastric cancer [Cunningham, D., et al 2008]. Results from this study suggest that capecitabine and oxaliplatin are as effective as 5-FU and cisplatin, respectively, in patients with previously untreated esophagogastric cancer.

A meta-analysis of the REAL-2 and ML17032 studies suggested that OS was superior in the 654 patients treated with capecitabine-based combinations compared with the 664 patients treated with fluorouracil-based combinations, although no statistically significant difference in PFS between the treatment groups was seen [Okines, A. F., et al 2009].

Most commonly used doublet regimens are cisplatin and capecitabine (treatment regimen known as XP), cisplatin and 5-FU (treatment regimen known as FP), CAPOX, and 5-FU/oxaliplatin (known as FOLFOX). CAPOX has been studied extensively in advanced gastric cancer and is routinely used in clinical practice globally. Choices among these regimens are typically based on patients' general medical condition and comorbidities in consideration of the different toxicity profiles of the regimens. This practice pattern is supported by global consensus guidelines for treatment of advanced gastric cancer, which recommend use of any of the doublet regimens discussed above [National Comprehensive Cancer Network 2016a] [Cunningham, D. 2008a]. However, given the aggressive nature of gastric cancer, fluoropyrimidine plus platinum-based chemotherapy has historically demonstrated median OS <1 year.

Though cytotoxic chemotherapy alone is the mainstay of treatment, newer molecularly targeted immunotherapy agents have been added to standard chemotherapy regimens to improve clinical outcomes in advanced, metastatic gastric and GEJ adenocarcinoma. Immunotherapy is the only class of agents to begin to change the 1L treatment landscape of

gastric cancer with the recent approval of nivolumab in combination with fluoropyrimidine- and platinum-containing chemotherapy based on the CheckMate-649 study, which has positioned this as a new standard of care [Janjigian, Y. Y., et al 2021].

The anti-PD-1 monoclonal antibody pembrolizumab has also demonstrated durable immune-mediated antitumor activity in patients with advanced gastric cancer. Clinical proof of concept demonstrating activity of pembrolizumab in participants with advanced gastric cancer came from Cohort D of the Phase 1b KEYNOTE-012 study. This cohort enrolled 39 participants with PD-L1 positive advanced gastric or GEJ adenocarcinoma [Muro, K., et al 2016]. Eight of 39 participants had an OR by RECIST 1.1 using BICR for an ORR of 22% (95% CI: 10, 39).

The antitumor activity of pembrolizumab in locally advanced, unresectable and/or metastatic gastric or GEJ adenocarcinoma was further characterized in the Phase 2 KEYNOTE-059 study, which involved 3 separate cohorts of participants.

Cohort 1 tested pembrolizumab monotherapy as third-line and above treatment of advanced gastric/GEJ adenocarcinoma, regardless of PD-L1 expression. In this all-comer population of highly pretreated participants for whom there were no alternative effective agents, pembrolizumab monotherapy demonstrated durable OR with a clinically meaningful ORR of 12%. A higher response rate (16%) was observed in the PD-L1 positive population [Wainberg, Z. A., et al 2017].

Cohorts 2 and 3 evaluated pembrolizumab in the 1L treatment setting among participants with advanced, unresectable and/or metastatic gastric and GEJ adenocarcinoma. In both cohorts, ORR was assessed according to RECIST 1.1 by BICR.

Cohort 2 (n=25) enrolled participants regardless of PD-L1 expression; these participants received the combination of pembrolizumab and SOC cytotoxic chemotherapy consisting of cisplatin plus a fluoropyrimidine. This combination yielded an ORR of 60% (95% CI: 39, 79) and a DCR of 80% (95% CI: 59, 93). Responses were observed regardless of PD-L1 status. Median OS in Cohort 2 was 13.8 months (95% CI: 8.6, NR) [Wainberg, Z. A., et al 2017]. By historical comparison, this OS result compares favorably with that seen in the ML17032 study, which administered FP or XP alone to patients with advanced gastric cancer. Median OS for patients on the ML17032 study who received FP or XP alone was 9.3 months and 10.5 months, respectively [Ryu, M. H. and Kang, Y. K. 2009].

Cohort 3 (n=31) enrolled participants with PD-L1 positive (CPS ≥1) gastric/GEJ adenocarcinoma; these participants received pembrolizumab monotherapy which yielded an ORR of 26% (95% CI: 12, 45) and a median OS of 20.7 months (9.2, 20.7) [Wainberg, Z. A., et al 2017].

KEYNOTE-061 was a global Phase 3 study of single-agent pembrolizumab versus single-agent paclitaxel in the 2L treatment setting of advanced gastric and GEJ adenocarcinoma that progressed after 1L therapy with both a platinum and fluoropyrimidine agent. The study initially enrolled participants regardless of PD-L1 status. In the most recent analysis of this study [Fuchs, C. S., et al 2018], 67% of enrolled participants had

PD-L1 CPS ≥1. The ORR associated with single-agent pembrolizumab was 15.8% (95% CI: 11.0, 21.7); this compared favorably with the ORR associated with paclitaxel of 13.6% (95% CI: 9.1, 19.1). Median DOR for pembrolizumab and paclitaxel was 18.0 months (1.4, 26.0) and 5.2 months (1.3, 16.8), respectively. Median OS, the primary endpoint, was 9.1 months with pembrolizumab versus 8.3 months with paclitaxel (HR 0.82, 1 sided p=0.042). In participants with previously treated advanced and/or metastatic gastric and GEJ adenocarcinoma and PD-L1 CPS ≥1, pembrolizumab reduced numerically, but not statistically, the risk of death by 18% versus paclitaxel. The results from KEYNOTE-061, taken together with those from KEYNOTE-059, clearly indicate pembrolizumab is active in gastric cancer.

Overall, immunotherapy has proven efficacy in gastric cancer, and a larger benefit for immunotherapy is seen in PD-L1+ gastric cancer. Nivolumab added to chemotherapy received full approval for 1L gastric cancer regardless of PD-L1 status in the US but only for PD-L1+ (CPS ≥5) gastric cancer in Europe, based on the larger improvement in PFS and OS seen in PD-L1+ (CPS ≥5) gastric cancer in CheckMate-649 [Janjigian, Y. Y., et al 2021]. Importantly, these regimens offer short PFS and modest improvement in OS, even in PD-L1+ (CPS ≥1) gastric cancer (nivolumab with chemotherapy), median PFS 7.5 vs 6.9 months, HR 0.74 (95% CI: 0.65-0.85) and median OS 14.0 vs 11.3 months, HR 0.77 (95% CI: 0.64-0.92); pembrolizumab with chemotherapy in KEYNOTE-062, median PFS 6.9 vs 6.4 months, HR 0.84 (95% CI: 0.70-1.02) and median OS 12.5 vs 11.1 months, HR 0.85 (95% CI: 0.70-1.03) [Shitara, K., et al 2020]. Notwithstanding the lack of a statistically significant improvement in KEYNOTE-062, the more adequately powered ongoing KEYNOTE-859 study is evaluating the addition of pembrolizumab to SOC chemotherapy, similar to CheckMate-649 [Tabernero, J., et al 2021]. Altogether, this body of evidence reflects the critical need for novel therapeutic approaches to enhance anti-PD-(L)1 efficacy in this patient population. Vibostolimab is an attractive agent to combine with pembrolizumab and chemotherapy based on its good tolerability profile and similar T-cell immune checkpoint inhibitor mechanism of action, which is expected to work best in tumors most responsive to pembrolizumab.

This multicenter study will determine antitumor activity and safety of MK-7684A in combination with standard treatment (capecitabine/oxaliplatin) as first-line therapy in participants with advanced, unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma. Only participants with PD-L1-positive tumors (CPS ≥1) will be eligible to test the hypothesis that vibostolimab works best in tumors most likely to respond to pembrolizumab. As per internal Sponsor data, approximately 70% of all first-line gastric cancer patients are predicted to have PD-L1 positive tumor expression.

2.2.3 Preclinical and Clinical Studies

Refer to the respective IBs for a summary of preclinical and clinical study data for vibostolimab, pembrolizumab, and lenvatinib.

2.2.4 Ongoing Clinical Studies

Refer to the respective IBs for a summary of ongoing clinical studies for vibostolimab, pembrolizumab, and lenvatinib.

2.2.5 Information on Other Study-related Therapy

For additional information on 5-FU, bevacizumab, capecitabine, carboplatin, cisplatin, docetaxel, gemcitabine, oxaliplatin, and paclitaxel, refer to the respective approved product labels.

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.

The existing data suggest that blockade of TIGIT with vibostolimab offers a new immunological mechanism, which has been shown to enhance the activity of pembrolizumab in preclinical and early clinical observations. The combination of both vibostolimab and pembrolizumab as coformulated MK-7684A may achieve increased therapeutic efficacy with minimal added toxicity over pembrolizumab monotherapy.

Clinical activity was observed at the 200-mg dose level of vibostolimab in participants with advanced solid tumors, particularly, in PD-1/PD-L1 inhibitor treatment-naïve participants with NSCLC and cervical cancer treated with vibostolimab in combination with pembrolizumab. In preliminary efficacy analyses based on PD-L1 status, treatment with vibostolimab in combination with pembrolizumab had promising ORR in PD-1/PD-L1 inhibitor treatment-naïve participants with PD-L1 positive (TPS ≥1%) NSCLC (30.8%) and PD-L1 positive (TPS ≥1% or MIDS ≥2, equivalent to CPS ≥1) cervical cancer (20.8%).

As of 15-APR-2021, available safety data show that vibostolimab has generally been tolerable. The incidence and types of AE observed after treatment with vibostolimab in combination with pembrolizumab were similar to those observed after treatment with pembrolizumab monotherapy in previous studies. For more details refer to the pembrolizumab IB. The safety profile of participants treated with MK-7684A was consistent with the known safety profile of participants treated with 200 mg vibostolimab in combination with 200 mg pembrolizumab administered sequentially. CCI [redacted]. In addition, the incidence and types of AE observed after treatment with vibostolimab in combination with pembrolizumab and chemotherapy were generally consistent with those expected after treatment with pembrolizumab plus chemotherapy. Therefore, no special safety monitoring activities are required beyond the planned robust safety monitoring. This includes complete real-time review of individual safety reports and cumulative safety data, a standing internal data monitoring committee, periodic assessment of the totality of safety information in the development program for each investigational drug in this study, and communication of important safety issues in a timely manner to investigators and health authorities.

To better characterize the effect of MK-7684A versus pembrolizumab monotherapy, the cervical cohort of this study is designed as a randomized cohort in the CPS ≥1 biomarker subgroup. As pembrolizumab did not demonstrate a benefit in the PD-L1 negative population previously, participants whose tumors are PD-L1 negative (CPS <1) will be nonrandomly allocated only to the MK-7684A arm.

The purpose of the dMMR endometrial cohort is to study the efficacy of MK-7684A in participants with previously treated endometrial cancer. For participants with dMMR tumors, given the approval of pembrolizumab monotherapy, participants will be allocated to receive MK-7684A. For participants with pMMR tumors, MK-7684A will be given in combination with lenvatinib, consistent with the pembrolizumab plus lenvatinib approval in this indication. A safety lead-in of MK-7684A and lenvatinib will be performed for the initial participants enrolling in the pMMR cohort to confirm safety and RP2D of this treatment combination.

There is strong biologic rationale for the combination of vibostolimab and pembrolizumab in HNSCC, including the coexpression of PD-L1 and TIGIT on HNSCC tumors. The HNSCC cohort will evaluate the preliminary efficacy of MK-7684A in untreated advanced HNSCC in tumors expressing PDL1 CPS ≥1 to assess whether there is benefit to the combination compared to pembrolizumab monotherapy in the population which has shown benefit with pembrolizumab monotherapy on KEYNOTE-048.

Based on preclinical and clinical data showing enhancement of efficacy for vibostolimab and pembrolizumab given together compared with pembrolizumab alone in IO responsive tumors, MK-7684A may provide benefit to BTC patients in the clinical setting. In this study, a signal finding cohort of participants with advanced biliary cancer that have progressed on standard therapies will receive MK-7684A (Cohort D1). This study will also evaluate the combination of MK-7684A with chemotherapy in previously untreated participants (Cohort D2). A safety lead-in will be performed to confirm the tolerability and RP2D of chemotherapy to be used in this combination.

In participants with previously untreated esophageal cancer (adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the EGJ), MK-7684A will be tested in combination with chemotherapy based on the KEYNOTE-590 findings that pembrolizumab and chemotherapy provided superior OS, PFS, and ORR compared to chemotherapy in this patient population. A safety lead-in will be performed to confirm the tolerability and RP2D of chemotherapy to be used in this combination.

In locally recurrent inoperable or metastatic TNBC, KEYNOTE-355 demonstrated that pembrolizumab in combination with chemotherapy provided a statistically significant and clinically meaningful improvement in PFS compared with placebo and chemotherapy in participants with PD-L1 positive tumors (CPS ≥10). In the current study, MK-7684A will be tested in combination with paclitaxel in participants with previously untreated locally recurrent unresectable or metastatic TNBC as a signal finding cohort. A safety lead-in will be performed to confirm the tolerability and RP2D of paclitaxel to be used in this combination.

The combination of pembrolizumab and lenvatinib has demonstrated promising activity in unresectable HCC with confirmed ORR of 46%, median PFS of 8.6 months, median OS of 22 months, and no new safety signals [Finn, R. S., et al 2020a]. To test whether the addition of a TIGIT blocking antibody can improve upon the response rate observed for pembrolizumab and lenvatinib alone, a signal finding cohort of participants with previously untreated unresectable HCC will receive MK-7684A and lenvatinib at the approved lenvatinib dose and schedule for HCC. A safety lead-in will be performed to confirm the tolerability and RP2D of lenvatinib to be used in this combination.

Pembrolizumab has been approved for 1L treatment of patients with locally advanced or metastatic bladder cancer who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. It is also approved for the treatment of patients with locally advanced or metastatic UC who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment. There is an unmet medical need for safe and efficacious 1L therapy in patients with locally advanced or metastatic UC who are ineligible for any platinum-containing chemotherapy. As such, there is a continual need for novel therapies in this setting. In this study, participants with previously untreated locally advanced or metastatic UC who are ineligible for any platinum-containing chemotherapy receive MK-7684A as a signal finding cohort.

In participants with previously untreated BRCA1/2 nonmutated and HRD-negative advanced EOC who require interval debulking surgery, MK-7684A will be tested in combination with chemotherapy. Given the poor survival in this patient population [Kraus, F., et al 2021] [Sims, T. T., et al 2021], there is an unmet medical need for an effective and tolerable 1L treatment regimen. A safety lead-in will be performed to confirm the tolerability and RP2D of bevacizumab to be used in this combination.

In this study, MK-7684A will be tested in combination with chemotherapy as 1L therapy in participants with advanced, unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma that is PD-L1-positive (CPS ≥1). The safety and promising efficacy data described in Section 2.2.2.10 from multiple studies of pembrolizumab and chemotherapy in the target population, indicate a strong risk:benefit ratio. A safety lead-in will be performed to confirm the tolerability and RP2D of capecitabine/oxaliplatin to be used in this combination.

Overall, inhibiting TIGIT in combination with PD-1 blockade, with or without other anticancer therapies, is a promising therapeutic strategy for advanced solid tumors with limited treatment options, and the benefit/risk assessment for participants in this study is favorable.

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

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

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

As of Amendment 11, OS data will no longer be collected.

In male and female participants with selected solid tumors:

Primary Objective	**Primary Endpoint**
- Objective: To compare MK-7684A to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1. - Hypothesis (H1): MK-7684A is superior to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- Objective response: A confirmed CR or PR.
- Objective: To compare MK-7684A to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1. - Hypothesis (H2): MK-7684A is superior to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- PFS: The time from randomization to first documented disease progression or death due to any cause, whichever occurs first.

- Objective: To evaluate MK-7684A alone or in combination with other anticancer therapies with respect to ORR per RECIST 1.1 as assessed by the investigator in participants with selected solid tumors, excluding 1) those with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1, 2) those enrolled in Cohort I.	- Objective response: A confirmed CR or PR.
- Objective: To evaluate MK-7684A in combination with other anticancer therapies with respect to PFS per RECIST 1.1 at 9 months (PFS-9) and 12 months (PFS-12) as assessed by the investigator in participants with previously untreated BRCA1/2 nonmutated and HRD-negative advanced epithelial ovarian cancer enrolled in Cohort I.	- PFS: The time from first dose of study intervention to first documented disease progression or death due to any cause, whichever occurs first.
Secondary Objectives	**Secondary Endpoints**
- Objective: To evaluate MK-7684A alone or in combination with other anticancer therapies with respect to OS in participants with selected solid tumors.	- OS: The time from randomization/treatment allocation to death due to any cause.
- Objective: To evaluate MK-7684A alone or in combination with other anticancer therapies with respect to PFS per RECIST 1.1 as assessed by the investigator in participants with selected solid tumors, excluding those with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- PFS: The time from first dose of study intervention to first documented disease progression or death due to any cause, whichever occurs first.
- Objective: To evaluate MK-7684A alone with respect to DOR per RECIST 1.1 as assessed by BICR in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- DOR: For participants with a confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

- Objective: To evaluate MK-7684A alone or in combination with other anticancer therapies with respect to DOR per RECIST 1.1 as assessed by the investigator in participants with selected solid tumors, excluding those with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- DOR: For participants with a confirmed CR or PR, DOR is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.
- Objective: To compare MK-7684A to pembrolizumab alone with respect to ORR per RECIST 1.1 as assessed by investigator in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- Objective response: A confirmed CR or PR.
- Objective: To compare MK-7684A to pembrolizumab alone with respect to PFS per RECIST 1.1 as assessed by investigator in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1	- PFS: The time from randomization to first documented disease progression or death due to any cause, whichever occurs first.
- Objective: To evaluate change from baseline in HRQoL using the EORTC QLQ-C30 in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- Mean change from baseline in the following scales/items: - Global health status/QoL score (EORTC QLQ-C30 items 29 and 30) - Physical functioning score (EORTC QLQ-C30 items 1-5)
- To evaluate the safety and tolerability of MK-7684A alone or in combination with other anticancer therapies.	- AEs - Discontinuations of study intervention due to AEs.

Tertiary/Exploratory Objectives	Tertiary/Exploratory Endpoints
- To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-7684A and other treatments.	- Molecular (genomic, metabolic and/or proteomic) determinants of response or resistance to treatments, using blood and/or tumor tissue.
- Objective: To evaluate MK-7684A alone or in combination with other anticancer therapies with respect to efficacy per iRECIST 1.1 as assessed by the investigator in participants with selected solid tumors.	- Objective response: A confirmed iCR and iPR - PFS: The time from randomization or first document disease progression or death due to any cause, whichever occurs first.
- To evaluate changes in HRQoL assessments using the EORTC QLQ-C30, EORTC QLQ-CX24, and European Quality-of-Life (EuroQoL) EQ-5D-5L instruments.	- HRQoL will be assessed using the EORTC QLQ-C30 (scores other than global and physical functioning scores), EORTC QLQ CX24, and EuroQoL EQ-5D-5L.
- Objective: To evaluate health utilities using the European Quality-of-Life Five-dimension 5-level Scale Questionnaire (EQ-5D-5L) in participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) enrolled in Cohort A1.	- Health utilities using the EQ-5D-5L.
- Objective: To evaluate the rate of locally determined pathological complete response (pCR) of MK-7684A in combination with carboplatin/paclitaxel ±bevacizumab in participants with previously untreated BRCA1/2 nonmutated and HRD-negative advanced epithelial ovarian cancer enrolled in Cohort I.	- pCR, all surgical specimens collected during the interval debulking surgery are microscopically negative for malignancy.
- Objective: To evaluate the objective response rate (ORR) as assessed by investigator according to RECIST 1.1, in participants with measurable disease per RECIST 1.1 with previously untreated BRCA1/2 nonmutated and HRD-negative advanced epithelial ovarian cancer enrolled in Cohort I.	- Objective response, complete response (CR) or partial response (PR).

4 STUDY DESIGN

At implementation of Amendment 12 or upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments. Amendment 12 is adding to the updates implemented in Amendment 11.

- All cohorts are closed to enrollment. This study has enrolled 613 participants.
- Participants receiving MK-7684A will be transitioned to pembrolizumab monotherapy or in combination with another protocol-specified therapy.
- Pembrolizumab 200 mg will be administered IV q3w for all cohorts.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab alone or in combination with another protocol-defined therapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab alone or in combination with another protocol-defined therapy, but unable to access it as SOC outside the study, may continue on study and receive treatment until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- All assessments in the SoA will be done per local standard of care.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit. If currently receiving protocol-specified therapy that does not include pembrolizumab, the participants will be discontinued from the study.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 12, should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.
  - The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.
  - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention allocation up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

Existing protocol content is retained for historical reference.

NOTE: As of Amendment 11, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, assessments of tumor response by imaging should continue as per local institutional guidelines.

In addition:

- Vital status (ie, OS) data will no longer be collected.
- PRO assessments (EORTC QLQ-C30, EORTC QLQ-CX24, EQ-5D-5L) will no longer be performed.
- Blood for ctDNA analysis and PBMC analysis will no longer be collected.
- Blood for PK and ADA will no longer be collected.
- Participants still on treatment with MK-7684A or pembrolizumab who are benefiting may continue treatment.
- Participants who are only receiving treatment with chemotherapy will continue treatment as part of the standard of care off-study.
- Second Course will no longer be offered. However, any participant receiving Second Course treatment prior to implementation of Amendment 11 will be able to complete treatment as planned.
- Treatment beyond progression, unless previously approved, will no longer be available.

4.1 Overall Design

This is a Phase 2, parallel group, multisite, open-label, basket study of MK-7684A alone or in combination with other anticancer therapies in participants with selected solid tumors. Specific details regarding the eligibility criteria for the selected tumors can be found in Section 5.

Eligible participants will be randomly assigned in Cohort A1 or nonrandomly allocated in Cohort A2 to Cohort J to one of the following study intervention arms depending on selected cancer type (Section 4.1.1 to Section 4.1.10):

- Arm 1: MK-7684A (Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, and Cohort H)
- Arm 2: Pembrolizumab (Cohort A1)
- Arm 3: MK-7684A + lenvatinib (Cohort B2)
- Arm 4: MK-7684A + lenvatinib (Cohort G)
- Arm 5: MK-7684A + 5-FU/cisplatin (Cohort E)
- Arm 6: MK-7684A + paclitaxel (Cohort F)

- Arm 7: MK-7684A + gemcitabine/cisplatin (Cohort D2)
- Arm 8: MK-7684A + carboplatin/ paclitaxel/ bevacizumab (Cohort I)
- Arm 9: MK-7684A + capecitabine/oxaliplatin (Cohort J)

A safety lead-in will be performed to determine the tolerability and RP2D of lenvatinib, gemcitabine/cisplatin, 5-FU/cisplatin, paclitaxel, bevacizumab, and capecitabine/oxaliplatin to be used in combination with MK-7684A. Additional dose levels are included in the safety lead-in only to complete dose-finding and identification of the RP2D. Enrollment may be expanded in the event intermediate dose levels are explored during the safety lead-in to identify the RP2D for lenvatinib, gemcitabine/cisplatin, 5-FU/cisplatin, paclitaxel, and capecitabine/oxaliplatin to be used in combination with MK-7684A. Continued allocation into these cohorts will only occur if the starting dose (ie, Dose Level 0) is determined to be the RP2D (Section 4.3.5).

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

Refer to Appendix 7 for country-specific requirements.

4.1.1 Cohort A – Cervical Cancer

In Cohort A, approximately 200 participants with locally recurrent unresectable or metastatic cervical cancer) will be enrolled and assigned to study intervention based on PD-L1 status.

- Cohort A1: Approximately 170 participants whose tumors express PD-L1 (CPS ≥1) will be randomly assigned in a 1:1 ratio to either MK-7684A (Arm 1) or pembrolizumab (Arm 2). Participants with PD-L1 positive tumors (CPS ≥1) will be stratified by prior bevacizumab use (yes vs no).
- Cohort A2: Approximately 30 participants whose tumors do not express PD-L1 (CPS <1) will be assigned to MK-7684A (Arm 1).

Treatment with MK-7684A or pembrolizumab will continue for a total of 35 administrations (approximately 2 years) or until any of the discontinuation criteria are met (Section 7.1).

4.1.2 Cohort B – Endometrial Cancer

In Cohort B, approximately 80 participants with advanced endometrial cancer will be allocated by nonrandom assignment to study treatment based on MMR status.

- Cohort B1: Participants whose tumors are dMMR (n=40) will be allocated to MK-7684A (Arm 1)
- Cohort B2: Participants whose tumors are pMMR (n=40) will be allocated to MK-7684A plus lenvatinib (Arm 3).

Note: A total of 40 participants will be allocated to receive MK-7684A plus the RP2D for lenvatinib (Table 1).

An mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% will be used to identify the preliminary RP2D of lenvatinib to use in combination with MK-7684A for the treatment of participants with pMMR endometrial cancer (Section 4.3.5). If de-escalation is called for by mTPI, the dose of lenvatinib will be reduced while the dose of MK-7684A will remain fixed. There are 3 predetermined dose levels of lenvatinib that may be explored in the mTPI design for Cohort B2 (Table 1). If the mTPI calls for an additional de-escalation, enrollment into Cohort B2 will be stopped.

Treatment with MK-7684A will continue for a total of 35 administrations (approximately 2 years) or until any of the discontinuation criteria are met (Section 7.1). Treatment with the RP2D of lenvatinib will continue for up to 45 cycles or until any of the discontinuation criteria are met (Section 7.1).

4.1.3 Cohort C – HNSCC

In Cohort C, approximately 40 participants with locally recurrent unresectable or metastatic HNSCC whose tumors express PD-L1 (CPS ≥1) will be allocated by nonrandom assignment to MK-7684A (Arm 1).

Treatment with MK-7684A will continue for a total of 35 administrations (approximately 2 years) or until any of the discontinuation criteria are met (Section 7.1).

4.1.4 Cohort D – Biliary Cancer

In Cohort D, approximately 50 participants with locally recurrent unresectable or metastatic biliary cancer will be allocated by nonrandom assignment to study interventions.

- Cohort D1: Approximately 40 participants with locally recurrent unresectable or metastatic biliary cancer will be allocated by nonrandom assignment to MK-7684A (Arm 1).
- Cohort D2: Approximately 10 participants with locally recurrent unresectable or metastatic biliary cancer will be allocated by nonrandom assignment to MK-7684A plus gemcitabine/cisplatin (Arm 7).

  Note: A total of 10 participants will be allocated to receive MK-7684A plus the RP2D for gemcitabine/cisplatin (Table 3). An mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% will be used to identify the preliminary RP2D of gemcitabine/cisplatin to use in combination with MK-7684A for the treatment of participants with biliary cancer (Section 4.3.5). If de-escalation is called for by mTPI, the dose of gemcitabine/cisplatin will be reduced while the dose of MK-7684A will remain fixed. There are 2 predetermined dose levels of gemcitabine/cisplatin that may be explored in the mTPI design for Cohort D2 (Table 3). If the mTPI calls for an additional de-escalation, enrollment into Cohort D2 will be closed.

Treatment with MK-7684A will continue for a total of 35 administrations (approximately 2 years) or until any of the discontinuation criteria are met (Section 7.1). Treatment with the RP2D of gemcitabine and cisplatin will continue to progression and a maximum of 8 cycles, respectively, or until any of the discontinuation criteria are met (Section 7.1) Treatment with cisplatin will continue for a maximum of 8 cycles.

4.1.5 Cohort E – Esophageal Cancer

In Cohort E, approximately 40 participants with locally advanced unresectable or metastatic adenocarcinoma or ESCC or advanced/metastatic Siewert type 1 adenocarcinoma of the GEJ will be allocated by nonrandom assignment to MK-7684A + 5-FU/cisplatin (Arm 5). Note: A total of 40 participants will be allocated to receive MK-7684A plus the RP2D for 5-FU/cisplatin (Table 3).

An mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% will be used to identify the preliminary RP2D of 5-FU/cisplatin to use in combination with MK-7684A for the treatment of participants with esophageal cancer (Section 4.3.5). If de-escalation is called for by mTPI, the dose of 5-FU/cisplatin will be reduced while the dose of MK-7684A will remain fixed. There are 2 predetermined dose levels of 5-FU/cisplatin that may be explored in the mTPI design for Cohort E (Table 3). If the mTPI calls for an additional de-escalation, enrollment into Cohort E will be closed.

Treatment with MK-7684A will continue for a total of 35 administrations (approximately 2 years) or until any of the discontinuation criteria are met (Section 7.1). Treatment with the RP2D of 5-FU and cisplatin will continue for a total of 35 administrations and 6 administrations, respectively, or until any of the discontinuation criteria are met (Section 7.1).

4.1.6 Cohort F – TNBC

In Cohort F, approximately 40 participants with locally recurrent unresectable or metastatic TNBC, will be allocated by nonrandom assignment to MK-7684A + paclitaxel (Arm 6). Note: A total of 40 participants will be allocated to receive MK-7684A plus the RP2D for paclitaxel (Table 3).

An mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% will be used to identify the preliminary RP2D of paclitaxel to use in combination with MK-7684A for the treatment of participants with TNBC (Section 4.3.5). If de-escalation is called for by mTPI, the dose of paclitaxel will be reduced while the dose of MK-7684A will remain fixed. There are 2 predetermined dose levels of paclitaxel that may be explored in the mTPI design (Table 3). If the mTPI calls for an additional de-escalation, enrollment into Cohort F will be closed.

Treatment with MK-7684A will continue for a total of 35 administrations (approximately 2 years) or until any of the discontinuation criteria are met (Section 7.1). Treatment with the RP2D of paclitaxel will continue until any of the discontinuation criteria are met (Section 7.1).

4.1.7 Cohort G – HCC

In Cohort G, approximately 40 participants with locally recurrent unresectable or metastatic HCC will be allocated by nonrandom assignment to MK-7684A + lenvatinib (Arm 4). Note: A total of 40 participants will be allocated to receive MK-7684A plus the RP2D for lenvatinib (Table 2).

An mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% will be used to identify the preliminary RP2D of lenvatinib to use in combination with MK-7684A for the treatment of participants with HCC (Section 4.3.5). If de-escalation is called for by mTPI, the dose of lenvatinib will be reduced while the dose of MK-7684A will remain fixed. There are 2 predetermined dose levels of lenvatinib that may be explored in the mTPI design (Table 2). If the mTPI calls for an additional de-escalation, enrollment into Cohort G will be closed.

Treatment with MK-7684A will continue for a total of 35 administrations (approximately 2 years) or until any of the discontinuation criteria are met (Section 7.1). Treatment with lenvatinib at the RP2D will continue for up to 45 cycles or until any of the discontinuation criteria are met (Section 7.1).

4.1.8 Cohort H – Bladder Cancer

In Cohort H, approximately 40 participants with locally advanced/unresectable or metastatic UC who are ineligible for any platinum-containing chemotherapy will be allocated by nonrandom assignment to MK-7684A (Arm 1).

Treatment with MK-7684A will continue for a total of 35 administrations (approximately 2 years) or until any of the discontinuation criteria are met (Section 7.1).

4.1.9 Cohort I – Ovarian Cancer

In Cohort I, following a Lead-in Period* during which all participants will receive a single cycle of carboplatin/paclitaxel (± bevacizumab), approximately 28 participants with previously untreated BRCA1/2 nonmutated and HRD-negative advanced EOC will be allocated by nonrandom assignment to treatment with carboplatin/paclitaxel* for 5 cycles plus MK-7684A for up to 35 infusions and bevacizumab for up to 15 infusions or as per local SOC (if bevacizumab is started during lead-in phase, treatment is given for up to 16 infusions) according to the approved product label (Arm 8).

*At the investigator's discretion and determined prior to the participant being assigned to study treatment, one of the following regimens should be administered:

- Carboplatin AUC5 or AUC6 Q3W plus paclitaxel 175 mg/m^2 Q3W
- Carboplatin AUC5 or AUC6 Q3W plus paclitaxel 80 mg/m^2 QW
- Carboplatin AUC2 or AUC2.7 QW plus paclitaxel 60 mg/m^2 QW

- Bevacizumab 15 mg/kg or lower, per SOC

  Docetaxel may be considered for participants who experience either a severe hypersensitivity reaction to paclitaxel or an AE requiring discontinuation of paclitaxel only after consultation with the Sponsor. The recommended dose, as determined by the SGCTG [Vasey, P. A., et al 2004], is as follows:

- Docetaxel 75 mg/m^2 Q3W plus carboplatin AUC5 Q3W

  Note: Bevacizumab may be started at any time prior to surgery or the second cycle following surgery (or the decision to not perform surgery per local approvals). Bevacizumab should be interrupted at least 4 weeks prior to the planned date of surgery. Bevacizumab should resume 4 weeks after surgery OR after the wound has healed, whichever is longer. Bevacizumab should be continued with chemotherapy and study treatment for up to 15 infusions or as per local SOC and according to the approved product label.

  Note: a total of approximately 28 participants will be allocated to receive MK-7684A plus carboplatin/paclitaxel and the RP2D for bevacizumab.

An mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% will be used to identify the preliminary RP2D of bevacizumab to use in combination with MK-7684A for the treatment of participants with OC (Section 4.3.5). If de-escalation is called for by mTPI, bevacizumab will be discontinued while the dose of MK-7684A will remain fixed. There is 1 predetermined dose level of bevacizumab that may be explored in the mTPI design (Table 3). If the mTPI calls for an additional de-escalation, enrollment into Cohort I will be closed.

Participants must be candidates for interval debulking surgery. Participants will receive at least 2 cycles of carboplatin/paclitaxel plus MK-7684A prior to surgery (neoadjuvant treatment) and the remaining cycles of carboplatin/paclitaxel plus MK-7684A and bevacizumab after surgery (adjuvant treatment). Participants should resume study treatment when clinically appropriate but no longer than 7 weeks following interval debulking surgery (Figure 3).

Participants with SD, PR, CR, or non-PD will enter the Maintenance Period. Participants with disease progression will be discontinued from the study (Section 7.1). The Maintenance Period (continued MK-7684A treatment plus bevacizumab maintenance) will start at Cycle 6. Participants who are not able to complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity, may be eligible to start the Maintenance Period as early as Cycle 2 following consultation with the Sponsor. Note: participants may be able to start the Maintenance Period and receive only MK-7684A following consultation with the Sponsor.

MK-7684A may continue for up to 35 infusions (approximately 2 years starting with the first infusion in Cycle 1) or until meeting criteria for discontinuation of study treatment (Section 7.1).

4.1.10 Cohort J – Gastric Cancer

In Cohort J, approximately 40 participants with previously untreated, HER2 negative, PD-L1 positive advanced gastric or GEJ adenocarcinoma will be allocated by nonrandom assignment to MK-7684A in combination with capecitabine/oxaliplatin (Arm 9).

A mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% will be used to identify the preliminary RP2D of capecitabine/oxaliplatin to use in combination with MK-7684A for the treatment of participants with gastric cancer (Section 4.3.5). If de-escalation is called for by mTPI, the dose of capecitabine/oxaliplatin will be reduced while the dose of MK-7684A will remain fixed. There are 2 predetermined dose levels of capecitabine/oxaliplatin that may be explored in the mTPI design for Cohort J (Table 3). If the mTPI calls for an additional de-escalation, enrollment into Cohort J will be stopped.

Treatment with MK-7684A will continue for a total of 35 administrations (approximately 2 years) or until any of the discontinuation criteria are met (Section 7.1).

4.1.11 Efficacy and Safety Evaluations

Participants will be evaluated with radiographic imaging to assess response to treatment at regular intervals. On study imaging will be assessed as outlined in Section 8.2.1.2.

AE monitoring will be ongoing throughout the study and graded in severity according to the guidelines outlined in the NCI CTCAE v5.0. AEs and SAEs will be reported by the investigator or delegate as outlined in Section 8.4.1. This study will use an siDMC to monitor safety (Appendix 1). The siDMC will review safety data from all participants on a frequent basis throughout the study as outlined in the siDMC charter. The siDMC may meet on an ad hoc basis to review additional safety data as needed.

Safety will be evaluated in all cohorts throughout the study. DLTs will be evaluated for all participants. If a greater than or equal to 40% DLT rate is observed in evaluable participants in any given cohort (excluding the safety lead-in for Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J), enrollment in that cohort will be paused to review all available data. In this case, the cohort may be discontinued if the totality of the data does not support a favorable risk-benefit ratio for the treatment under evaluation.

Participants who discontinue treatment for reasons other than confirmed PD will have posttreatment follow-up for disease status (including imaging) until PD, initiation of a new anticancer therapy, withdrawal of consent, becoming lost to follow-up, pregnancy, or death. After confirmed progressive disease, each participant will be contacted by telephone approximately every 12 weeks (84 days ± 7 days) for survival until withdrawal of consent, becoming lost to follow-up, death, or end of the study, whichever occurs first.

The risks of solid organ transplant after treatment with PD-1 and/or TIGIT inhibitor therapy have not been extensively studied. The timeframe for safe or appropriate solid organ transplantation after the last dose of pembrolizumab or MK-7684A is unknown. Therefore, it is recommended not to perform solid organ transplantation within at least 120 days

(5 half-lives) of stopping either pembrolizumab or MK-7684A. The risks and benefits of transplant should be discussed with the participant by the treating investigator.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary objective of this study is to evaluate the antitumor effect of MK-7684A alone or in combination with other anticancer therapies in participants with any one of a "basket" of advanced malignancies. This study will use ORR (cohorts A1-H and J) and PFS (Cohorts A1 and I) based on RECIST 1.1 criteria as assessed by BICR (Cohort A1) or by investigator (Cohort I) as primary endpoints. The study will also use OS, PFS (all cohorts except for Cohort A1), and DOR as secondary endpoints.

ORR and PFS are acceptable measures 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 ORR and PFS is typically considered acceptable by regulatory authorities. Images will be submitted to an iCRO and read by an independent central review blinded to treatment assignment to minimize bias in the response assessments. For Cohort A1 only, 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.

OS has been recognized as the gold standard for the demonstration of superiority of a new antineoplastic therapy in randomized clinical studies. As of Amendment 11, OS data will no longer be collected.

DOR is considered an acceptable measure of clinical benefit when considered with ORR.

4.2.1.1.1 RECIST 1.1

RECIST 1.1 will be used by the BICR and the investigator when assessing images for efficacy measures. Although original RECIST 1.1 publication recommends a maximum of 5 target lesions in total and 2 per organ, this protocol has implemented an adjustment to RECIST 1.1 to allow a maximum of 10 target lesions in total and 5 per organ, if a larger number of target lesions is needed to adequately represent the tumor burden. Refer to Section 8.2.1.5 for additional detail.

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. AEs will be assessed as defined by CTCAE, Version 5.0.

4.2.1.3 Pharmacokinetic Endpoints

Pharmacokinetic endpoints will not be evaluated in this study.

4.2.1.4 Pharmacodynamic Endpoints

Pharmacodynamic endpoints will not be evaluated in this study.

4.2.1.5 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 study, HRQoL and disease-related symptoms will be investigated among participants enrolled in Cohort A via the following assessment tools: EORTC QLQ-C30, and EORTC QLQ-CX24 questionnaires. Health utilities will be evaluated using the EQ-5D-5L PRO instrument.

These measures are not pure efficacy or safety endpoints because they are affected by both disease progression and treatment tolerability.

4.2.1.5.1 EORTC QLQ-C30

EORTC QLQ-C30 is a psychometrically and clinically validated instrument appropriate for assessing HRQoL in oncology studies [Aaronson, N. K., et al 1993]. The EORTC QLQ-C30 is the most widely used cancer-specific HRQoL instrument, which contains 30 items and measures 5 functional dimensions (physical, role, emotional, cognitive, and social), 3 symptom items (fatigue, nausea/vomiting, and pain), 6 single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact), and a global health and QoL scale [Aaronson, N. K., et al 1993]. For the global health status or QoL and function scales, a higher value indicates a better level of function; for symptom scales and items, a higher value indicates increased severity of symptoms. TTD and mean change from baseline in global health status or QoL scale of the EORTC QLQ-C30, will be evaluated as secondary objectives.

4.2.1.5.2 EQ-5D-5L

The EQ-5D-5L is a standardized instrument for use as a measure of health outcome and will provide data to develop health utilities for use in health economic analyses [Rabin, R. and de Charro, F. 2001]. The 5 health state dimensions in the EQ-5D-5L include the following: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each dimension is rated on a 5-point scale from 1 (no problem) to 5 (unable to/extreme problems). The EQ-5D-5L also includes a graded (0 to 100) vertical visual analog scale on which the participant rates their general state of health at the time of the assessment. 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].

4.2.1.5.3 EORTC QLQ-CX24

The EORTC QLQ-CX24 is a disease-specific questionnaire developed and validated to address measurements specific to cervical cancer. It is one of multiple disease-specific modules developed by the EORTC QLG (Quality-of-Life Group) designed for use in clinical studies, to be administered in addition to the EORTC QLQ-C30 to assess disease-specific treatment measurements. The 24-items are classified into 3 multiitem scales, 11 items with symptom experience domain, 3 items with body image domain, and 4 items with sexual/ vaginal functioning domain. The other domains of the questionnaire are single item scales, including lymphedema, peripheral neuropathy, menopausal symptom, sexual worry, sexual activity, and sexual enjoyment.

4.2.1.6 Planned Exploratory Biomarker Research

The mechanism of action of many antitumor agents is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer treatments administered, as well as determinants of AEs in the course of our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapy with antineoplastic drugs. 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 may include, but are not limited to:

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

This research may evaluate whether genetic variation within a clinical study population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome to interpret tumor-specific DNA mutations. Finally, MSI may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

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). Key molecular changes of interest to oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes called a ‘hyper-mutated’ state) may generate neoantigen presentation in the tumor microenvironment. 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. Note that to understand tumor-specific mutations, it is necessary to compare the tumor genome with the germline genome. Microsatellite instability may also be evaluated as this is an

important biomarker for some cancers (ie, colorectal cancer). Circulating tumor DNA and/or RNA may also be evaluated from blood samples.

Tumor and/or blood RNA analyses

Both genome-wide and targeted mRNA expression profiling and sequencing in tumor tissue and/or in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/immune phenotype. Specific immune-related gene sets (ie, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued as well as exosomal profiling.

Proteomics and IHC using blood and/or tumor

Tumor and/or blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an IVD device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. 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 for pembrolizumab (MK-3475) therapy.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as 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.

Other molecular changes of interest include the subtype of T-cells in the tumor microenvironment. The T-cell repertoire from tumor tissue and blood components may be evaluated.

Changes in tumor structure seen by medical imaging scans

Medical imaging scans collected during the study for measurement of efficacy endpoints may be used for additional analyses, including changes in shape, internal architecture, or size change dynamics. Measurements of growth kinetic parameters and of changes in non-size-based features have been shown to correlate with response to treatment and with clinical outcomes in a variety of tumor types. Analysis of these correlations may support the development of new approaches for response assessment, to be used in future trials.

4.2.2 Rationale for the Use of Comparator/Placebo

Pembrolizumab is approved in several countries for the treatment of participants with PD-L1 positive (CPS ≥1) cervical cancer and is used as a comparator in Cohort A1. For more information on the data for pembrolizumab in cervical cancer, please refer to Section 2.2.2.1.

For all other cohorts, this basket study is intended to evaluate the preliminary efficacy of MK-7684A alone or in combination with other anticancer therapies; no comparator or placebo will be used.

4.3 Justification for Dose

4.3.1 MK-7684A

Based on the totality of available data, including preliminary clinical PK, pharmacodynamics, safety, and efficacy from the dose escalation and confirmation portion of Study MK-7684-001, the selected dose of vibostolimab is 200 mg, to be administered as MK-7684A (a coformulation with 200 mg pembrolizumab) as a 30-minute IV infusion Q3W.

PK data from Study MK-7684-001 in 323 participants across tumor types indicate that observed PK parameters were generally similar across tumor types. Observed PK profiles of vibostolimab suggest that target-mediated clearance of vibostolimab is saturated at the 200 mg, 210 mg, and 700 mg doses. The PK of vibostolimab is generally consistent with that of other humanized mAbs, which typically have low CL and a limited Vc [Dirks, N. L. and Meibohm, B 2010] [Dostalek,M., et al 2012] [Keizer,R.J., et al 2010]. As with other mAbs, body weight was found to be related to vibostolimab CL and Vc parameters, but the relationship was weak for both parameters. As such, this supports that fixed dosing would provide better control of PK variability than body weight-based dosing [Bai,S., et al 2012] [Hendrikx, J. J. M. A., et al 2017].

Available clinical safety data indicated that vibostolimab is tolerable at doses up to and including 700 mg, both when used as monotherapy and in combination with pembrolizumab. No DLTs were observed at any of the vibostolimab doses tested either as monotherapy or in combination with pembrolizumab during the dose escalation and confirmation portion of Study MK-7684-001, and the MTD was not reached.

Clinical activity was observed at the 200/210-mg and the 700-mg dose levels of vibostolimab both during the dose escalation and confirmation portion of Study MK-7684-001 in participants with advanced solid tumors of all types and during the dose-expansion portion, particularly in PD-1/PD-L1 inhibitor treatment-naïve participants with NSCLC, ovarian cancer, breast cancer, and cervical cancer treated with vibostolimab in combination with pembrolizumab.

The 200 mg and 700 mg doses were compared in a randomized dose-finding cohort of participants with anti-PD-1/PD-L1 treatment-naïve cervical cancer in MK-7684-001 Part B.

CCI [redacted]

CCI [redacted] Therefore, tumor size reduction showed no significant difference between the 2 dose groups.

Overall, the totality of data, including lack of a clinically meaningful effect of body weight on PK, consistency of PK across indications and a flat dose-exposure-tumor size response relationship support that a fixed dose of 200 mg Q3W is an optimal dose for vibostolimab in combination with 200 mg pembrolizumab.

For additional information, refer to the vibostolimab IB.

4.3.1.1 Biocomparability of Vibostolimab and Pembrolizumab as Sequential Infusions Versus Coformulated Product MK-7684A in Solid Tumors

Preliminary PK data from participants enrolled in Part A and Part B that received 200 mg vibostolimab in combination with pembrolizumab as sequential infusions, and in Part B participants in the ovarian cancer cohort received coformulated product MK-7684A are available. The observed PK parameters including AUC exposure, $C_{max,}$ and C_{trough} for the first dosing cycle for both treatment groups are generally consistent. The range of observed C_{max} and C_{trough} for both vibostolimab and pembrolizumab largely overlap when administered as sequential infusions or as a coformulated product. The overall preliminary data suggest that the PK remain generally similar for the coformulated product MK-7684A and the sequential infusions of vibostolimab and pembrolizumab, for both compounds.

For details and most updated data, please refer to the vibostolimab IB.

4.3.2 Pembrolizumab

The planned dose of pembrolizumab for this study is 200 mg Q3W. Based on the totality of data generated in the pembrolizumab development program, 200 mg Q3W is an appropriate dose of pembrolizumab for adults across all indications. This dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to the pembrolizumab IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from PBPK analysis) at 200 mg Q3W.

For additional information, refer to the pembrolizumab IB.

4.3.3 Lenvatinib

There are 2 different dosing regimens for lenvatinib that will be used in this study based on the indication studied.

4.3.3.1 Cohort B2 – Endometrial Cancer

The dosing regimen of lenvatinib for Cohort B2 was selected based on the results of the Phase 1b portion of Phase 1b/2 Study 111/KEYNOTE-146, the primary endpoint of which was to determine the MTD and RP2D for lenvatinib in combination with pembrolizumab 200 mg Q3W. Thirteen participants (lenvatinib 24 mg/day + pembrolizumab 200 mg IV Q3W: n=3; lenvatinib 20 mg/day + pembrolizumab 200 mg: n=10) were enrolled in the Phase 1b portion of the study. Eight of the participants had RCC, 2 had NSCLC, 2 had endometrial carcinoma, and 1 had melanoma. There were 2 DLTs at the dose of lenvatinib 24 mg/day + pembrolizumab 200 mg IV Q3W (1 participant had Grade 3 arthralgia, and another had Grade 3 fatigue); hence, this was defined as the toxic dose. No DLTs were reported in the next 10 participants (expansion part), all of whom received the lenvatinib 20 mg/day + pembrolizumab 200 mg Q3W dose.

Based on review of all of the clinical data from these 13 participants, the MTD and RP2D were determined to be 20 mg lenvatinib daily in combination with a fixed dose of 200 mg pembrolizumab given Q3W. Based on the promising antitumor efficacy and tolerable safety profile seen in both the endometrial carcinoma and RCC expansion cohorts from Study 111/KEYNOTE-146 [Makker, V., et al 2018], multiple Phase 3 studies have been initiated evaluating the efficacy of this combination. Based on the clinical tolerability of vibostolimab given alone and in combination with pembrolizumab, significant added toxicity is not anticipated for the combination of MK-7684A and lenvatinib. Nonetheless, a safety lead-in will be performed to limit exposure of participants in the event of unexpected toxicity, characterize safety and tolerability, and confirm RP2D of the combination.

There are 3 predetermined dose levels of lenvatinib that may be explored in the mTPI design for Cohort B2 (Table 1). If the mTPI calls for an additional de-escalation, enrollment into Cohort B2 will be put on hold while the Sponsor evaluates the observed DLTs.

Table 1 Predetermined Dose Levels of Lenvatinib for Determining the Recommended Phase 2 Dose in pMMR Endometrial Cancer

Study Intervention	Dose Level 0	Dose Level –1	Dose Level –2	Dose Level –3
Lenvatinib (Cohort B2)	20 mg qd	14 mg qd	10 mg qd	Enrollment stopped
pMMR=mismatch repair proficient; qd=once daily.				

4.3.3.2 Cohort G – HCC

The starting dose of lenvatinib for Cohort G will be 12 mg (BW ≥60 kg) or 8 mg (BW <60 kg) orally qd. Based on dose modification results in an earlier Phase 1/2 study of lenvatinib in participants with HCC (E7080-J081-202) and population PK analyses showing higher lenvatinib AUC and lower BW resulting in earlier drug withdrawal or dose reduction, 2 different starting doses were planned in a Phase 3 study of lenvatinib monotherapy in participants with unresectable HCC (E7080-G000-304): 12 mg for participants with BW ≥60 kg and 8 mg for participants weighing <60 kg. The final PK model including data from E7080-G000-304 confirmed that lenvatinib was affected by BW. The decrease in CL/F in participants with low BW resulted in an increase in lenvatinib AUC. The median value and range of individual AUCs at steady state for participants in E7080-G000-304 were comparable between the 8 mg starting dose group for BW <60 kg and the 12 mg dose group for BW ≥60 kg. Furthermore, a similar median OS was observed in both BW subgroups (BW ≥60 kg and <60 kg: 13.7 months and 13.4 months, respectively), and the HR favored lenvatinib in both subgroups (HR: 0.95 and 0.85, respectively). Lastly, the duration-adjusted rate of treatment-emergent AEs was similar for participants treated with either starting dose [Kudo, M., et al 2018]. These findings support the appropriateness of the lower starting dose of 8 mg for participants with BW <60 kg. Lenvatinib has subsequently received approval in most major world markets for this dosing as 1L therapy for advanced HCC. Based on the clinical tolerability of vibostolimab given alone and in combination with pembrolizumab, significant added toxicity is not anticipated for the combination of MK-7684A and lenvatinib. Nonetheless, a safety lead-in will be performed to limit exposure of participants in the event of unexpected toxicity, characterize safety and tolerability, and confirm RP2D of the combination.

There are 2 predetermined dose levels of lenvatinib that may be explored in the mTPI design for Cohort G (Table 2). If the mTPI calls for an additional de-escalation, enrollment into Cohort G will be put on hold while the Sponsor evaluates the observed DLTs.

Table 2 Predetermined Dose Levels of Lenvatinib for Determining the Recommended Phase 2 Dose in HCC

Study Intervention	Dose Level 0	Dose Level –1	Dose Level –2
Lenvatinib (Cohort G)	12 mg qd (BW ≥60 kg) 8 mg qd (BW <60 kg)	8 mg qd (BW ≥60 kg) 4 mg qd (BW <60 kg)	Enrollment stopped
BW=body weight; HCC=hepatocellular carcinoma; qd=once daily.			

4.3.4 Chemotherapy

The planned dosing regimens of gemcitabine/cisplatin (Section 8.1.8.1.3), cisplatin/5-FU (Section 8.1.8.1.4/Section 8.1.8.1.5), paclitaxel (Section 8.1.8.1.6), carboplatin/paclitaxel (Section 8.1.8.1.7), and capecitabine/oxaliplatin (Section 8.1.8.1.8) that will be used in this study have been efficacious and well tolerated when used in combination with pembrolizumab in clinical studies (Section 2.2.2.4, Section 2.2.2.5, Section 2.2.2.6, Section 2.2.2.9, and Section 2.2.2.10).

The RP2D to be used in combination with MK-7684A will be determined using a mTPI design (Table 3). There are 2 predetermined dose levels of chemotherapy that may be explored in the mTPI design for Cohort D2 (gemcitabine/cisplatin), Cohort E (5-FU/cisplatin) and Cohort F (paclitaxel), Cohort J (capecitabine/oxaliplatin), and 1 predetermined dose level of bevacizumab (Cohort I). If the mTPI calls for an additional de-escalation, enrollment will be put on hold while the Sponsor evaluates the observed DLTs.

Table 3 Predetermined Dose Levels of Gemcitabine/Cisplatin, 5-FU/Cisplatin, Paclitaxel, Bevacizumab, and Capecitabine/Oxaliplatin for Determining the Recommended Phase 2 Dose of Chemotherapy

Study Cohort	Study Intervention	Dose Level 0	Dose Level –1	Dose Level –2
Cohort D2	Gemcitabine[a]	1000 mg/m^2 Q3W	800 mg/m^2 Q3W	Enrollment stopped
Cohort D2	Cisplatin[a]	25 mg/m^2 Q3W	20 mg/m^2 Q3W	Enrollment stopped
Cohort E	5-FU[b]	4000 mg/m^2/cycle	3000 mg/m^2/cycle	Enrollment stopped
Cohort E	Cisplatin	80 mg/m^2 Q3W	60 mg/m^2 Q3W	Enrollment stopped
Cohort F	Paclitaxel[c]	90 mg/m^2 QW	80 mg/m^2 QW	Enrollment stopped
Cohort I	Bevacizumab	15 mg/kg Q3W	Discontinued	Not applicable
Cohort J	Capecitabine[d]	1000 mg/m^2 twice daily	750 mg/m^2 twice daily	Enrollment stopped
Cohort J	Oxaliplatin	130 mg/m^2 Q3W	100 mg/m^2 Q3W	Enrollment stopped

Q3W=every 3 weeks; QW=once weekly.

[a] Administered on Days 1 and 8 of every 21-day cycle.

[b] Administered as a continuous infusion over Days 1 to 5 in every 21-day cycle.

[c] Administered on Days 1, 8, and 15 of every 28-day cycle.

[d] Administered orally, twice daily on Days 1 to 14 of each 21-day treatment cycle.

4.3.5 Modified Toxicity Probability Interval in the Safety Lead-in Phase

During the safety lead-in phase of Cohorts B2, D2, E, F, G, I, and J, an mTPI design will be applied to identify the RP2D of the combination treatment detailed in Section 4.1. The predetermined dose levels that will be assessed are described in Section 4.3.3 and Section 4.3.4.

Note that this section describes the process for finding a dose for respective cohorts. For decision criteria guiding dose modification for individual participants due to toxicity, please refer to Sections 6.6.2 through 6.6.5.

Dose-finding will follow the mTPI design [Ji, Y., et al 2007] with a target DLT rate of 30% to define the RP2D of lenvatinib, 5-FU/cisplatin, gemcitabine/cisplatin, paclitaxel, bevacizumab, and capecitabine/oxaliplatin to use in combination with MK-7684A. Dose de-escalation decisions will depend on the number of participants enrolled and number of DLTs observed at the current dose level (Table 4).

Ten participants are planned at the starting doses of lenvatinib (Table 1 and Table 2) and chemotherapy (Table 3). However, depending on the accrual rate, the completion of DLT evaluation period and number of DLTs observed, fewer participants may be enrolled at the starting dose. Participants will be closely followed for DLTs (Section 6.6.1) for the first cycle after the first dose of study intervention (the DLT evaluation period). The dose will be evaluated on an ongoing basis as participants complete the DLT evaluation period. In Table 4, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing a DLT. The entries of the table are the dose-finding decisions: E, S, D, and DU represent escalating the dose, staying at the same dose, de-escalating the dose, and excluding the dose from the study due to unacceptable toxicity, respectively. For example, if 2 out of 3 participants at this dose level develop a DLT, the dose will be de-escalated to the next lower dose level but may be re-escalated at a later time if the lower dose is well tolerated. If 3 out of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be de-escalated, if allowed per-protocol, and the current dose will not be explored further.

If either a dose de-escalation or re-escalation decision is made before 10 participants have completed enrollment at the starting dose, the enrollment at this dose level will be halted and a new set of participants will be enrolled and treated at the next lower dose level. This process will continue, with up to 10 DLT-evaluable participants enrolled at each dose explored, until 10 participants have been enrolled at any of the tested doses and a dosing decision of “S” (for staying at current dose) is made for the 10^{th} participant evaluated. If, at any point, the dosing decision is “E” after evaluation of all enrolled participants at a dose, the dose may be escalated to a higher predetermined dose provided that the higher dose has not previously been discontinued due to a “DU” decision.

A “D” or “DU” decision at the lowest dose level will stop the evaluation of the combination under study. An “E” decision at the highest dose level (ie, Dose Level 0 [Table 1] [Table 2] [Table 3]) will result in staying at that level. During dose-finding, it may be acceptable to de-escalate or escalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired.

The totality of the data will be considered to determine RP2D.

Table 4 Dose-finding Rules per mTPI Design (Target Toxicity Rate up to 30%)

	Number of Participants Evaluable for DLT at Current Dose							
Number of participants with at least 1 DLT	3	4	5	6	7	8	9	10
0	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E
2	D	S	S	S	S	S	S	S
3	DU	DU	D	S	S	S	S	S
4		DU	DU	DU	D	D	S	S
5			DU	DU	DU	DU	DU	D
6				DU	DU	DU	DU	DU
7					DU	DU	DU	DU
8						DU	DU	DU
9							DU	DU
10								DU

D=Deescalate to the next lower dose; DLT=dose-limiting toxicity; DU=The current dose is unacceptably toxic; E=Escalate to the next higher dose; mTPI=modified toxicity probability interval; S=Stay at the current dose.
Note: Target toxicity rate = up to 30% (inclusive). Flat noninformative prior Beta (1,1) is used as a prior and ε1=ε2=0.05 [Ji, Y., et al 2007] [Ji, Y. and Wang, S.-J. 2013] [Ji, Y., et al 2010].
Note: In this study, the dose will not be escalated above Dose Level 0, so an "Escalate" can also mean "Stay."

4.3.6 Maximum Dose Exposure for This Study

The maximum dose/exposure of MK-7684A allowed in this study is 200 mg vibostolimab/ 200 mg pembrolizumab for up to 2 years (35 treatment cycles) of initial treatment/first course (Section 6.1.1).

The maximum dose/exposure of pembrolizumab allowed in this study is 200 mg Q3W for up to 2 years (35 treatment cycles) of initial treatment/first course (Section 6.1.1).

The maximum dose of lenvatinib for participants with pMMR tumors in Cohort B2 is 20 mg/day. The maximum dose of lenvatinib in Cohort G is 12 mg/day (BW ≥60 kg) or 8 mg/day (BW <60 kg). Lenvatinib may be continued for up to 2.5 years (45 treatment cycles) of initial treatment/first course or until a discontinuation criterion is met (Section 7.1).

In Cohort D2, based on global clinical practice patterns, gemcitabine at 1000 mg/m^2 on Day 1 and Day 8 of a 21-day cycle will be administered until PD or unacceptable toxicity. Cisplatin at 25 mg/m^2 will be administered on Day 1 and Day 8 of a 21-day cycle for a maximum of 8 cycles.

The maximum dose/exposure of 5-FU allowed in Cohort E is 4000 mg/m^2/cycle (21-day cycle) for up to 2 years (35 treatment cycles) of initial treatment.

The maximum dose/exposure of cisplatin allowed in Cohort E is 80 mg/m^2 for up to 6 cycles.

Paclitaxel will be administered in Cohort F as per the approved product label and applicable institutional standards.

Carboplatin/paclitaxel will be administered in Cohort I for up to 6 cycles (this includes the Lead-in Period) at investigator's choice of dose:

- Carboplatin AUC5 or 6 Q3W plus paclitaxel 175 mg/m^2 Q3W
- Carboplatin AUC5 or 6 Q3W plus paclitaxel 80 mg/m^2 QW
- Carboplatin AUC2 or 2.7 QW plus paclitaxel 60 mg/m^2 QW

Bevacizumab will be administered in Cohort I as per the approved product label and applicable institutional standards. The maximum dose of bevacizumab allowed in Cohort I is 15 mg/kg for up to 15 cycles or as per local SOC and according to the approved product label.

Note: On a case-by-case basis, Bevacizumab may be administered for up to 21 cycles following consultation with the Sponsor.

In Cohort J, the capecitabine/oxaliplatin dose regimen will be oxaliplatin (130 mg/m^2 IV) on Day 1 of each treatment cycle (Q3W) plus capecitabine (1000 mg/m^2 orally twice daily) on Days 1 to 14 of each treatment cycle (Q3W). Duration of oxaliplatin treatment may be capped at 6 cycles as per local country guidelines. See Appendix 7 for country-specific requirements.

4.4 Beginning and End-of-Study Definition

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

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

The Sponsor estimates that the maximum duration of the study from first participant entered through long-term follow-up will be 5.5 years (~2.5 years after study intervention has been completed) to attain the final assessment of the study (eg, to evaluate safety and/or long-term efficacy) for all evaluable participants. Refer to the Synopsis, Section 1.1, for the duration of participation of participants.

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 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 as described in Appendix 1.10.

In the event of early termination, the decision to permit actively enrolled participants to continue on study intervention would depend on the reason that the study was terminated.

5 STUDY POPULATION

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

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

Male/female participants ≥18 years of age with selected solid tumors will be enrolled in this study.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

Has histologically or cytologically confirmed, advanced (unresectable or metastatic) solid tumor as follows:

1. **Cohort A (≥2L treatment)**: squamous cell carcinoma, adenosquamous carcinoma, or adenocarcinoma of the cervix which has progressed on standard of care chemotherapy but must not have been treated with prior anti-PD-1/PD-L1 therapy.

   Note: Participants with mucinous carcinoma are not allowed.

- **Cohort A1**: participants whose tumors are PD-L1 positive (CPS ≥1) as determined by the central laboratory.
- **Cohort A2**: participants whose tumors are PD-L1 negative (CPS <1) as determined by the central laboratory.

  Note: participants who are ineligible for standard treatment or who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will also be eligible.

  Note: Prior neoadjuvant or adjuvant therapy included in initial treatment may not be considered first- or later-line SOC treatment unless such treatments were completed less than 6 months before the current tumor recurrence. Chemotherapy given concurrently with radiation therapy will not be considered a 1L therapy, regardless of the interval between treatment and recurrence.

2. **Cohort B (1L or 2L treatment)**: endometrial cancer that has progressed after 1 prior systemic, platinum-based chemotherapy regimen for endometrial cancer but must not have been treated with prior anti-PD-1/ PD-L1 therapy. Participants may have received up to 2 lines of platinum-based chemotherapy if 1 was given in the neoadjuvant or adjuvant treatment setting.

   Note: There is no restriction regarding prior hormonal therapy.

- **Cohort B1**: participants with endometrial cancer whose tumors are dMMR as determined by the central laboratory
- **Cohort B2**: participants with endometrial cancer whose tumors are pMMR as determined by the central laboratory

   Note: Participants with uterine mesenchymal tumor such as an endometrial stromal sarcoma, leiomyosarcoma, or other types of pure sarcomas are not eligible. Adenosarcomas and neuroendocrine tumors are not allowed.

   Note: When Cohort B2 (pMMR) reaches its enrollment limit, participants must meet Cohort B1 (dMMR) criteria only to be eligible for inclusion in the study. When this occurs, participants who are pMMR will be considered screen failures.

3. **Cohort C (1L treatment)**: HNSCC that is considered incurable by local therapies and whose tumors express PD-L1 (CPS ≥1) as determined by the local laboratory using the PD-L1 IHC 22C3 pharmDx assay.

   Note: participants should not have received prior systemic therapy, including anti-PD-1/PD-L1 therapy, administered in the recurrent or metastatic setting. Systemic therapy which was completed more than 6 months before providing documented informed consent if given as part of multimodal treatment for locally advanced disease is allowed.

   Note: prior (neo)adjuvant treatment is allowed provided it was completed at least 6 months before diagnosis of advanced disease.

   Note: the eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx.

   Note: participants may not have a primary tumor site of nasopharynx (any histology).

4. **Cohort D**: unresectable biliary adenocarcinoma (gallbladder or biliary tree [intrahepatic or extrahepatic] cholangiocarcinoma)

- **Cohort D1 (2L treatment)**: participants whose tumors have progressed after 1 prior systemic therapy but must not have been treated with prior anti-PD-1/ PD-L1 therapy.

  Note: Participants may have received prior neoadjuvant or adjuvant therapy in consideration of the following:

  - Assessment of disease progression should be confirmed by CT scan. In certain situations, clinical evidence of disease progression such as any new or worsening malignant effusion (documented by ultrasound) and confirmation by pathologic criteria (histology and/or cytology) may be acceptable for assessment after Sponsor consultation.
  - Treatment with curative intent, including neoadjuvant/adjuvant treatment, given as chemotherapy or chemoradiotherapy, using standard of care agents or definitive chemoradiation, will count as a line of therapy if disease progression occurs during treatment or within 6 months of cessation of treatment.

- **Cohort D2 (1L treatment)**: participants with previously untreated, histologically confirmed diagnosis of advanced (metastatic) and/or unresectable (locally advanced) biliary tract cancer.

  Note: neoadjuvant/adjuvant therapy is allowed for participants in Cohort D2, if disease progression occurs more than 6 months after cessation of treatment. Refer to Exclusion Criteria 3.

  Note (Cohorts D1 and D2): participants with mixed HCC/cholangiocarcinoma may be included.

  Note (Cohorts D1 and D2): participants with Ampulla of Vater cancers are not eligible.

  Note (Cohorts D1 and D2): small cell cancer, neuroendocrine tumors, lymphoma, sarcoma, mixed tumor histology and/or mucinous cystic neoplasms are not eligible.

5. **Cohort E (1L treatment)**: adenocarcinoma or squamous cell carcinoma of the esophagus or advanced/metastatic Siewert type 1 adenocarcinoma of the GEJ (defined as adenocarcinomas of the lower esophagus with the center located within 1 cm to 5 cm above the anatomic GEJ) that is unresectable and has not been previously treated with systemic therapy, including anti-PD-1/ PD-L1 therapy, administered in the recurrent or metastatic setting.

   Note: participants with a history of clinically significant GI bleeding in the past 6 months or direct invasion into adjacent organs such as the aorta or trachea (T4b disease) should be closely evaluated for bleeding risk before enrollment and a Sponsor consultation before enrollment is required.

Note: participants with Siewert type 1 adenocarcinoma of the GEJ with known HER-2/neu-positive tumors are not eligible. If HER-2/neu status is unknown, site should follow local standards for HER-2/neu testing.

Note: Participants may have received prior neoadjuvant or adjuvant therapy, including chemotherapy or chemoradiotherapy, as long as 1) assessment of disease progression can be confirmed by CT scan and 2) disease progression occurred at least 12 months after cessation of treatment.

Note: treatment with curative intent, including neo(adjuvant) treatment, given as chemotherapy or chemoradiotherapy, using standard of care agents or definitive chemoradiation, will count as a line of therapy if disease progression occurs during treatment or within 12 months of cessation of treatment.

6. **Cohort F (1L treatment)**: locally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines, that is either locally recurrent unresectable not previously treated with chemotherapy and that cannot be treated with curative intent or metastatic that has not been previously treated with chemotherapy.

   Note: Participants initially diagnosed with hormone receptor positive and/or HER2/neu-positive breast cancer must have local confirmation of TNBC in a tumor biopsy obtained from a local recurrence or distant metastasis site.

   Note: Participants with a history of locally recurrent TNBC, which was previously treated with curative intent, may be eligible.

   Note: Participants with de novo metastatic TNBC are eligible if anthracycline is contraindicated or not considered the best treatment option for the participant in the opinion of the treating physician.

   Note: For participants initially diagnosed with Stage I-III breast cancer, ≥6 months must have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence. Adjuvant radiation therapy is not considered treatment with curative intent for the purpose of calculating the ≥6-month interval requirement.

   Note: First documentation of local or distant disease recurrence must be in the form of a dated biopsy, pathology, or imaging study report. A laboratory report indicating tumor marker elevation cannot be used as documentation of local or distant disease recurrence, unless accompanied by dated biopsy, pathology, or imaging study report.

   Note: For participants who received a taxane in the (neo)adjuvant setting, ≥12 months must have elapsed between the completion of treatment with curative intent (eg, date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence.

7. **Cohort G (1L treatment)**: HCC with all of the following criteria:

- Radiologically, histologically, or cytologically confirmed diagnosis of HCC, excluding fibrolamellar, sarcomatoid or mixed cholangio-HCC tumors that has not been previously treated with systemic therapy, including anti-PD-1/PD L1 therapy. Radiographic confirmation of the diagnosis must be confirmed by the study site.
- Clinically confirmed diagnosis of HCC according to AASLD criteria.
- Have BCLC Stage C disease, or BCLC Stage B disease not amenable to locoregional therapy or refractory to locoregional therapy, and not amenable to a curative treatment approach (see Appendix 10).
- Have a Child-Pugh class A liver score within 7 days before first dose of study intervention (see Appendix 11).

8. **Cohort H (1L treatment)**: UC with all of the following criteria:

- Histologically or cytologically confirmed diagnosis of advanced/unresectable (inoperable) or metastatic urothelial carcinoma of the renal pelvis, ureter (upper urinary tract), bladder, or urethra. Both transitional cell and mixed transitional/nontransitional cell histology are allowed, but transitional cell carcinoma must be the predominant histology.

  Note: Participant must have at least 1 lesion that is measurable per RECIST 1.1 and suitable for selection as a target lesion.

- Have received no prior systemic chemotherapy for advanced or metastatic UC with the following exceptions:
  - Neoadjuvant platinum-based chemotherapy for treatment of muscle-invasive bladder cancer with recurrence >12 months from completion of the therapy is permitted.
  - Adjuvant platinum-based chemotherapy following radical cystectomy, with recurrence >12 months from completion of the therapy, is permitted.

  Note: Low-dose chemotherapy (eg, low-dose cisplatin, cisplatin plus 5-FU, mitomycin plus 5-FU, or cisplatin plus paclitaxel), given concurrently with radiation to the primary tumor site for curative intent treatment of muscle-invasive bladder cancer, is not considered systemic therapy. In the clinical setting, chemotherapy is given with the sole purpose of sensitizing the tumor to local radiation and is not administered at doses with any systemic efficacy. Surgery is not considered 1L therapy following diagnosis of advanced/metastatic disease.

- In the opinion of the investigator, be considered ineligible to receive any platinum-based chemotherapy (ie, ineligible for cisplatin and carboplatin).

  Criteria for platinum ineligibility include any of the following:

  - ECOG PS 2 within 7 days prior to allocation
  - CrCl ≥30 to <60 mL/min
  - NCI CTCAE Version 5.0 Grade ≥2 audiometric hearing loss
  - NCI CTCAE Version 5.0 Grade ≥2 peripheral neuropathy
  - Other reason, identified on the CRF, for the participant being unable to receive any platinum-based chemotherapy safely, such as advanced age or other comorbidities

  Note: The reason(s) for ineligibility for any platinum-based chemotherapy must be documented in the participant's medical record and on the eCRF.

9. **Cohort I (1L treatment)**: OC, with all the following criteria:

- Histologically confirmed FIGO Stage III or Stage IV high grade serous OC, primary peritoneal cancer, or fallopian tube cancer.
- Participant has not received primary debulking surgery and is a candidate for interval debulking surgery.
- Participant must start lead-in chemotherapy within 8 weeks of first diagnostic tumor tissue biopsy.
- Participant is a candidate for carboplatin and paclitaxel chemotherapy, to be administered in the neoadjuvant setting.
- Participant has a CA-125 (kilounits/L): CEA (ng/mL) ratio greater than or equal to 25 [Vergote, I., et al 2010].

  Note: if the serum CA-125/CEA ratio is less than 25, then a workup should be negative for the presence of a non-OC to determine eligibility (eg, breast or gastrointestinal cancers [including CRC]).

- Participant is able to provide a newly obtained core or excisional biopsy (preferred) or archival sample of a tumor lesion for prospective testing of BRCA1/2 and HRD status prior to allocation. Details pertaining to tumor tissue submission can be found in the Laboratory Manual and should be submitted to central laboratory.

- Participant is BRCA1 and BRCA2 nonmutated and is HRD-negative.

10. **Cohort J (1L treatment)**: gastric cancer with all the following criteria:

- Has histologically or cytologically confirmed diagnosis of locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.
- Has HER2 negative cancer as confirmed by local laboratory testing.

  Note: HER2 negative is defined as: IHC (0, or 1+) or FISH negative (HER2:CEP17 ratio <2 with an average HER2 copy number <4.0 signals/cell). FISH can be replaced with locally available ISH methods acceptable as per institutional guidelines (eg, DISH).

- Has provided tumor tissue sample for prospective central testing of PD-L1 status prior to allocation and retrospective MSI biomarker analysis.
- Has a PD-L1 positive tumor (defined as CPS ≥1) as confirmed centrally.

11. Has measurable disease per RECIST 1.1 as assessed by the BICR (Cohort A1 only) or local site investigator/radiology (all other cohorts). Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.

    Note: For Cohort A1, BICR must verify the presence of measurable disease as defined by RECIST 1.1 for the participant to be eligible for the study.

12. Can provide a newly obtained core or excisional biopsy of a tumor lesion or either an archival FFPE tumor tissue block or slides for determination of biomarker status (eg, PD-L1, MMR, ER, PgR, BRCA, and HER2/neu). A newly obtained biopsy is preferred, but not required if archival tissue is available for analysis.

    Note: For planned exploratory biomarker analyses, FFPE tumor blocks are preferred to slides (refer to Section 8.1.12).

    Note: Participants who have undergone PD-L1 (per PD-L1 IHC 22C3 pharmDx assay [**Cohort C only**]), ER and PgR (**Cohort F only**), HER2/neu (**Cohort E [participants with Siewert type 1 adenocarcinoma of the GEJ only] and Cohort F only**) or HPV (**Cohort C [participants with oropharyngeal cancer only]**) testing as part of standard of care do not need to have the test repeated for the purpose of this study.

Demographics

13. Is male or female, who is at least 18 years of age at the time of providing informed consent.

    Note: For Cohort I: participant must be female.

14. Has an ECOG Performance Status of either 0 or 1 (ECOG PS of 2 allowed for Cohort H only), as assessed within 7 days before starting study intervention.

    Note: For Cohort I: ECOG performance status must meet eligibility before start of lead-in chemotherapy and before C1D1.

15. Has a predicted life expectancy of at least 3 months.

Male Participants

Cohorts D2, E, F, and J (MK-7684A + Chemotherapy)

16. If male, agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

    - Chemotherapy: 95 days

- Refrains from donating sperm

  PLUS either:

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

  OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

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

  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Refer to Appendix 7 for country-specific requirements.

Cohort G (MK-7684A + Lenvatinib)

17. If male, agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:

    - Lenvatinib: 7 days

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

  OR

- Uses contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:

  - Uses a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

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

  - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

Female Participants

Cohort A, Cohort B1, Cohort C, Cohort D1, and Cohort H (MK-7684A or Pembrolizumab Monotherapy)

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

- Not a WOCBP

  OR

- A WOCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), 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 120 days after the last dose of study intervention. 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.
  - Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.
  - Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention .
  - Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Cohort D2, Cohort E, Cohort F, Cohort I, and Cohort J (MK-7684A + Chemotherapy)

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

- Not a WOCBP

  OR

- A WOCBP and:
  - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:
    - MK-7684A: 120 days
    - Chemotherapy: 180 days
    - Bevacizumab (Cohort I): 100 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 is more stringent than the requirements above, the local label requirements are to be followed.

- Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.
- Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.
- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Refer to Appendix 7 for country-specific requirements.

Cohort B2 and Cohort G (MK-7684A + Lenvatinib)

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

- Not a WOCBP

  OR

- A WOCBP and:
  - Uses 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 length of time required to continue contraception for each study intervention is as follows:
    - MK-7684A: 120 days
    - Lenvatinib: 30 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 is more stringent than the requirements above, the local label requirements are to be followed.

- Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours (urine) or 72 hours (serum) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.
- Abstains from breastfeeding during the study intervention period and for at least 120 days after study intervention.
- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

21. The participant (or legally acceptable representative) has provided documented informed consent/assent for the study.

Additional Categories

22. Has adequately controlled BP with or without antihypertensive medications, defined as bp ≤150/90 mm Hg at Screening and no change in antihypertensive medications within 1 week before allocation.

    Note: this criterion applies to participants who will receive lenvatinib in either Cohort B2 or Cohort G.

    Note: this criterion applies to participants who will receive bevacizumab in Cohort I.

23. HIV-infected participants must have well controlled HIV on ART, defined as:

- Participants on ART must have a CD4+ T-cell count >350 cells/mm^3 at the time of Screening.
- Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of Screening and for at least 12 weeks before Screening.
- Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (randomization/allocation).

- The combination ART regimen must not contain any antiretroviral medications other than: abacavir, dolutegravir, emtricitabine, lamivudine, raltegravir, rilpivirine, or tenoforvir. (Note: not applicable for cohorts with MK-7684A and MK-3475 monotherapy).

Refer to Appendix 7 for country-specific requirements.

24. Participants who are HbsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load before randomization/allocation.

Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

Hepatitis B screening tests are not required unless:

- Known history of HBV infection
- As mandated by local health authority

Refer to Appendix 7 for country-specific requirements.

25. Participants with history of HCV infection are eligible if HCV viral load is undetectable at Screening.

Note: Participants must have completed curative antiviral therapy at least 4 weeks before randomization/allocation.

Hepatitis C screening tests are not required unless:

- Known history of HCV infection
- As mandated by local health authority

Refer to Appendix 7 for country-specific requirements.

26. Has adequate organ function as defined in Table 5. Specimens must be collected within 10 days before the start of study intervention. Refer to Appendix 7 for country-specific requirements.

Note: For Cohort I: Adequate organ functions must meet eligibility before start of lead-in chemotherapy and before C1D1.

Table 5 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	>1500/μL
Platelets	>100,000/μL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a]
Renal	
Measured or calculated creatinine clearance **OR** GFR	≥30 mL/min OR ≥60 mL/min (**Cohort D2 and Cohort E only**)[b]
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)
Albumin (**Cohort J only**)	≥ 2.5 g/dL
Coagulation	
INR or PT aPTT/PTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic-pyruvic transaminase); ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); GFR=glomerular filtration rate; INR=international normalized ratio; PT=prothrombin time; PTT=partial thromboplastin time; ULN=upper limit of normal.

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.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within last 2 weeks.

[b] The cisplatin product label should be followed for acceptable creatinine clearance rates.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

All Cohorts:

1. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 3 years.

   Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer, or other in situ cancers.

   Note (**Cohorts B1 and B2 only**): Participants with synchronous primary endometrial cancer or a history of primary endometrial cancer that met the following conditions are not excluded: Stage not greater than I-A; no more than superficial myometrial invasion, without vascular or lymphatic invasion; no poorly differentiated subtypes, including papillary serous, clear cell or other FIGO Grade 3 lesions.

   Note (**Cohort H only**): Has a history of prostate cancer (T2NXMX or lower with Gleason score ≤7) treated with definitive intent (surgically or with radiation therapy) at least 1 year prior to study entry is acceptable, provided that the participant is considered prostate cancer-free and the following criteria are met:

   - Participants who have undergone radical prostatectomy must have undetectable PSA for >1 year and at screening.
   - Participants who have had radiation must have a PSA doubling time >1 year (based on at least 3 values determined >1 month apart) and a total PSA value which does not meet Phoenix criteria for biochemical recurrence (ie, <2.0 ng/mL above nadir).

     Note: Participants with untreated low-risk prostate cancer (Gleason score ≤6) on active surveillance with PSA doubling time >1 year (based on at least 3 values determined >1 month apart) are also eligible.

   Note (**Cohort J only**): Has a known additional malignancy that is progressing or has required active treatment within the past 5 years.

2. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

Cohort D2 only:

3. Has had previous systemic therapy for advanced (metastatic) or unresectable (locally advanced) biliary tract cancer (intra-or extra-hepatic cholangiocarcinoma or gallbladder cancer), with the exception of neoadjuvant/adjuvant therapy which is allowed. Neoadjuvant/adjuvant therapy should have been completed at least 6 months prior to diagnosis of advanced and/or unresectable disease, and participants should not have received gemcitabine and/or cisplatin in the neoadjuvant/adjuvant setting. Participants who received prior neoadjuvant/adjuvant therapy with R2 postoperative pathology of the oncologic resection are excluded.

Cohort H only:

4. Has disease that is suitable for local therapy administered with curative intent (eg, chemotherapy and radiation for Stage 3 disease).
5. Has tumor with any neuroendocrine or small cell component.

Cohort I only:

6. Participant has mucinous, germ cell, endometroid type, clear cell type, carcinosarcoma, or borderline tumor of the ovary.
7. Participant has ongoing Grade 3 or Grade 4 toxicity, excluding alopecia, following chemotherapy administered during the Lead-in Period.
8. Participant has received colony-stimulating factors (eg, G-CSF, GM CSF or recombinant erythropoietin) within 4 weeks (28 days) prior to receiving chemotherapy during the Lead-in Period.
9. Participant is considered to be of 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, or extensive interstitial bilateral lung disease on HRCT scan.
10. Participant has had surgery <6 months prior to screening to treat borderline tumors, early stage EOC or early stage fallopian tube cancer.
11. Participant has uncontrolled hypertension.

    Note: This should be confirmed prior to the first administration of bevacizumab during the Lead-in Period. Use of antihypertensive medications to control blood pressure is allowed.

12. Participant has current, clinically relevant bowel obstruction (including subocclusive disease), abdominal fistula or gastrointestinal perforation, related to underlying EOC.

13. Participant has a history of hemorrhage, hemoptysis or active gastrointestinal bleeding within 6 months prior to allocation.
14. Participant has factor V Leiden and/or other inherited thrombophilias.

Cohort J only:

15. Has squamous cell or undifferentiated gastric cancer.
16. Has preexisting peripheral neuropathy >Grade 1.

Prior/Concomitant Therapy

All Cohorts:

17. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-TIGIT agent.
18. Has received prior systemic anticancer therapy including investigational agents within 4 weeks before randomization/allocation.

    Note: This does not include lead-in chemotherapy in Cohort I.

19. Has received prior radiotherapy within 2 weeks of start of study intervention or radiation-related toxicities requiring corticosteroids.

    Note: 2 weeks or fewer of palliative radiotherapy for non-CNS disease, with a 1-week washout, is permitted.

20. Has 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 for information on COVID-19 vaccines.

Cohorts B1 and B2 only:

21. Greater than 1 prior systemic chemotherapy regimen (other than adjuvant or neoadjuvant) for endometrial cancer. Participants may receive up to 2 regimens of platinum-based chemotherapy in total, as long as 1 is given in the neoadjuvant or adjuvant treatment setting. Prior chemotherapy regimens that do not contain a platinum are not permitted.

    Note: Prior hormonal and/or targeted therapy is permitted.

Cohort D2 only:

22. Has received prior anticancer therapy (eg, TACE, palliative surgery) for advanced unresectable biliary tract cancer (intra- or extra-hepatic cholangiocarcinoma or gallbladder cancer), including investigational agents within 4 weeks prior to allocation.

Cohort H only:

23. Has received prior therapy with an IDO1 inhibitor, or agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137), or any other antibody or drug targeting T-cell costimulatory pathways in the adjuvant or advanced/metastatic setting.

Cohort I only:

24. Participant has received prior treatment for any stage of OC, including radiation or systemic anticancer therapy (eg, chemotherapy, hormonal therapy, immunotherapy, investigational therapy).

    Note: Treatment with 1 cycle of standard of care chemotherapy (lead-in dose) for EOC, fallopian tube cancer, or primary peritoneal cancer prior to allocation in the study is allowed.

25. Is a participant for whom intraperitoneal chemotherapy is planned or has been administered as 1L therapy.
26. Participant has severe hypersensitivity (≥Grade 3) to pembrolizumab, carboplatin, paclitaxel, or bevacizumab and/or any of their excipients.

    Note: If severe hypersensitivity to paclitaxel occurs during lead-in, docetaxel may be considered instead of paclitaxel after consultation with the Sponsor.

Cohort J only:

27. Has had previous therapy for locally advanced, unresectable or metastatic gastric/GEJ cancer. Participants may have received prior neoadjuvant and/or adjuvant therapy as long as it was completed at least 6 months prior to randomization.
28. Has received prior therapy with an agent directed to a stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137) within 4 weeks of randomization/allocation.

Prior/Concurrent Clinical Study Experience

29. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

All Cohorts:

30. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days before the first dose of study medication.

31. 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 4 weeks by repeat imaging (Note: The repeat imaging should be performed during study Screening.), clinically stable, and without requirement of steroid treatment for at least 14 days before the first dose of study intervention.

    Note: Participants with known untreated, asymptomatic brain metastases (ie, no neurological symptoms, no requirement for corticosteroids, no or minimal surrounding edema, and no lesion >1.5 cm) may participate but will require regular imaging of the brain as a site of disease.

32. Known severe hypersensitivity (≥Grade 3) to MK-7684A, pembrolizumab (Cohort A1 only), lenvatinib (Cohort B2 and Cohort G only), or chemotherapy for the cohort to which the participant is allocated (including dihydropyrimidine dehydrogenase deficiency for 5-FU and capecitabine in Cohorts E and J, respectively) and/or any of their excipients.
33. Has an active autoimmune disease that has required systemic treatment in past 2 years except replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid).
34. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids or has current pneumonitis/interstitial lung disease.
35. Has an active infection requiring systemic therapy.
36. 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.
37. Has a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
38. Has present or progressive accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks before randomization/allocation.

    Note: This exclusion criterion does not apply to Cohort I.

39. Has concurrent active hepatitis B (defined as HbsAg positive and /or detectable HBV DNA) and hepatitis C virus (defined as anti-HCV Ab positive and detectable HCV RNA) infection.

    Note: Hepatitis B and C screening tests are not required unless:

    - Known history of HBV and HCV infection
    - As mandated by local health authority (refer to Appendix 7 for country-specific requirements)

All Cohorts except Cohort B1:

40. Has known MSI-H or MMR deficient cancer (as determined by either PCR or IHC). MSI-H is defined as at least 2 allelic shifts occurring among the 5 analyzed microsatellite markers as detected by PCR. MMR deficient is defined as loss of expression of at least 1 of 4 proteins (MLH1, MSH2, MSH6, and/or PMS2) by IHC. If a participant's MSI status is unknown, testing is not required to determine eligibility.

Cohort H only:

41. Is receiving hemodialysis.

Cohort I only:

42. Participant has resting ECG indicating uncontrolled, potentially reversible cardiac conditions, as judged by the investigator (eg, unstable ischemia, uncontrolled symptomatic arrhythmia, congestive heart failure, QTcF prolongation >500 ms, electrolyte disturbances) or participant has congenital long QT syndrome.
43. Participant either had major surgery within 3 weeks of allocation or has not recovered from any effects of any major surgery.

Other Exclusions

All Cohorts:

44. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.
45. Participant, in the judgment of the investigator, is unlikely to comply with the study procedures, restrictions, and requirements of the study.
46. Has had an allogenic tissue/solid organ transplant.

For participants who will receive lenvatinib in either Cohort B2 or Cohort G:

47. Has received previous treatment with lenvatinib.

    Note: Prior therapy with other kinase inhibitors that target VEGF are not exclusionary.

48. Has had major surgery within 3 weeks before first dose of study interventions.

    Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility

49. Has current, clinically relevant ≥Grade 3 GI or non-GI fistula.
50. Has urine protein ≥1 g/24 hours.

    Note: Participants with proteinuria ≥2+ (≥100 mg/dL) on urine dipstick testing (urinalysis) will undergo 24-hour urine collection for quantitative assessment of proteinuria.

51. Has a LVEF below the institutional (or local laboratory) normal range, as determined by MUGA or ECHO.
52. Has radiographic evidence of encasement or invasion of a major blood vessel, or of intratumoral cavitation.

    Note: The degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis after lenvatinib therapy.

53. Has prolongation of QTcF interval to >480 ms.
54. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including NYHA Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. Note: Medically controlled arrhythmia would be permitted.
55. Has serious nonhealing wound, ulcer, or bone fracture.
56. Has GI malabsorption or any other condition that might affect the absorption of lenvatinib.
57. Has active hemoptysis (bright red blood of at least 0.5 teaspoon) within 3 weeks before the first dose of study intervention.
58. Has a history of arterial thromboembolism within 12 months of start of study intervention.

For participants who will receive lenvatinib in Cohort G:

59. Has had esophageal or gastric variceal bleeding within the last 6 months.

    Note: All participants in Cohort G will be screened for esophageal varices unless such screening has been performed in the past 3 months before first dose of treatment. If varices are present, they should be treated according to institutional standards before starting study intervention; esophageal or gastric varices that require interventional treatment within 28 days prior to first dose of study intervention are excluded.

For participants who will receive paclitaxel in Cohort F:

60. Has a history of class II-IV congestive heart failure or myocardial infarction within 6 months of allocation.

Refer to Appendix 7 for country-specific exclusion criteria.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

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

5.4 Screen Failures

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

Participants who fail Screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

A participant who discontinues from study intervention OR withdraws consent will not be replaced. Note: This excludes the safety lead-in for Cohorts B2, D2, E, F, G, I, and J (Section 5.5.1).

5.5.1 Safety Lead-in of Cohorts B2, D2, E, F, G, I, and J

To determine safety, all participants selected must meet the criteria for evaluability for Cycle 1. Participants are considered nonevaluable and will be replaced during the safety lead-in of Cohorts B2, D2, E, F, G, I, and J if:

- They are enrolled but not treated
- They discontinue from the study before completing all the safety evaluations for reasons other than treatment-related AEs
- They receive less than 90% of the total MK-7684A, gemcitabine/cisplatin, 5-FU, cisplatin, paclitaxel, carboplatin/paclitaxel+bevacizumab, or oxaliplatin infusion in Cycle 1 (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT

6 STUDY INTERVENTION

At implementation of Amendment 12 or upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments. Amendment 12 is adding to the updates implemented in Amendment 11.

- All cohorts are closed to enrollment. This study has enrolled 613 participants.
- Participants receiving MK-7684A will be transitioned to pembrolizumab monotherapy or in combination with another protocol-specified therapy.
- Pembrolizumab 200 mg will be administered IV q3w for all cohorts.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab alone or in combination with another protocol-defined therapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab alone or in combination with another protocol-defined therapy, but unable to access it as SOC outside the study, may continue on study and receive treatment until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- All assessments in the SoA will be done per local standard of care.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit. If currently receiving protocol-specified therapy that does not include pembrolizumab, the participants will be discontinued from the study.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 12, should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.
  - The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.
  - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention allocation up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

Existing protocol content is retained for historical reference.

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

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 6.

Country-specific requirements are noted in Appendix 7.

Table 6 Study Interventions

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
ARM 1	Experimental	MK-7684A	Biological/Vaccine	Solution	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 mg/200 mg	IV Infusion	Q3W up to 35 cycles	Test Product	IMP	Central
All Participants	Experimental	PEMBROLIZUMAB	Biological/Vaccine	Solution	25 mg/mL	200 MG	IV Infusion	Q3W UP TO 35 CYCLES	Comparator	IMP	Central or Local
ARM 3	Experimental	MK-7684A	Biological/Vaccine	Solution	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W UP TO 35 CYCLES	Test Product	IMP	Central
ARM 3	Experimental	Lenvatinib	Drug	Capsule	10 mg; 4 mg	20 MG	Oral	ONCE DAILY UP TO 45 CYCLES	Test Product	IMP	Central
ARM 4	Experimental	MK-7684A	Biological/Vaccine	Solution	vibostolimab 200 mg + pembrolizumab 200 mg/20 mL	200 MG/200 MG	IV Infusion	Q3W UP TO 35 CYCLES	Test Product	IMP	Central
ARM 4	Experimental	Lenvatinib	Drug	Capsule	10 mg/ 4 mg	12 mg/ 8 mg	Oral	ONCE DAILY UP TO 45 CYCLES	Test Product	IMP	Central
ARM 5	Experimental	MK-7684A	Biological/Vaccine	Solution	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W UP TO 35 CYCLES	Test Product	IMP	Central

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
ARM 5	Experimental	CISPLATIN	Drug	Solution	1 mg/mL	80 MG/M^2	IV Infusion	Q3W UP TO 6 CYCLES	Background Treatment	NIMP/AxMP	Central or local
ARM 5	Experimental	5-FU	Drug	Solution	50 mg/mL	800 MG/M^2/DAY	IV Infusion	CONTINUOUS IV INFUSION ON EACH OF DAYS 1 TO 5 Q3W FOR UP TO 35 CYCLES	Background Treatment	NIMP/AxMP	Central or local
ARM 6	Experimental	MK-7684A	Biological/Vaccine	Solution	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W FOR UP TO 35 CYCLES	Test Product	IMP	Central
ARM 6	Experimental	PACLITAXEL	Drug	Solution	6 mg/mL	90 MG/M^2	IV Infusion	QW; DAYS 1, 8, AND 15 OF EVERY 4-WEEK CYCLE	Background Treatment	NIMP/AxMP	Central or local
ARM 7	Experimental	MK-7684A	Biological/Vaccine	Solution	vibostolimab 200 mg + pembrolizumab 200 mg/20 mL	200 MG/200 MG	IV Infusion	Q3W FOR UP TO 35 CYCLES	Test Product	IMP	Central
ARM 7	Experimental	CISPLATIN	Drug	Solution	1 mg/mL vial, 20 mg vial, or 50 mg vial	25 MG/M^2	IV Infusion	DAY 1 AND DAY 8 OF EACH 3-WEEK CYCLE, UP TO 8 CYCLES	Background Treatment	NIMP/AxMP	Central or local

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
ARM 7	Experimental	GEMCITABINE	Drug	Solution	1 g/ vial	1000 MG/M^2	IV Infusion	DAY 1 AND DAY 8 OF EACH 3-WEEK CYCLE, UNTIL PD OR UNACCEPTABLE TOXICITY	Background Treatment	NIMP/AxMP	Central or local
ARM 8	Experimental	MK-7684A	Biological/Vaccine	Solution	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W FOR UP TO 35 CYCLES	Test Product	IMP	Central
ARM 8	Experimental	CARBOPLATIN	Drug	Solution	10 mg/mL (60 mL)	AUC5 – AUC6	IV Infusion	Q3W; DAY 1 OF EACH 3-WEEK CYCLE FOR UP TO 5 CYCLES	Background Treatment	NIMP/AxMP	Central or local
ARM 8	Experimental	CARBOPLATIN	Drug	Solution	10 mg/mL (60 mL)	AUC2-AUC2.7	IV Infusion	QW; DAY 1, 8, AND 15 OF EACH 3-WEEK CYCLE FOR UP TO 5 CYCLES	Background Treatment	NIMP/AxMP	Central or local
ARM 8	Experimental	PACLITAXEL	Drug	Solution	6 mg/mL (16.7 mL)	175 MG/M^2	IV Infusion	Q3W; DAY 1 OF EACH CYCLE FOR UP TO 5 CYCLES	Background Treatment	NIMP/AxMP	Central or local
ARM 8	Experimental	PACLITAXEL	Drug	Solution	6 mg/mL (16.7 mL)	80 MG/M^2	IV Infusion	QW; DAY 1, 8, AND 15 OF EACH 3-WEEK CYCLE FOR UP TO 5 CYCLES	Background Treatment	NIMP/AxMP	Central or local

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
ARM 8	Experimental	PACLITAXEL	Drug	Solution	6 mg/mL (16.7 mL)	60 MG/M^2	IV Infusion	QW; DAY 1, 8, AND 15 OF EACH 3-WEEK CYCLE FOR UP TO 5 CYCLES	Background Treatment	NIMP/AxMP	Central or local
ARM 8	Experimental	DOCETAXEL	Drug	Solution	20 mg/mL	75 MG/M^2	IV Infusion	Q3W, DAY 1 OF EACH CYCLE FOR UP TO 5 CYCLES	Background Treatment	NIMP/AxMP	Central or local
ARM 8	Experimental	Bevacizumab (or biosimilars: MVASI®, Zirabev®, Aybintio®, ALYMSYS®, Abevmy®, Onbevezy®, Vegzelma®, CTNK®, Daiichi Sankyo®)	Drug	Solution	25 mg/mL (4 mL)	VARIABLE	IV Infusion	Q3W; DAY 1 OF EACH 3-WEEK CYCLE FOR UP TO 15 CYCLES OR AS LOCAL SOC	Background Treatment	NIMP/AxMP	Local
ARM 9	Experimental	MK-7684A	Biological/Vaccine	Solution	vibostolimab 200 mg + pembrolizumab 200 mg /20 mL	200 MG/200 MG	IV Infusion	Q3W FOR UP TO 35 CYCLES	Test Product	IMP	Central
ARM 9	Experimental	CAPECITABINE	Drug	Tablet	150 mg tablet 500 mg tablet	1000 MG/M^2	Oral	TWICE DAILY ON DAYS 1 TO 14 OF EACH CYCLE (Q3W) FOR UP TO 35 CYCLES	Background Treatment	NIMP/AxMP	Central or local

Arm Name	Arm Type	Intervention Name	Intervention Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use	IMP or NIMP/ AxMP	Sourcing
ARM 9	Experimental	OXALIPLATIN	Drug	Solution	5 mg/mL vial 50 mg vial or 100 mg vial	130 MG/M² ON DAY 1 OF EACH CYCLE	IV Infusion	Q3W FOR UP TO 35 CYCLES	Background Treatment	NIMP/AxMP	Central or local

AUC=area under the curve; IMP=investigational medicinal product; IV=intravenous; NIMP/AxMP=noninvestigational/auxiliary medicinal product; PD=progressive disease; QW=once weekly; 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 European Economic Area (EEA). Country differences with respect to the definition/classification of IMP and NIMP/AxMP may exist. In these circumstances, local legislation is followed. Refer to Appendix 7 for country-specific requirements.

All study interventions will be administered on an outpatient basis.

All products indicated in Table 6 will be provided centrally by the Sponsor or locally by the study site, subsidiary, or designee, depending on local country operational or regulatory requirements.

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

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

6.1.1 Treatment/First Course

The initial treatment/first course of MK-7684A and pembrolizumab monotherapy consists of 35 treatments. Note: The number of treatments is calculated starting with the first dose.

For participants who have attained a confirmed CR (RECIST 1.1) and have received at least 8 cycles (at least 24 weeks) of MK-7684A or pembrolizumab beyond the initial CR confirmation date, treatment may be stopped.

These participants may be eligible for Second Course described in Section 6.1.2.

6.1.2 Second Course

Note: As of implementation of Amendment 11, Second Course will no longer be offered for all the cohorts. Any participant receiving Second Course treatment prior to implementation of Amendment 11 will be able to complete treatment as planned.

All participants who have completed initial treatment/first course (those that have received at least 4 cycles of MK-7684A, MK-7684A in combination with lenvatinib, or pembrolizumab and either achieve a complete response per RECIST 1.1 as determined by the investigator or who complete 35 cycles of MK-7684A or pembrolizumab having achieved a response of stable disease or better) may be eligible for up to an additional 17 cycles of MK-7684A, MK-7684A in combination with lenvatinib, or pembrolizumab (based on original treatment assignment) if there is investigator-determined PD by RECIST 1.1 (and, in Cohort A1, verified by BICR) specified in Section 6.1.1. This retreatment is the Second Course of this study.

Note: Sponsor consultation is required prior to starting participants on Second Course and is only available if the study remains open and the participant meets the criteria specified in Section 7.1. If continued, participants will be retreated at the same dose level and frequency as when they last received the MK-7684A, MK-7684A in combination with lenvatinib, or pembrolizumab.

For participants in Cohort B2, Cohort E, Cohort F, and Cohort G, continuation or resumption of the same concomitant therapy received during the initial treatment phase (ie, chemotherapy or lenvatinib) may be administered with Second Course MK-7684A at the discretion of the investigator. For participants in Cohort D2 and Cohort I, continuation or resumption of gemcitabine or bevacizumab, respectively, may be administered with Second Course MK-7684A at the discretion of the investigator. Note that chemotherapy or agent other than lenvatinib that is different from that received in the initial treatment phase is not permitted. Lenvatinib second course treatment is permitted up to 17 cycles or until discontinuation criteria are met.

Participants may enter the Second Course if all of the following criteria are met:

1. No new anticancer treatment was administered after the last dose of study intervention
2. The participant meets all of the inclusion criteria and none of the exclusion criteria
3. The study is ongoing

An OR or disease progression that occurs during the Second Course will not be counted as an event for the primary analysis of either endpoint in this study.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

Details on preparation and administration of MK-7684A and pembrolizumab are provided in the Pharmacy Manual. 5-FU, bevacizumab, capecitabine, carboplatin, cisplatin, docetaxel, gemcitabine, oxaliplatin, and paclitaxel will be prepared and administered as per the approved product labels, local standard procedures, and institutional guidelines.

Cohort B2: There are no specific calculations or evaluations required to be performed to administer the proper dose of lenvatinib to each participant.

Cohort D2: Gemcitabine and cisplatin

The BSA in m^2 should be calculated per local guidance. The dose of gemcitabine and cisplatin shall not be recalculated by BW fluctuation in principle, but for 10% or higher fluctuation of BW, recalculation is possible at the discretion of the investigator. When recalculating, BSA in m^2 should be calculated per local guidance.

Cohort J: Oxaliplatin

The BSA in m^2 should be calculated per local guidance. The dose of oxaliplatin shall not be recalculated by BW fluctuation in principle, but for 10% or higher fluctuation of BW, recalculation is possible at the discretion of the investigator. When recalculating, BSA in m^2 should be calculated per local guidance.

Cohort G: Lenvatinib dosing is based on BW (Table 6).

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 IRT system.

There are 9 study intervention arms (Section 4.1). In Cohort A1, participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) will be assigned randomly in a 1:1 ratio to either MK-7684A (Arm 1) or pembrolizumab (Arm 2), respectively.

All other eligible participants will be nonrandomly allocated to study intervention:

- Cohort A2, Cohort B1, Cohort C, Cohort D1, and Cohort H: MK-7684A (Arm 1)
- Cohort B2: MK-7684A + lenvatinib (Arm 3)
- Cohort G: MK-7684A + lenvatinib (Arm 4)
- Cohort E: MK-7684A + 5-FU/cisplatin (Arm 5)

- Cohort F: MK-7684A + paclitaxel (Arm 6)
- Cohort D2: MK-7684A + gemcitabine/cisplatin (Arm 7)
- Cohort I: MK-7684A + carboplatin/ paclitaxel/ bevacizumab (Arm 8)
- Cohort J: MK-7684A + capecitabine/oxaliplatin (Arm 9)

6.3.2 Stratification

Participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) eligible for Cohort A1 will be stratified according to prior bevacizumab use (yes vs no).

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

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption or infusion/injection cessation of study intervention will be documented in the participant's medical record.

Refer to Section 6.6.2 for dose modification and toxicity management for irAEs associated with MK-7684A/pembrolizumab and for other allowed dose interruption of MK-7684A/pembrolizumab. Refer to Section 6.6.3 for dose modification and toxicity management for AEs associated with lenvatinib.

Administration of study intervention(s) will be monitored by the investigator and/or study staff, and/or qualified designee per institutional guidelines and procedures. The total volume of study medication infused will be compared with the total volume prepared to determine compliance with each dose administered. When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The site should ensure and confirm that the study intervention is administered at the correct dose for the assigned study participant's ID. When applicable, study-site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules, etc, during the site visits and documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

A record of the number of lenvatinib tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention

start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5 Concomitant Therapy

6.5.1 Prohibited Concomitant Medication

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during 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 is to discuss prohibited medications/vaccinations with the Sponsor's Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Participants are prohibited from receiving the following concomitant therapy or vaccination during the study:

- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Anticancer hormonal therapy (eg, anti-estrogens)
  Note: HRT is allowed.
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
  Note: Topical anticancer agents to treat skin lesions (eg, in situ melanoma or squamous cell carcinoma) are allowed, excluding skin metastasis of melanoma.
- Investigational agents other than MK-7684A and pembrolizumab
- Radiation therapy
  Note: Radiation therapy to a symptomatic solitary lesion or to the brain is allowed at the investigator’s discretion.
- Live or live-attenuated vaccines within 30 days before the first dose of study intervention and while participating in the study.
  Note: Killed vaccines are allowed. Refer to Appendix 7 for country-specific requirements.
  Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed as long as they are mRNA vaccines, replication-incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated as concomitant therapy. Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.
- Systemic glucocorticoids are permitted only for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - As needed for the prevention of emesis

- Premedication for IV contrast allergies
- Short-term oral or IV use in doses >10 mg/day prednisone equivalent for asthma or COPD exacerbations
- For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent
- For supportive care (ie, for chemotherapy or other anticancer therapies) or for allergic reactions (ie, paclitaxel) to chemotherapy administered on study

- In addition, the following glucocorticoid use is allowed:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or chronic obstructive pulmonary disease

For further information on prohibited concomitant therapies for 5-FU, bevacizumab, capecitabine, carboplatin, cisplatin, docetaxel, gemcitabine, oxaliplatin, and paclitaxel, please refer to the respective locally approved product label.

If the investigator determines that a participant requires any of the aforementioned treatments for any reason, study intervention MK-7684A or pembrolizumab must be discontinued.

6.5.2 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days prior to the first dose of study intervention and up to 30 days after the last dose of study intervention should be recorded. All concomitant medications administered during SAEs or ECIs are to be recorded. SAEs and ECIs are defined in Section 8.4.

Cohort D2 only – Listed below are concomitant therapies that should be avoided or carefully monitored:

- Hepatotoxic drugs (examples below):
  - Etifoxine
  - Isoniazid
  - Nitrofurantoin
  - Ketoconazole
  - Amiodarone
  - Phenytoin

- Herbal supplements or alternative medicines should also be avoided during the Screening and Intervention Phase of this study.
- Possible interaction between gemcitabine and warfarin has been reported and may occur at any time. Close monitoring is recommended (monitor INR weekly during gemcitabine treatment and for 1 to 2 months after discontinuing gemcitabine treatment).
- Any use of other myelosuppressive medications should be carefully monitored for risk of infection.
- Participants with controlled hepatitis B enrolled in the study may require close monitoring of liver function tests and other parameters for hepatitis reactivation if they are exposed to prolonged corticosteroids, anti-TNF therapy or other immunosuppressive therapy for management of irAEs.

Cohort E only – the following concomitant medications, if used, are to be used with caution:

- Cimetidine, metronidazole, and interferons may increase levels of 5-FU.
- Phenytoin should not be started with cisplatin therapy. Follow label and local guidelines for usage and dose adjustments.
- Participants who are taking phenytoin in conjunction with 5-FU should be examined regularly due to a potential elevation in phenytoin plasma levels.
- Hepatotoxic effects (ie, increase in alkaline phosphatase, transaminase, or bilirubin levels) are frequently observed under the treatment with 5-FU and levamisole.

Cohort J only – the following concomitant medications, if used, are to be used with caution:

- Drugs known to prolong the QTc interval should be used with caution. Please refer to the website https://www.crediblemeds.org prior to administration of oxaliplatin.
- For participants receiving capecitabine: brivudine, sorivudine analogs, and other inhibitors of the enzyme DPD.

6.5.3 Rescue Medications and Supportive Care

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

Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 6.6.2.

For participants receiving MK-7684A + lenvatinib in Cohort B2 and Cohort G, suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 7 in Section 6.6.2.1 along with the dose modification guidelines in Table 9 in Section 6.6.3. The treatment guidelines are intended to be applied when the investigator determines the events to be related to either MK-7684A or lenvatinib.

6.5.4 Drug Interactions

There are no DDI-related concomitant medication prohibitions or restrictions with respect to MK-7684A and either chemotherapy or lenvatinib.

For Cohort D2, Cohort E, Cohort F, Cohort I, and Cohort J:

Refer to the local approved product label for drug-drug interactions for each chemotherapy agent used in this study.

For Cohort B2 and Cohort G:

Lenvatinib is not expected to clinically meaningfully alter exposure to CYP3A4/Pgp substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and Pgp substrate).

Clinical studies also showed that coadministration of lenvatinib with either inducers or inhibitors of CYP3A4/Pgp are not of clinical concern.

No drug interaction is expected between pembrolizumab and lenvatinib because of their divergent metabolic pathways. MK-7684A is a monoclonal antibody and is primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and nonenzymatic processes (lenvatinib IB).

Concomitant medications with potential for overlapping toxicity with study medications should be given judiciously and with close monitoring. For Cohort B2 and Cohort G, QTc prolongation has been seen in some lenvatinib studies. Drugs known to prolong the QTc interval (including Class Ia and III antiarrhythmics) must be used cautiously. Please refer to the lenvatinib IB.

6.6 Dose Modification (Escalation/Titration/Other)

Dose modifications in response to treatment-related AEs are permitted to keep the participant on study medication, when appropriate. Details on the modifications for each study intervention are provided in the sections below. In general:

- MK-7684A, 5-FU, cisplatin, paclitaxel, and lenvatinib may be interrupted together or separately at the investigator's discretion to determine which treatment component is the source for a given toxicity.
- Action may be taken independently for each component of study treatment (eg, chemotherapy should be discontinued for prohibitive toxicity that is chemotherapy-related, but MK-7684A may continue if well tolerated).
- Chemotherapy and lenvatinib may be interrupted, dose reduced or discontinued.
- MK-7684A and pembrolizumab may only be interrupted or discontinued.

Refer to Section 6.6.4 for dose modification guidance for overlapping toxicity for the pembrolizumab plus lenvatinib combination.

6.6.1 Definition of Dose-limiting Toxicity

All toxicities will be graded using NCI CTCAE Version 5.0 based on the investigator assessment. The DLT window of observation will be during Cycle 1 for each dose level.

The occurrence of any of the following toxicities during Cycle 1 of each dose level will be considered a DLT, if assessed by the investigator to be related to study intervention administration:

a. Grade 4 nonhematologic toxicity (not laboratory).
b. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia:
   - Grade 4 thrombocytopenia of any duration
   - Grade 3 thrombocytopenia associated with clinically significant bleeding
c. Any nonhematologic AE ≥Grade 3 in severity should be considered a DLT, with the following exceptions: Grade 3 fatigue lasting ≤3 days; Grade 3 diarrhea, nausea, or vomiting without use of antiemetics or antidiarrheals per standard of care; Grade 3 rash without use of corticosteroids or anti-inflammatory agents per standard of care.

   Exception: This excludes Grade 3 hypertension able to be controlled by medication for those participants receiving lenvatinib in Cohorts B2 and G

   Exception: This excludes Grade 3 nonimmune cholangitis manageable with intervention in Cohort D2

d. Any Grade 3 or Grade 4 nonhematologic laboratory value if:
   - Clinically significant medical intervention is required to treat the participant, or
   - The abnormality leads to hospitalization, or
   - The abnormality persists for >1 week
   - The abnormality results in a DILI (see Section 8.4.7 for criteria)

   Exceptions: Clinically nonsignificant, treatable, or reversible laboratory abnormalities including liver function tests, uric acid, etc.

e. Febrile neutropenia Grade 3 or Grade 4:
   - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than 1 hour.
   - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
f. Prolonged delay (>2 weeks) in initiating Cycle 2 due to intervention-related toxicity.
g. Any intervention-related toxicity that causes the participant to discontinue intervention during Cycle 1.
h. Grade 5 toxicity.

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

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

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab monotherapy, coformulation, or IO combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO combination administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Attribution of Toxicity:

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

Holding Study Interventions:

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

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

Restarting Study Interventions:

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 7.

Table 7 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

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

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea/Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST or ALT Elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer antihyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2, 3 or 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Asymptomatic cardiac enzyme elevation with clinical suspicion of myocarditis (previously CTCAE v4.0 Grade 1)	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		

irAEs	Toxicity Grade (CTCAE v5.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

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

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

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

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

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

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

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

6.6.2.2 Dose Modification and Toxicity Management of Infusion Reactions Related to Either MK-7684A or Pembrolizumab

MK-7684A and Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on either MK-7684A or pembrolizumab associated infusion reaction are provided in Table 8.

Table 8 MK-7684A or Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

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

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine[a] IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. [a]In cases of anaphylaxis, epinephrine should be used immediately. Participant is permanently discontinued from further study drug intervention.	No subsequent dosing

IV=intravenous; NCI=National Cancer Institute; NSAID=nonsteroidal anti-inflammatory drug.
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.
For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov

6.6.2.3 Other Allowed Dose Interruption for MK-7684A or Pembrolizumab

MK-7684A or pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks of the originally scheduled dose and within 6 weeks of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.3 Dose Modification for Lenvatinib

Lenvatinib dose reduction and interruption for participants who experience lenvatinib-MK-7684A combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 9. An interruption of study intervention for more than 28 days will require Sponsor approval before treatment can be resumed.

The starting dose of lenvatinib is either 20 mg/day (Cohort B2), 12 mg/day (Cohort G; BW ≥60 kg), or 8 mg/day (Cohort G; BW <60 kg). Dose reductions of lenvatinib occur in succession based on the previous dose level (ie, 14, 10, 8, 4 mg/day, 4 mg on alternate days) [Table 9]. Any dose reduction below 8 mg/day (Cohort B2) or 4 mg on alternate days (Cohort G) must be discussed with the Sponsor. Once the lenvatinib dose has been reduced,

it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Based on the safety profile of lenvatinib to date, the following subsections are provided for the management of hypertension (Section 6.6.3.1), proteinuria (Section 6.6.3.2), diarrhea (Section 6.6.3.3), hepatotoxicity (Cohort B2 [pMMR endometrial cancer] only; Section 6.6.3.4), hepatic ECIs (Cohort G only; Section 6.6.3.5), thromboembolic events (Section 6.6.3.6), PRES/RPLS (Section 6.6.3.7), hypocalcemia (Section 6.6.3.8), hemorrhage (Section 6.6.3.9), GI perforation or fistula formation (Section 6.6.3.10), QT prolongation (Section 6.6.3.11), and osteonecrosis of the jaw (Section 6.6.3.12) as appropriate, before consulting the dose modification table (Table 9). For other allowed dose interruptions for lenvatinib, please refer to Section 6.6.3.13. For overlapping toxicities of MK-7684A and lenvatinib, please refer to Section 6.6.4.

Participants who discontinue lenvatinib may continue receiving MK-7684A.

Table 9 Dose Modification Guidelines for Lenvatinib-related Adverse Events

Treatment-related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] or Grade 3[e, f]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	**Cohort B2:** Reduce lenvatinib dose to 14 mg once a day (1-level reduction) **Cohort G:** Reduce lenvatinib dose to either 8 mg/day (BW ≥60 kg) or 4 mg/day (BW <60 kg) (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	**Cohort B2:** Reduce lenvatinib dose to 10 mg once a day (1-level reduction) **Cohort G:** Reduce lenvatinib dose to either 4 mg/day (BW ≥60 kg) or 4 mg every other day (BW <60 kg)

Treatment-related Toxicity[a,b]	Management	Dose Adjustment
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	**Cohort B2:** Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction) **Cohort G:** Reduce lenvatinib dose to 4 mg every other day (BW ≥60 kg) or discontinue (BW <60 kg)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[g]: Discontinue Study Treatment		

AE=adverse event; BMI=body mass index; BW=body weight; CTCAE=Common Terminology Criteria for Adverse Events.

Note: For grading see CTCAE version 5.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade).

Note: If weight loss is Grade 3, then it should lead to dose reduction per the lenvatinib dose modification table above.

[a] An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed.

[b] Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea before any lenvatinib interruption or dose reduction.

[c] Applicable only to Grade 2 toxicities judged by the participant and/or physician to be intolerable.

[d] Obese participants (BMI ≥30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These participants may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they have a minimum BMI of 25. The new stable weight should be used as the new baseline for further dose reductions.

[e] For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor.

[f] For Grade 3 thromboembolic event, permanently discontinue lenvatinib. See Section 6.6.3.6.

[g] Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.

6.6.3.1 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that participants enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 1.3). Hypertension will be graded using NCI CTCAE v5.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. The choice of antihypertensive treatment should be individualized to the participant's clinical circumstances and follow standard medical practice. For previously normotensive participants, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those participants already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a participant is at imminent risk to develop a hypertensive crisis or has uncontrolled hypertension (eg, BP ≥160/100 mm Hg) with significant risk factors for severe complications, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant comorbidities. Once the participant has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

Participants who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the participant must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on 2 BP assessments at least 30 minutes:

1. Continue study drug and institute antihypertensive therapy for participants not already receiving this.
2. For those participants already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.

3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
   - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
   - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at a third dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the participant has been on a stable dose of antihypertensive medication for at least 48 hours.
   - Additional dose reduction should be discussed with the Sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life-threatening consequences):

1. Institute appropriate medical management
2. Discontinue study drug

6.6.3.2 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the SoA (Section 1.3). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing or urinalysis per the SoA (Section 1.3). Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine dipsticks is not feasible.
2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot UPCR test) is required in the following situations:
   - The first (initial) occurrence of ≥2+ (≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while the participant is receiving lenvatinib
   - A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level
   - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+ (≥100 mg/dL)

3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

- Grading according to NCI CTCAE v5.0 will be based on the 24-hour urinary protein result if one has been obtained. If the participant has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 10.

Monitoring

- Urine dipstick or urinalysis testing for participants with proteinuria ≥2+ (≥100 mg/dL) should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles.
- Proteinuria monitoring can be performed at the local laboratory or investigator site but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

6.6.3.3 Management of Diarrhea

An anti-diarrheal agent should be recommended to the participant at the start of study treatment, and participants should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the participant's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 9 should be followed.

6.6.3.4 Management of Hepatotoxicity (Cohort B2 only)

Liver function tests (ALT, AST, bilirubin levels) should be conducted as detailed in the SoA (Section 1.3) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 10 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per CTCAE v5) occurs, lenvatinib must be discontinued.

6.6.3.5 Management of Hepatic Events of Clinical Interest (Cohort G Only)

HECIs are described in Section 8.4.7. All HECIs will require holding study intervention and notification of the event(s) to the Sponsor within 24 hours and recorded in the database.

All cases of retreatment after interruption of study intervention for HECI must be reported to the sponsor and recorded in the database.

Immediate assessment in case of HECI:

All Participants

- All participants should be considered for evaluation according to the directions below within 72 hours of the alert for a nonoverdose ECI.
  - Procedures:
    - Consider obtaining a consultation with a hepatologist
    - Obtain a workup for hepatitis if there is no underlying hepatitis, including hepatitis A, B, C, D, E, Epstein-Barr virus, and cytomegalovirus
    - Assess for ingestion of drugs/supplements with hepatotoxic potential
    - Assess for alcohol ingestion
    - Assess for potential bacterial infection, biliary obstruction, or occult gastrointestinal bleeding
    - Repeat ALT, AST, total bilirubin, direct bilirubin, alkaline phosphatase, γ glutamyl transpeptidase, INR, and complete blood count with differential
    - Measure HCV RNA viral load (applies only for participants who have current active HCV infection or had infection in the past)
    - HBV DNA, HBsAg, anti-HBcAb (total and IgM), and anti-HBsAb regardless of prior HBV status (Note: participants should be questioned about compliance with the use of antiviral agents)
    - Other laboratories or imaging studies as clinically indicated
    - Consider liver biopsy if indicated

HCC patients are at risk for a range of complications that can cause hepatic laboratory abnormalities with or without clinical decompensation. Those with a history of chronic HCV or HBV infection also have the potential to experience virologic flares. The following section provides further guidance on the diagnosis and management of potential hepatic complications among HCC participants in this study. The recommendation is to hold both MK-7684A and lenvatinib interventions and initiate “Management of HECI for Lenvatinib Toxicity” (Section 6.6.3.5.1). If toxicity does not improve within 1 to 2 days or worsens, follow “Management of HECI for MK-7684A” (Section 6.6.3.5.2).

6.6.3.5.1 Management of Hepatic Events of Clinical Interest for Lenvatinib Toxicity (Cohort G Only)

Instructions for dose reductions or interruptions for lenvatinib are in Table 10.

Table 10 Lenvatinib Dose Reduction and Interruption Instructions for HECI (Cohort G)

Lenvatinib Dose Reduction and Interruption Instructions Dose reductions occur in succession based on the previous dose level (12, 8, and 4 mg/day, and 4 mg every other day [QoD]). Any dose reduction below 4 mg QoD must be discussed with the Sponsor. Once the dose has been reduced, it cannot be increased at a later date.		
Lenvatinib Induced HECI	**Management**	**Dose Adjustment**
First occurrence	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Reduce lenvatinib by 1 dose level.
Second occurrence (same toxicity or new toxicity)	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Reduce lenvatinib by 1 more dose level.
Third occurrence (same toxicity or new toxicity)[a]	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Reduce lenvatinib by 1 more dose level.
Fourth occurrence (same toxicity or new toxicity)	Interrupt for up to 28 days. Restart only if resolved to Grade 0-1 or baseline within 28 days; otherwise, permanently discontinue lenvatinib.	Discontinue lenvatinib.

HECI=hepatic events of clinical interest; QD=once daily.

[a] Not applicable for participants who start at 8 mg QD.

6.6.3.5.2 Management of Hepatic Events of Clinical Interest for MK-7684A (Cohort G Only)

Instructions for management of HECI for MK-7684A are shown in Table 11.

Table 11 Management of HECI for MK-7684A

	Diagnosis	**Management**
Hepatitis B considered flare or change in HBV immunologic status	Rapid elevation of ALT to >5 × ULN and/or >3 × baseline	Interrupt MK-7684A intervention for **up to 12** weeks. Start antiviral therapy or check for compliance if HBV is detectable. Measure safety labs for AST, ALT, ALP, total bilirubin, direct bilirubin, and INR on **weekly** basis. Measure HBsAg and HBV DNA on **weekly** basis (if detected at the time of onset of ECI). Evaluate the following every 2-3 weeks: • HBsAg, and HBV DNA levels (if not detected at the onset of ECI) Restart MK-7684A intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should be permanently discontinued.
Hepatitis C exacerbation in participants with HCV RNA positive	Rapid elevation of ALT to >5 × ULN and/or >3 × baseline	Interrupt MK-7684A intervention for **up to 12** weeks. Assess use of injection or inhalation drugs. Recheck HCV genotype at the time of relapse of HCV RNA to rule out new infection. Measure safety labs for AST, ALT, ALP, total bilirubin, direct bilirubin, and INR on **weekly** basis Measure HCV RNA levels **every 2 weeks.** Please discuss benefit:risk with Sponsor before starting HCV antiviral therapy. Restart MK-7684A intervention only if ALT returns to normal or Grade 1 (if normal at baseline), or to baseline grade (if Grade 2 at baseline) within 12 weeks, and the participant is clinically stable; otherwise, the participant should be permanently discontinued.
Relapse of HCV infection for participants with successfully treated or new HCV infection	If HCV RNA was TND at baseline, and now has confirmed detectable HCV RNA (2 specimens, 1 week apart)	

	Diagnosis	Management
Immune-related hepatitis	If any of the HECI criteria is met as defined in the protocol Section 8.4.7 Note: Immune-related hepatitis is a diagnosis made after excluding other possible etiologies such as viral flare, biliary or vascular obstruction, infection, medications, and alcohol use usually immune-related hepatitis response to dechallenge and/or steroids and reoccurs with rechallenge	Interrupt MK-7684A study intervention for **up to 12 weeks.** Start IV corticosteroid 60 mg/day of prednisone or equivalent followed by oral corticosteroid. Monitor with biweekly laboratory tests, including AST, ALT, total bilirubin, direct bilirubin, ALP, and INR. **Restart MK-7684A intervention only if:** • Abnormal laboratory values resolve to Grade ≤1 or baseline (if abnormal at baseline) • Taper steroid over 28 days • Steroid treatment is tapered to prednisone <10 mg/day or equivalent **Permanently Discontinue MK-7684A intervention if:** • Laboratory abnormalities do not resolve within 3 weeks • Steroids cannot be lowered to ≤10 mg/day (or prednisone equivalent) within 12 weeks • Decompensation to CP-C status
Other Causes	Rule out infection with blood, urine, and ascites culture – antibiotics should be started if infection is found If total bilirubin is elevated, imaging should be obtained to rule out vascular compromise, biliary obstruction, and/or tumor progression by imaging Ruled out alcohol use and hepatotoxic drugs including herbal and alternative medications	Restart MK-7684A only if laboratory values have returned to Grade 1 or baseline (if normal or Grade 1 at start) or to baseline grade **within 6 weeks.** If biliary obstruction is present, consultation with a gastroenterologist and/or an interventional radiologist should be obtained to see if the obstruction may be relieved.
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CP-C=Child-Pugh Grade C; DNA=deoxyribonucleic acid; ECI=event of clinical interest; HBV=hepatitis B virus; HBsAg=hepatitis B surface antigen; HCV=hepatitis C virus; HECI=hepatic events of clinical interest; INR=international normalized ratio; IV=intravenous; RNA=ribonucleic acid; TND=target not detected; ULN=upper limit of normal.		

6.6.3.6 Management of Thromboembolic Events

Participants should be advised to pay attention to symptoms suggestive of venous thromboembolic events, which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, participants should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 9 should be followed. Appropriate supportive care should be provided together with close monitoring.

If a participant experiences a Grade 3 or a life-threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

6.6.3.7 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome

PRES/RPLS is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In participants with signs or symptoms of PRES/RPLS, instructions in Table 9 should be followed.

6.6.3.8 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 1.3). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v5.0, using the following formula:

$$\text{Corrected calcium} = ([4 - \text{serum albumin in g/dL}] \times 0.8 + \text{serum calcium})$$

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

6.6.3.9 Management of Hemorrhage

Instructions in Table 9 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

6.6.3.10 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any participants who develop gastrointestinal perforation of any grade or Grade 4 fistula.

6.6.3.11 Management of QT Prolongation

Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to <480 msec or baseline. Monitor potassium, calcium and magnesium, and replenish as appropriate.

6.6.3.12 Management of Osteonecrosis of the Jaw

Perform an oral examination before treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgment of adequate resolution (see Section 6.6.3.13).

6.6.3.13 Other Allowed Dose Interruptions for Lenvatinib

If the participant is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) before surgery and then restart it at least 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.

6.6.4 Dose Modifications for Overlapping Toxicities of MK-7684A and Lenvatinib

Based on the known toxicity profiles of MK-7684A and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for MK-7684A treatment. However, certain AEs, such as such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to either study drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

   Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), and MK-7684A is dosed Q3W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following 2 scenarios:

   - If an AE is identified during a treatment cycle (ie, between 2 MK-7684A doses), only lenvatinib dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of MK-7684A should be held.

   If the participant recovers from an AE in response to lenvatinib interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE

   If an AE is suspected to be treatment-related and is severe/life-threatening at the time of onset or is rapidly worsened, action including interrupting both drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

3. Participants receiving the combination therapy (MK-7684A + lenvatinib) must discontinue study therapy if any of the criteria outlined in Section 7.1 for Cohort B2 and Cohort G are met.

6.6.5 Dose Modifications for Chemotherapy

Recommended dose modifications for key chemotherapy toxicities are provided in Table 12 through Table 19. These guidelines serve only as guides and do not replace investigator judgment and applicable local label or institutional guidelines if clinically appropriate. An interruption of chemotherapy or bevacizumab for more than 6 weeks will require Sponsor approval before the treatment can be resumed.

For participants experiencing an AE requiring dose modification of study intervention, the next treatment period with this(these) drug(s) may be delayed, if the scheduled off-drug periods are not adequate to allow for recovery of the AE to ≤Grade 1 or the baseline status of the participant.

6.6.5.1 Dose Modification of Gemcitabine or Cisplatin (Cohort D2)

Dose modifications for gemcitabine and cisplatin are detailed in Table 12. **The following serves as a guide and does not replace investigator's clinical judgment. Follow local applicable product label recommendations if dosing considerations are clinically appropriate.**

- CrCl will be based on the original weight-based Cockcroft and Gault formula. If the calculated CrCl is <60 or >120 mL/min, measure EDTA clearance or CrCl before prescribing. CrCl must be ≥60 mL/min prior to administration of first dose of cisplatin and ≥40 mL/min prior to the administration subsequent doses of cisplatin. Cisplatin may be delayed for up to 42 days to allow the participant time to recover from the cisplatin-related toxicity. If a participant's CrCl value has not returned to ≥40 mL/min within 42 days after the previous dose, cisplatin must be discontinued. Additional details for dose modifications for cisplatin use are listed in Table 12.
- Gemcitabine should be administered with caution in participants with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations. For significant renal impairment defined as CrCl <30 mL/min, consider dose reduction and discuss with Sponsor. For serum bilirubin >1.6 mg/dL, consider dose reduction of gemcitabine to 800 mg/m^2. Monitor carefully and discontinue gemcitabine if any drug-related worsening occurs [Venook, A. P., et al 2000].

- Gemcitabine should be discontinued at the first signs of any evidence of microangiopathic hemolytic anemia, such as rapidly falling hemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH, which may indicate development of hemolytic uremic syndrome. Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required.
- Maximal dose reduction permitted is up to 40% of starting dose of cisplatin (10 mg/m^2) and gemcitabine (400 mg/m^2). Doses below this level are not considered therapeutic and the participant will be discontinued from the related chemotherapy.

Table 12 Dose Modification Guidelines for Gemcitabine/Cisplatin-related Adverse Events

Category	Toxicity	Grade	Gem dose	Cis dose	Timing for Restarting Study Intervention	Subsequent Dose
Hematologic[a]	Neutrophil count decreased[b]	1-2[b]	None	None	N/A	N/A
		3	75%	None	N/A	Gemcitabine dose should be re-escalated to full dose (100%) on the subsequent cycles upon recovery of hematologic toxicity. If reduction required for 2 consecutive doses, permanently reduce dose of gemcitabine by 25%[d]
		4[c]	Hold	Hold	Neutrophil count recovers to >1000/mm^3 [d]	Reduce gemcitabine dose by 25% of last dose[d,e]
	Febrile Neutropenia[b]	3-4[c]	Hold	Hold	Toxicity resolves and Neutrophil count recovers to >1000/mm^3 [d]	Reduce gemcitabine dose by 25% of last dose[d,e]
	Platelet count decreased	3	75%	100%	N/A	Gemcitabine dose should be re-escalated to full dose (100%) on the subsequent cycles. If reduction is required for 2 consecutive doses, permanently reduce gemcitabine dose by 25%[d]
		4[c]	Hold	Hold	Platelet count recovers to >50,000/mm^3 [d]	Reduce gemcitabine dose by 25% of last dose[d,e]

Category	Toxicity	Grade	Gem dose	Cis dose	Timing for Restarting Study Intervention	Subsequent Dose
Non-hematologic[a]	Renal dysfunction	Serum creatinine increased above baseline	100%[f]	Subsequent dosing based on CrCl (mL/min)[g] <u>Cisplatin Dose:</u> **>60:** Give 100%, **51 – 60:** Give 75%, **40 – 50:** Give 50%, **<40 mL/min:** Hold and follow modifications above on recovery and if not recovered to at least ≥40 mL/min within 42 days after the previous dose permanently discontinue		
	Peripheral Sensory Neuropathy[h]	2	100%	75%	N/A	Reduce cisplatin dose by 25% of last dose
		3[c]	100%	Hold	Toxicity resolves to ≤Grade 2[a]	Reduce cisplatin dose by 25% of last dose. Continue to reduce cisplatin by 25% for each additional episode.
		4	100%	N/A	N/A	Permanently discontinue
	Nausea and vomiting	3-4[c]	Hold	Hold	Toxicity resolves to ≤Grade 2[a]	Resume at 100%
	All Other Non-Hematologic Toxicities[a,f,i]	3-4[c]	Hold	Hold	Toxicity resolves to ≤Grade 2[a]	Follow standard of care guidelines

AE=adverse event; Cis=cisplatin; CrCl=creatinine clearance; G-CSF=granulocyte colony-stimulating factor; Gem=gemcitabine; N/A=not applicable.

[a] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.

[b] See the package insert of each of the G-CSF drugs for administration of G-CSF for neutropenia.

[c] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after a Grade 4 drug-related AE.

[d] Permanently discontinue gemcitabine and cisplatin if gemcitabine-/cisplatin-related hematologic toxicity does not resolve to ≤Grade 2 within 6 weeks.

[e] If Day 8 study intervention is delayed by ≥2 weeks, then subsequent therapy should start with next cycle. MK-7684A should be given on Day 1 of each new cycle. There should be at minimum a 3-week interval between MK-7684A doses and a minimum 1-week interval between the chemotherapy doses.

[f] Gemcitabine should be administered with caution in participants with evidence of significant renal or hepatic impairment as there is insufficient information from clinical studies to allow clear dose recommendation for these patient populations.

[g] Follow local cisplatin product label recommendations if dosing considerations are more stringent.

[h] Administration may be interrupted or reduced at the discretion of the investigator.

[i] Allow continuous treatment for laboratory AEs that are asymptomatic and deemed to be not clinically significant.

Other Allowed Dose Interruption for Gemcitabine or Cisplatin

Gemcitabine or cisplatin may be interrupted for situations other than treatment-related AEs such as medical or surgical events and/or unforeseen circumstances not related to study intervention. However, study intervention is to be restarted within 3 weeks of the originally scheduled dose and within 6 weeks of the previously administered dose, unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

6.6.5.2 Dose Modification for 5-FU/Cisplatin (Cohort E)

The investigator may attribute each toxicity event to 5-FU, cisplatin, or MK-7684A and use a stepwise approach to dose reduction of 5-FU and cisplatin (Table 13). Participants may have a maximum of 2 dose reductions to each of the components throughout the course of the study. Once the dose has been reduced, it may not be re-escalated. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (ie, dose reduction appropriate to the most severe toxicity). Participants who require a third dose modification to any component will have that agent discontinued.

Reduction of one chemotherapy agent and not the other is appropriate if, in the opinion of the investigator, the toxicity is clearly related to one of the agents. If the toxicity is related to the combination of both chemotherapy agents, both drugs should be reduced according to recommended dose modifications. If the toxicity is related to the combination all study intervention administered, chemotherapy should be reduced, interrupted, or discontinued, and MK-7684A should be interrupted or discontinued according to the recommended dose modifications (Table 7).

Participants may discontinue either 5-FU or cisplatin and continue receiving the other component in combination with MK-7684A. Participants may discontinue both 5-FU and cisplatin and continue receiving MK-7684A.

Dose modification criteria for 5-FU and cisplatin are provided in Table 14 and Table 15, respectively.

Note: In participants with unrecognized dihydropyrimidine dehydrogenase deficiency, acute, life-threatening toxicity may occur when participants are treated with 5-FU. It is recommended that dihydropyrimidine dehydrogenase testing be performed as appropriate per local guidelines.

Table 13 Dose Reductions for 5-FU and Cisplatin

	Dose level 0	Dose level -1	Dose level -2	Dose level -3
Cisplatin	80 mg/m^2	60 mg/m^2 (75% of Level 0)	40 mg/m^2 (50% of Level 0)	Discontinue
5-FU	4000 mg/m^2/cycle	3000 mg/m^2/cycle (75% of Level 0)	2000 mg/m^2/cycle (50% of Level 0)	Discontinue

Table 14 Dose Modification Guidelines for 5-FU-related Adverse Events

Category	Toxicity	Hold 5-FU Treatment for Grade[a]	Timing for Restarting 5-FU Treatment	Dose for Restarting 5-FU Treatment	Discontinue 5-FU
Hematologic[b]	Neutropenia	3	Neutrophil count resolves to >1,000/mm^3	No Reduction (consider G-CSF)	Toxicity does not resolve within 4 or 5 weeks of last infusion or if >2 dose level reductions exceeded
		4	Neutrophil count resolves to >1,000/mm^3	Reduce by 1 DL (consider G-CSF)	Toxicity does not resolve within 4 or 5 weeks of last infusion or if >2 dose level reductions exceeded
	Febrile neutropenia	3	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if >2 dose level reductions exceeded
		4	N/A	Discontinue	Permanently discontinue
	Thrombo-cytopenia	3 or 4	Platelet count resolves to >75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if >2 dose level reductions exceeded

Category	Toxicity	Hold 5-FU Treatment for Grade[a]	Timing for Restarting 5-FU Treatment	Dose for Restarting 5-FU Treatment	Discontinue 5-FU
Non-hematologic	Diarrhea, mucositis, or hand-foot syndrome	2 or 3	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if >2 dose level reductions exceeded
		4	N/A	Discontinue	Permanently discontinue
	All other non-hematologic toxicities[c]	3 or 4	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if >2 dose level reductions exceeded
	Laboratory AEs	4	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 or 5 weeks of last infusion or if >2 dose level reductions exceeded

AE=adverse event; DL=dose level; G-CSF=granulocyte colony-stimulating factor; N/A=not applicable.

[a] **Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.**

[b] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.

[c] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held and did not recover to Grade 0 or 1 within 12 weeks of the last dose.

Table 15 Dose Modification Guidelines for Cisplatin-related Adverse Events

Category	Toxicity	Hold Cisplatin Treatment for Grade[a]	Timing for Restarting Cisplatin Treatment	Dose for Restarting Cisplatin Treatment	Discontinue Cisplatin
Hematologic[b]	Neutropenia	3	Neutrophil count resolves to >1,000/mm^3	No Reduction (consider G-CSF)	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
		4	Neutrophil count resolves to >1,000/mm^3	Reduce by 1 DL (consider G-CSF)	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
	Febrile neutropenia	3	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
		4	N/A	Discontinue	Permanently discontinue cisplatin
	Thrombo-cytopenia	3 or 4	Platelet count resolves to >75,000/mm^3 or baseline	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
Nonhematologic	Creatinine increased	2	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
		3 or 4	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
	Sensory neuropathy	3 or 4	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
	Ototoxicity[c]	1 or 2[c]	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
		3 or 4	N/A	Discontinue	Permanently discontinue cisplatin
	All other non-hematologic toxicities[d]	3 or 4	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded
	Laboratory AEs	4	Toxicity resolves to Grade 0 or 1	Reduce by 1 DL	Toxicity does not resolve within 4 weeks of last infusion or if >2 dose level reductions exceeded

Category	Toxicity	Hold Cisplatin Treatment for Grade[a]	Timing for Restarting Cisplatin Treatment	Dose for Restarting Cisplatin Treatment	Discontinue Cisplatin
AE=adverse event; DL=dose level; G-CSF=granulocyte colony-stimulating factor; N/A=not applicable. [a] **Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.** [b] Participants with intolerable or persistent Grade 2 drug-related AEs may hold at physician discretion. [c] Cisplatin is known to cause high frequency hearing loss. Follow local product label and institutional guidelines. If Grade 1 or 2 hearing loss occurs, the risk of additional hearing loss versus the potential benefit of continuing cisplatin chemotherapy should be made. Grade 3 and 4 hearing loss is an indication to discontinue cisplatin. [d] Participants with intolerable or persistent Grade 2 drug-related AEs may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held and did not recover to Grade 0 or 1 within 12 weeks of the last dose.					

6.6.5.3 Dose Modification for Paclitaxel (Cohort F)

The investigator may attribute each toxicity event to paclitaxel or MK-7684A and use a stepwise approach to dose reduction of paclitaxel (Table 16). Once the dose has been reduced, it may not be re-escalated. If a participant experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (ie, dose reduction appropriate to the most severe toxicity).

If the toxicity is related to the combination all study intervention administered, paclitaxel should be reduced, interrupted, or discontinued, and MK-7684A should be interrupted or discontinued according to the recommended dose modifications (Table 7).

Participants may discontinue paclitaxel and continue receiving MK-7684A. If paclitaxel is discontinued, the participants does not need to come to the clinic on dates when only the chemotherapy would have been administered (Section 1.3.3).

Dose modification criteria for paclitaxel are provided in Table 16.

Table 16 Dose Modification Guidelines for Paclitaxel-related Adverse Events

Toxicities	Grade or actual value	Paclitaxel
Hematological		
Neutropenia	≥1000/mm^3 Grade 2/Grade 1	No change
	<1000/mm^3 Grade 3/Grade 4	Hold paclitaxel until ANC ≥1000/mm^3. Administer G-CSF until ANC ≥1000/ mm^3. Resume paclitaxel based on timing of recovery: • <3 weeks: Dose-reduce paclitaxel per institutional guidelines for all subsequent cycles. • ≥3 weeks: Stop paclitaxel.

Toxicities	Grade or actual value	Paclitaxel
Febrile neutropenia	ANC ≤1000/mm^3, fever ≥38.5°C Grade 3 and Grade 4	Hold paclitaxel until resolved (ANC >1000/mm^3, fever <38.5°C, and resolution of any signs of infection). Administer G-CSF until ANC ≥1000/ mm^3. Resume paclitaxel according to number of episodes: • First episode: Reduce paclitaxel to 80 mg/m^2 for all subsequent doses. • Second episode: Reduce paclitaxel to 70 mg/m^2 for all subsequent doses. • Third episode: Discontinue paclitaxel.
Thrombocytopenia	75-<100,000/mm^3 Grade 1	Hold paclitaxel until ≥100,000/mm^3, resume treatment based on timing of recovery: • ≤1 week — no change to paclitaxel. • >1 but <3 weeks — Reduce paclitaxel per institutional guidelines for all subsequent doses. • ≥3 weeks: Discontinue paclitaxel.
	<75,000/mm^3 ≥Grade 2	Hold paclitaxel until ≥100,000/mm^3. • Reduce paclitaxel per institutional guidelines for all subsequent doses. • Stop paclitaxel.
Anemia	All grades	No change to paclitaxel • Iron studies should be done, and iron should be replaced as indicated. • Red blood cell transfusions can be given at the investigator's discretion.
Nausea/Vomiting	Grade 1 or 2	No change
	≥Grade 3	Hold paclitaxel until resolved to ≤Grade 1. • Resume paclitaxel at previous dose with modification of premedication • Second episode ≥Grade 3 despite with maximum supportive care, reduce paclitaxel per institutional guidelines for all subsequent cycles
Mucositis/Stomatitis	Grade 1 or 2	No change
	≥Grade 3	Hold paclitaxel until resolved to ≤Grade 1. • Resume paclitaxel at previous dose with modification of premedication • Second episode ≥Grade 3 despite with maximum supportive care, reduce paclitaxel per institutional guidelines for all subsequent cycles
Neurotoxicity	Grade 1–2	No change
	Grade 3	Hold paclitaxel until neuropathy improves to ≤Grade 2. • Resume paclitaxel dose reduced per institutional guidelines for all subsequent doses. • Discontinue paclitaxel if held for ≥3 weeks in a row.
	Grade 4	• Discontinue paclitaxel if held for ≥3 weeks in a row

Toxicities	Grade or actual value	Paclitaxel
Hepatic	Grade 1	• No change
	≥Grade 2 or 3	• Bilirubin fractionation should be performed if total bilirubin >1.5 × ULN. Dose may continue if isolated bilirubinemia is mostly indirect such as in participants with Gilbert • Hold paclitaxel until resolve to Grade 1 and resume the dose at previous level • Discontinue paclitaxel if held for ≥3 weeks in a row
	Grade 4	• Discontinue paclitaxel Note all concurrent ALT/AST >3 × ULN and Total bilirubin >2 × ULN should be discontinued and evaluated for potential DILI.
Anaphylaxis / Hypersensitivity	Mild	• Complete paclitaxel infusion, observe until symptom resolved
	Moderate	• Stop infusion and treat per standard practice • Resume infusion at half of the infusion speed if symptom resolve • Stop if symptom recurs
	Severe	• Stop infusion immediately and discontinue treatment
Other significant toxicities excluding fatigue, alopecia and leukopenia at discretion of the investigators	Grade 2	• Hold paclitaxel until resolve to ≤Grade 1 • Resume at the previous dose and increase supportive care measure, if available
	≥Grade 3	• Hold paclitaxel and discuss with Sponsor medical monitor for further instructions • If ≥Grade 3 toxicity recurs upon rechallenge, discontinue treatment permanently
ALT=alanine aminotransferase; AST=aspartate aminotransferase; ANC=absolute neutrophil count; DILI=drug induced liver injury; G-CSF= granulocyte colony-stimulating factor; ULN=upper limit of normal.		

6.6.5.4 Dose Modification for Chemotherapy and Bevacizumab (Cohort I)

6.6.5.4.1 Lead-in Period

Dose modifications of chemotherapy are not allowed during the Lead-in Period; all participants must receive the full dose of chemotherapy to be eligible to move into the Treatment Period.

6.6.5.4.2 Treatment Period

Carboplatin and/or paclitaxel (or docetaxel) may be reduced, interrupted, or discontinued at the investigator's discretion per the approved product labels, local regulations, and/or institutional standards. If chemotherapy (either carboplatin or paclitaxel [or docetaxel] or both) is interrupted or discontinued, MK-7684A should be continued. If MK-7684A is interrupted or discontinued, chemotherapy should be continued.

Bevacizumab may be interrupted or discontinued at the investigator's discretion per the approved product label and local regulations. If bevacizumab is interrupted or discontinued,

MK-7684A may be continued. If MK-7684A is interrupted or discontinued, bevacizumab may be continued as per the approved product label, local regulations, and/or institutional standards.

Interruptions from either carboplatin and paclitaxel (or docetaxel) or bevacizumab of greater than 6 weeks (42 days) from the originally scheduled dose require consultation between the investigator and the Sponsor. Discontinuation of both carboplatin and paclitaxel (or docetaxel) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

Supportive care measures (eg. G-CSF, erythropoietin, blood transfusion) should be used according to local standards to manage chemotherapy-induced myelosuppression, including to prevent severe infections linked to febrile neutropenia. In order to minimize dose reductions, interruptions, and discontinuations of chemotherapy, these supportive care measures should be used before implementing dose modifications, when appropriate.

Dose modifications of chemotherapy are not allowed during Cycle 1 of the safety lead-in phase (10 participants).

6.6.5.5 Dose Modification for Capecitabine/Oxaliplatin (Cohort J)

Dose modifications for capecitabine/oxaliplatin combination, oxaliplatin, and capecitabine are detailed in Table 17, Table 18, and Table 19, respectively.

Note: In participants with unrecognized dihydropyrimidine dehydrogenase deficiency, acute, life-threatening toxicity may occur when participants are treated with capecitabine. It is recommended that dihydropyrimidine dehydrogenase testing be performed as appropriate per local guidelines.

Table 17 Dose Modification Guidelines for Capecitabine and Oxaliplatin Drug-related Adverse Events

	Dose Level 0	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**	**Dose Level -4**
Oxaliplatin	130 mg/m^2	100 mg/m^2	75 mg/m^2	50 mg/m^2	Discontinue
Capecitabine	1000 mg/m^2 twice daily	750 mg/m^2 twice daily	500 mg/m^2 twice daily	Discontinue	Discontinue

Table 18 Dose Modification Guidelines for Oxaliplatin Drug-related Adverse Events

Category	**Toxicity**	**Hold Oxaliplatin Treatment for Grade**	**Timing for Restarting Oxaliplatin Treatment**	**Dose for Restarting Oxaliplatin Treatment**	**Discontinue Oxaliplatin**
Hematologic[a]	Neutropenia[b]	2-3[c]	Neutrophil count resolves to ≥1,500/mm^3	No Reduction If the criteria for starting the course are not met at Day 22, reduce by 1 DL	If >3 DL reductions exceeded
		4[c]	Neutrophil count resolves to ≥1,500/mm^3	Reduce by 1 DL	If >3 DL reductions exceeded
	Febrile Neutropenia	3[c]	Toxicity resolves	Reduce by 1 DL	If >3 DL reductions exceeded
		4[c]	N/A	Discontinue	Permanently discontinue oxaliplatin
	Thrombocytopenia	3-4[c]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL[d]	If >3 DL reductions exceeded

Category	Toxicity	Hold Oxaliplatin Treatment for Grade	Timing for Restarting Oxaliplatin Treatment	Dose for Restarting Oxaliplatin Treatment	Discontinue Oxaliplatin
Non-hematologic[a]	Creatinine Increased	≥1.5 mg/dL[c]	<1.5 mg/dL	No reduction	If >3 DL reductions exceeded
	Peripheral Sensory Neuropathy[e]	3-4[c]	Grade 0-2	Reduce by 1 DL	If >3 DL reductions exceeded
	All Other Nonhematologic Toxicities	3-4[c]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >3 DL reductions exceeded
	Laboratory Adverse Events[f]	3-4[c]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	If >3 DL reductions exceeded

AE=adverse event; DL=dose level; G-CSF=granulocyte colony-stimulating factor; N/A=not applicable.

[a] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.

[b] See the package insert of each of the G-CSF drugs for administration of G-CSF for neutropenia.

[c] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.

[d] Dose reduction at Grade 3 is at the discretion of the investigator but not required.

[e] Administration may be interrupted or reduced at the discretion of the investigator.

[f] Allow continuous treatment for laboratory AEs that are asymptomatic and deemed to be not clinically significant.

Table 19 Dose Modification Guidelines for Capecitabine Drug-related Adverse Events

Category	Toxicity	Hold Capecitabine Treatment for Grade	Timing for Restarting Capecitabine Treatment	Dose for Restarting Capecitabine Treatment	Discontinuation of Capecitabine
Hematologic[a]	Neutropenia	3[b]	Neutrophil count resolves to >1,000/mm^3	No Reduction (consider G-CSF)	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded
		4[b]	Neutrophil count resolves to >1,000/mm^3	Reduce by 1 DL (consider G-CSF)	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded
	Febrile Neutropenia	3[b]	Toxicity resolves	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded
		4[b]	N/A	Discontinue	Permanently discontinue
	Thrombocytopenia	3-4[b]	Platelet count resolves to ≥75,000/mm^3	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded

Category	Toxicity	Hold Capecitabine Treatment for Grade	Timing for Restarting Capecitabine Treatment	Dose for Restarting Capecitabine Treatment	Discontinuation of Capecitabine
Non-hematologic	Diarrhea, Mucositis, or Hand-foot Syndrome	2-3	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded
		4	N/A	Discontinue	Permanently discontinue
	All Other Non-hematologic Toxicities[c]	3-4[b]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded
	Laboratory Adverse Events[d]	4[b]	Toxicity resolves to Grade 0-1	Reduce by 1 DL	Toxicity does not resolve within 4-5 weeks of last oral intake or if >2 DL reductions exceeded

AE=adverse event; DL=dose level; G-CSF=granulocyte colony-stimulating factor; N/A=not applicable.

[a] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion.

[b] Permanent discontinuation should be considered for any severe or life-threatening event. Consult Sponsor before restarting treatment after Grade 4 drug-related AE.

[c] Participants with intolerable or persistent Grade 2 drug-related AE may hold at physician discretion. Permanently discontinue from agent for persistent Grade 2 adverse reactions for which treatment has been held and did not recover to Grade 0-1 within 12 weeks of the last dose.

[d] Allow continuous treatment for laboratory AEs that are asymptomatic and deemed to be not clinically significant.

6.7 Intervention After the End of the Study

The study is complete upon consent of the last active treatment participant for an extension study using pembrolizumab monotherapy, coformulations, or in combination with a compound (eg, lenvatinib), if available.

All study-related procedures and data collection as defined per protocol will be terminated at study completion. In addition, survival follow-up will be stopped upon study completion as defined in Section 4.4.

6.8 Clinical Supplies Disclosure

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

6.9 Standard Policies

For studies using controlled substances, all Federal, State, Province, Country, etc, regulations must be adhered to in regard to their shipping, storage, handling, and dispensing of controlled substances. Additionally, the investigator should have the appropriate controlled drug license(s) as mandated by Federal, State, Province, Country, etc, laws in which the study is being conducted.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

At implementation of Amendment 12 or upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments. Amendment 12 is adding to the updates implemented in Amendment 11.

- All cohorts are closed to enrollment. This study has enrolled 613 participants.
- Participants receiving MK-7684A will be transitioned to pembrolizumab monotherapy or in combination with another protocol-specified therapy.
- Pembrolizumab 200 mg will be administered IV q3w for all cohorts.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab alone or in combination with another protocol-defined therapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab alone or in combination with another protocol-defined therapy, but unable to access it as SOC outside the study, may continue on study and receive treatment until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- All assessments in the SoA will be done per local standard of care.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit. If currently receiving protocol-specified therapy that does not include pembrolizumab, the participants will be discontinued from the study.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 12, should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.
  - The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.

- For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention allocation up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

Existing protocol content is retained for historical reference.

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in the study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.4 unless the participant has withdrawn from the study (Section 7.2).

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

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

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- Any prolonged interruption of study intervention beyond the permitted periods, for irAE management or other allowed dose interruptions, as noted in Section 6.6.2, require Sponsor consultation prior to restarting treatment. If treatment will not be restarted, the participant will continue to be monitored in the study and the reason for discontinuation of study intervention will be recorded in the medical record.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- The participant has a positive urine drug screen at any time during the course of the study.

- Radiographic disease progression outlined in Section 8.2.1.5 (after obtaining documented informed consent addendum and Sponsor communication, the investigator may elect to continue treatment beyond iCRO-verified disease progression [Cohort A1] or investigator-assessed disease progression [Cohorts A2 to G]).
- Any progression or recurrence of malignancy, or any occurrence of another malignancy that requires active treatment.
- Any study intervention-related toxicity specified as a reason for permanent discontinuation as defined in the guidelines for dose modification due to AEs in Section 6.6.
- The participant requires any of the prohibited concomitant medication listed in Section 6.5.1.
- Participants receiving the combination of MK-7684A + lenvatinib in Cohort B2 must discontinue study therapy if any of the following occur:
  - ALT or AST elevation meeting the following criteria:
    - ALT or AST >5 × ULN for more than 2 weeks
      MK-7684A will have already been permanently discontinued per Table 7, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.
    - ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5)
      Although Table 7 advises MK-7684A to be withheld (interrupted), and Table 9 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, both drugs must be permanently discontinued immediately.
- Participants receiving the combination of MK-7684A + lenvatinib in Cohort G must discontinue study therapy if any of the following nonoverdose HECIs occur:
  - ALT >20 × ULN (confirmed within 1 week).
  - Drug-related total bilirubin >10 × ULN.
  - Child-Pugh score of >9 points if not improved to Child-Pugh score <9 by intervention within 3 days.
  - Hepatic encephalopathy not manageable by therapy within 3 days.
  - Clinical ascites not manageable by therapy within 3 days.
- Recurrence of a severe or life-threatening event, or of any of the laboratory abnormalities listed above, that are presumed to be immune-related.

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, are outlined in Section 8.1.9. 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

At implementation of Amendment 12 or upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments. Amendment 12 is adding to the updates implemented in Amendment 11.

- All cohorts are closed to enrollment. This study has enrolled 613 participants.
- Participants receiving MK-7684A will be transitioned to pembrolizumab monotherapy or in combination with another protocol-specified therapy.
- Pembrolizumab 200 mg will be administered IV q3w for all cohorts.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab alone or in combination with another protocol-defined therapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab alone or in combination with another protocol-defined therapy, but unable to access it as SOC outside the study, may continue on study and receive treatment until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- All assessments in the SoA will be done per local standard of care.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit. If currently receiving protocol-specified therapy that does not include pembrolizumab, the participants will be discontinued from the study.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 12, should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.
  - The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.
  - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention allocation up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

Existing protocol content is retained for historical reference.

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical or dental (**Cohort B2 and Cohort G only**) decisions must be made by an investigator who is a qualified physician (or dentist when appropriate).
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before providing documented informed consent may be used for screening or baseline purposes provided the procedures meet the protocol-specified criteria and were performed within the time frame defined in the SoA.
- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.
- The amount of blood collected from each participant over the duration of the study is detailed in the laboratory manual.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Note: If chemotherapy (Cohort D2, Cohort E, Cohort F, Cohort I, and Cohort J) or lenvatinib (Cohort B2 or Cohort G) is discontinued due to toxicity, any assessments and procedures specifically required while on these study interventions may no longer be necessary after consultation with the Sponsor.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

investigator or medically qualified designee must ensure the appropriate documented informed consent is in place.

Refer to Appendix 7 for country-specific requirements.

8.1.1.1 General Informed Consent

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

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

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

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

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

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

An optional Authorization for Release of Tumor Tissue will be collected from participants with cervical cancer (Cohorts A1 and A2), endometrial cancer (Cohorts B1 and B2), gastric cancer (Cohort J), and ovarian cancer (Cohort I) who agree to provide a previously obtained tumor tissue sample for central determination of biomarker status prior to providing main ICF. Participants may provide documented Authorization for Release of Tumor Tissue before the start of the Screening Period and while on prior treatment.

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 allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

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

8.1.4 Medical History

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

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

8.1.4.1 Advanced Cancer History

Comprehensive details regarding the participant's cancer history will be recorded separately and not listed as medical history. These details include, but are not limited to, stage at diagnosis, histopathology, location(s) of tumor burden, investigator-determined tumor size per RECIST 1.1, and all prior treatment (including prior radiation, prior chemotherapy, and prior surgery).

For participants in Cohort A, if available, collect history of HPV status at baseline. For participants in Cohort C, history of HPV status is only to be collected for participants with oropharyngeal cancer.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review before medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before the first dose of study intervention (Cohorts A to H and Cohort J) or within 56 days before the first dose of study intervention (Cohort I).

8.1.5.2 Concomitant Medications

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

8.1.6 Assignment of Screening Number

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

Any individual who is screened multiple times will retain the original screening number assigned at the initial Screening Visit. Specific details on the Screening/rescreening visit requirements are in Section 8.11.1.

8.1.7 Assignment of Treatment/Randomization Number

8.1.7.1 Cohort A1

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

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

8.1.7.2 Cohorts A2 to H, and J

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

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

8.1.7.3 Cohort I

All eligible participants will receive a randomization number. The randomization number identifies the participant for all procedures occurring. Once a randomization number is assigned to a participant, it can never be reassigned to another participant. A single participant cannot be assigned more than 1 randomization number.

All non-eligible participants that have received Lead-In treatment will receive an allocation number. Once an allocation number is assigned, it cannot be reused.

8.1.8 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or appropriately qualified designee according to the specifications within the pharmacy manual.

Study intervention should begin within 3 days of randomization (Cohort A1) or intervention allocation/assignment (Cohort A2 to Cohort J).

> Note (**Cohort I only**): There must be a minimum of 20 days between the start of lead-in chemotherapy and C1D1.

8.1.8.1 Timing of Dose Administration

For in-clinic dosing, study intervention will be administered after all procedures and assessments have been performed. For cohorts that will evaluate MK-7684A in combination with another anticancer therapy, administer treatments in the following order:

Cohort B2 and Cohort G (Day 1, Cycle 1 and Day 1, Cycle 2)

- MK-7684A
- Lenvatinib

Cohort D2

- MK-7684A
- Gemcitabine
- Cisplatin

Cohort E

- MK-7684A
- Cisplatin
- 5-FU

Cohort F

- MK-7684A
- Paclitaxel

Cohort I

- MK-7684A
- Paclitaxel (or docetaxel)
- Carboplatin
- Bevacizumab

Cohort J

- MK-7684A
- Oxaliplatin
- Capecitabine

8.1.8.1.1 MK-7684A and Pembrolizumab

MK-7684A and pembrolizumab will be administered using a 30-minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 25 to 40 minutes). The Pharmacy Manual contains specific instructions for MK-7684A and pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

After Cycle 1 Day 1, MK-7684A or pembrolizumab be administered up to 3 days before or after the scheduled Day 1 of each subsequent cycle for administrative reasons.

8.1.8.1.2 Lenvatinib (Cohorts B2 and G)

On C1D1 and C2D1, lenvatinib will be administered after MK-7684A administration. Lenvatinib capsules are to be taken orally once daily at approximately the same time without regard to food intake from C1D1 onwards. Participants should not take lenvatinib on PK sampling days before their appointment (ie, C1D1, C1D15, and C2D1). On C1D1, C1D15, and C2D1, participants should be instructed to bring their lenvatinib to the clinic. Lenvatinib should be administered at the study site at approximately the same time of day to accommodate PK sample collection timing. Lenvatinib should be administered for up to 45 cycles.

If a participant misses a dose, it may be taken within 12 hours after the usual time of the dose. If more than 12 hours have elapsed from the time of the usual daily dose, lenvatinib should be taken the next day at the usual time. In the event a participant vomits after lenvatinib administration, the participant should not take another dose until the next scheduled dose.

Lenvatinib compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100%

compliance and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

8.1.8.1.3 Gemcitabine and Cisplatin (Cohort D2)

Cisplatin will be administered as an IV infusion on Day 1 and Day 8 of a 3-week cycle and should be immediately preceded and followed by hydration procedures and administered according to approved prescribing information in each country/region or local institutional guidelines. Cisplatin may be administered on Day 2, if required per local guidelines; however, Day 1 is the preferred day for intervention administration. Gemcitabine will be administered as an IV infusion on Days 1 and 8 of a 3-week cycle, according to approved prescribing information in each country/region or local institutional guidelines.

Premedication with antiemetic therapy can be given prior to cisplatin and gemcitabine administration. Consider following MASCC guidelines [Davis, M., et al 2021] and, including a 5-HT3 receptor antagonist, dexamethasone (or equivalent) and aprepitant (or equivalent) as per the MASCC guidelines. Based on data showing potential impact of steroid use on efficacy of PD-1 and PD-L1 blockade, systemic steroid use as antinausea medication should be limited as deemed safe by the investigator [Arbour, K. C., et al 2018].

8.1.8.1.4 Cisplatin (Cohort E)

Cisplatin 80 mg/m^2 will be administered as a 60- or 120-minute IV infusion (or per site's standard practice) Q3W on Day 1 of each treatment cycle after MK-7684A administration according to approved prescribing information in each country/region or local institutional guidelines. Duration of cisplatin treatment will be capped at 6 doses; cisplatin dosing may occur after Cycle 6 if cisplatin was withheld for 1 or more cycles during Cycles 2 to 6. Treatment with cisplatin may follow 1 to 2 days after MK-7684A (eg, Day 2 or Day 3) as needed per local standard of care.

8.1.8.1.5 5-Fluorouracil (Cohort E)

5-FU will be administered as a continuous IV infusion of 800 mg/m^2/day on each of Days 1 to 5 Q3W according to approved prescribing information in each country/region or per local standard for 5-FU administration duration as long as total dose of 4000 mg/m^2 per 3-week cycle is followed (eg, 1000 mg/m^2/day on Days 1 to 4 Q3W is also acceptable). 5-FU will be administered after MK-7684A and cisplatin administration. Treatment with 5-FU may follow 1 to 2 days after MK-7684A (eg, Day 2 or Day 3) as needed per local standard of care. Duration of 5-FU treatment will not exceed 35 cycles.

Investigators are advised to counsel participants about the risk of photosensitivity and to take sun protection measures accordingly.

8.1.8.1.6 Paclitaxel (Cohort F)

Paclitaxel will be administered as a dose of 90 mg/m^2 on Day 1, 8, and 15 of each 28-day treatment cycle according to approved prescribing information in each country/region or local institutional guidelines. When MK-7684A and paclitaxel are administered on the same day, paclitaxel will be administered after MK-7684A administration.

8.1.8.1.7 Paclitaxel (or Docetaxel), Carboplatin, and Bevacizumab (Cohort I)

Paclitaxel / Docetaxel:

Paclitaxel (175 mg/m^2 Q3W, 80 mg/m^2 QW, or 60 mg/m^2 QW) will be administered as an IV infusion for 6 treatment cycles (including lead-in) as per local practice and labels. For Q3W and QW infusions of paclitaxel, the infusion time should follow local practice and labels. All participants should be premedicated with oral or IV steroid and antihistamines according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

Docetaxel (75 mg/m^2 Q3W), if approved by the Sponsor, will be administered as an IV infusion as per local practice and labels. The infusion time should follow local practice and labels. All participants should be premedicated with an oral steroid according to the approved product label and/or standard practice. Additional premedications should be administered as per standard practice.

Carboplatin:

Carboplatin (AUC5-6 mg/mL•min Q3W or AUC2-2.7 mg/mL•min QW) will be administered as an IV infusion for 6 treatment cycles (including lead-in) as per local practice and labels. The infusion time of carboplatin should follow local practice and labels. The carboplatin dose should be calculated using Calvert formula (see below) and should not exceed 900 mg.

Calvert Formula:

$$\text{Total Dose (mg)} = \text{target AUC} \times (\text{GFR} + 25)$$

The estimated GFR used in the Calvert formula should not exceed 125 mL/min to calculate the maximum carboplatin dose (mg):

$$\text{Target AUC 6 (mg/mL•min)} \times (125 + 25) = 6 \times 150 \text{ mL/min} = 900 \text{ mg}$$

Bevacizumab:

Bevacizumab should be administered, as per local practice and label, on Day 1 of each treatment cycle administered, after carboplatin. The local practice for drug administration sequence can be followed if preferred. The date and dose of bevacizumab administered will be recorded in the eCRF.

Note: Bevacizumab should be used at the investigator's discretion for up to 15 infusions or as per local SOC and according to the approved product label:

- Participants may receive bevacizumab starting with the lead-in dose of chemotherapy. Bevacizumab should be interrupted at least 4 weeks prior to the planned date of surgery. Bevacizumab should resume 4 weeks after surgery OR after the wound has healed, whichever is longer.
- The investigator may wait to administer the first dose of bevacizumab, as long as it is administered by the second cycle following surgery.

  Note: For all participants who will start bevacizumab after lead-in chemotherapy, blood pressure measurements need to be performed to ensure that the participant does not have uncontrolled hypertension (Section 8.3.2). Blood pressure must be controlled prior to starting bevacizumab.

  Note: Any delay in restarting/starting bevacizumab beyond what is defined in the protocol requires Sponsor approval.

8.1.8.1.8 Capecitabine/Oxaliplatin (Cohort J)

Oxaliplatin 130 mg/m^2 will be administered as a 60- to 120-minute IV infusion or per the site's standard practice on Day 1 of each treatment cycle.

Capecitabine will be administered orally as a 1000 mg/m^2 dose twice daily from Day 1 to Day 14 of each treatment cycle. The evening dose of capecitabine should be taken approximately 12 hours after the morning dose. Capecitabine should be taken with food, or within 30 minutes after food/meal, with approximately 200 mL of water. Sites may follow local practice patterns regarding calculation of capecitabine milligram dose. Refer to the product label for additional guidance on administration procedures for capecitabine.

Note: If the participant is enrolled later in the day, it is acceptable for the first dose to be taken on Day 1, and twice daily dosing can continue on Days 2 to 14; the final dose will be taken in the morning of Day 15.

Investigators are advised to counsel participants assigned to receive capecitabine about the risk of photosensitivity and to take sun protection measures accordingly. Participants receiving capecitabine should be carefully monitored for ophthalmological complications and skin reactions (Section 8.3.1).

8.1.9 Discontinuation and Withdrawal

Participants who discontinue study intervention before completion of the treatment period should be encouraged to continue to be followed for all remaining study visits as outlined in the SoA and Section 8.11.4.

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

8.1.10 Participant Blinding/Unblinding

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

8.1.11 Calibration of Equipment

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

8.1.12 Tumor Tissue for Biomarker Status

During the Screening Period, a tumor sample for each participant is required and is to be:

- A newly obtained core or incisional biopsy of a tumor lesion, which was not previously irradiated

  Note: For Cohort I participants who will undergo interval debulking surgery, newly obtained tissue must be obtained within 8 weeks prior to the administration of systemic cytotoxic treatment for the treatment of current OC. A newly obtained core or excision biopsy of a tumor lesion is preferred. Submission of either FFPE tumor blocks or unstained slides is acceptable. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from the date the slides are cut, otherwise a new sample will be requested. Tissue from the interval debulking surgery will also be mandatory.

  Or

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

FFPE tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue. Participants who have undergone PD-L1 (per PD-L1 IHC 22C3 pharmDx assay [**Cohort C only**]), ER and PgR (**Cohort F only**), HER2/neu (**Cohort E [participants with Siewert type 1 adenocarcinoma of the GEJ only], Cohort F, and Cohort J only**) or HPV (**Cohort C [participants with oropharyngeal cancer only]**) testing as part of standard of care do not need to have the test repeated (Section 5.1).

Details pertaining to tumor tissue submission can be found in the laboratory manual.

8.1.12.1 PD-L1 Status

Prospective testing for PD-L1 status is required for Cohort A, Cohort C, and Cohort J:

- For Cohort A, PD-L1 status will be determined by the central laboratory, using the PD-L1 IHC 22C3 pharmDx assay kit, which is currently approved to assess PD-L1 status in participants with cervical cancer for treatment with pembrolizumab.
- For Cohort C, PD-L1 status can be determined by the local laboratory, using the PD-L1 IHC 22C3 pharmDx assay kit, which is currently approved to assess PD-L1 status in participants with HNSCC for treatment with pembrolizumab. If PD-L1 status is determined locally, a tissue sample should be submitted to the central laboratory for confirmation of results.
- For Cohort J, PD-L1 status will be determined by the central laboratory, using the PD-L1 IHC 22C3 pharmDx assay kit, which is analytically validated to assess PD-L1 status in participants with gastric cancer. PD-L1 status will be determined for participants that are HER2 negative only. Results from the central determination of PD-L1 status are needed before allocation to study treatment.

For all other cohorts, PD-L1 status will be determined retrospectively by the central laboratory. The central laboratory will use the tissue sample to ascertain PD-L1 status using the PD-L1 IHC 22C3 pharmDx (Investigational Use Only) diagnostic kit. The diagnostic test is identical to the US FDA-approved PD-L1 IHC 22C3 pharmDx diagnostic kit except it is labeled IUO. For Cohort F, the central laboratory will use the PD-L1 IHC 22C3 pharmDx assay kit, which is currently approved to assess PD-L1 status in participants with TNBC for treatment with pembrolizumab.

8.1.12.2 Mismatch Repair Status

Prospective testing for MMR status is required for Cohort B. For all other cohorts, MMR status will be determined retrospectively.

For Cohort B, MMR testing will be performed using the Roche MMR IHC Panel.

8.1.12.3 Hormone Receptor and HER2/neu Status

Prospective testing for HR and HER2/neu status is required for Cohort F. For Cohort E, HER2/neu results from the local laboratory are needed for participants with Siewert type 1

adenocarcinoma of the GEJ only. For Cohort J, prospective testing for HER2 status is required before allocation. If HER2/neu status is unknown, the site should follow local standards for HER2/neu testing. For TNBC, the diagnosis must be histologically or cytologically documented as negative for ER or PgR by IHC (<1% positive tumor nuclei per ASCO-CAP guidelines) and negative for HER2/neu by IHC or FISH or CISH. Participants with equivocal HER2 results by IHC must have their status confirmed by FISH or CISH.

Testing will be performed by the local laboratory using commercially validated assays.

8.1.12.4 BRCA Status

For Cohort F, BRCA status (BRCA1 and BRCA2) will be determined retrospectively by the local laboratory using a commercially validated assay.

For Cohort I, participants are required to have an excisional or core biopsy performed during the Screening Period for the central determination of BRCA1/2 status. The results of central testing to assess BRCA1/2 status will yield information about other genes, including those potentially involved in HRR, and will support exploratory translational science objectives.

8.1.12.5 Tumor Tissue for HRD Biomarker

For Cohort I, participants are required to have an excisional or core biopsy collected/submitted during the Screening Period for determination of HRD status by the central laboratory.

8.2 Efficacy/Immunogenicity Assessments

8.2.1 Tumor Imaging and Assessment of Disease

As of Amendment 11, 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 study treatment and will continue receiving study treatment until criteria for discontinuation are met, assessments of tumor response by imaging should continue per local institutional guidelines.

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

In addition to survival, efficacy will be assessed based on evaluation of scan changes in tumor burden over time, until the participant is discontinued from the study or goes into Survival Follow-up. The process for scan collection and transmission to the iCRO can be found in the SIM. Tumor scans by CT are strongly preferred. For the abdomen and pelvis, contrast-enhanced MRI may be used when CT with iodinated contrast is contraindicated, or when mandated by local practice. For participants with HCC enrolled in Cohort G, triple phase imaging of the liver is required, as described in the SIM. The same scan technique

should be used in a participant throughout the study to optimize the reproducibility of the assessment of existing and new tumor burden and improve the accuracy of the response assessment based on scans.

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

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

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

Other imaging modalities that may be collected, submitted to the iCRO, and included in the response assessment and those that should not be submitted to the iCRO and will not be included in response assessment are defined in the SIM.

Cohort A1 – Radiologic Assessment by BICR

Participant eligibility will be determined by BICR. All scheduled scans for each participant will be submitted to the iCRO. In addition, unscheduled scans to determine disease progression and scans obtained for other reasons but demonstrate radiologic progression are to be submitted to the iCRO.

When the investigator identifies RECIST 1.1 disease progression, the iCRO will verify this progression and email the results to the study site and Sponsor (see Section 8.2.1.5 and Figure 4). In clinically stable participants, scans are to continue until disease progression has been verified by BICR. If investigator-assessed progression was not verified by BICR, each subsequent scan must be submitted to the iCRO. Once progression is verified by BICR, subsequent scans (if acquired) should not be submitted to the iCRO.

Cohort A2 to Cohort J – Radiologic Assessment by Investigator

At Screening, participant eligibility will require radiographic documentation of at least 1 lesion that meets the requirements for selection as a target lesion, before participant allocation.

All scheduled scans for participants will be submitted to the iCRO. In addition, a scan that is obtained at an unscheduled time point, for any reason (including suspicion of progression or other clinical reason), should also be submitted to the iCRO if it shows disease progression, or if it is used to support a response assessment. All scans acquired within the protocol-specified window of time around a scheduled scan visit are to be classified as pertaining to that visit. Once progression is determined by investigator, subsequent scans (if acquired) should not be submitted to the iCRO.

8.2.1.1 Initial Tumor Scans

Initial tumor scans at Screening must be performed within 28 days before the date of randomization/allocation. Any scans obtained after Cycle 1 Day 1 cannot be included in the Screening assessment. The site must review Screening scans to confirm the participant has measurable disease per RECIST 1.1 (Section 5.1). **For Cohort A1**, the scans at Screening must be submitted to the iCRO to verify that eligibility criteria (Section 5.1) have been met before randomization.

Tumor scans performed as part of routine clinical management are acceptable for screening if they are of acceptable diagnostic quality and performed within 28 days of randomization/allocation and can be assessed by the iCRO.

If brain scans are required to document the stability of existing metastases, the brain MRI should be acquired during Screening.

Bone scans are required at Screening for participants with a history of bone metastases and/or for those participants with indicative clinical signs/symptoms such as bone pain or elevated alkaline phosphatase levels.

8.2.1.2 Tumor Scans During the Study

Cohort A1 to Cohort H and Cohort J:

The first on study scan should be performed at 9 weeks (63 days ±7 days) from the date of:

- Randomization (Cohort A1 only)
- Cycle 1 Day 1 (Cohort A2 to Cohort H and Cohort J).

Subsequent tumor scans should be performed every 9 weeks (63 days ±7 days) or more frequently if clinically indicated. After 54 weeks (378 days ±7 days), participants who remain on treatment will have scans performed every 12 weeks (84 days ±7 days). Scan timing should follow calendar days and should not be adjusted for delays in cycle starts.

- For participants in Cohort A1, scans are to be performed until RECIST 1.1 disease progression is identified by the investigator and verified by BICR or until the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.
- For all other cohorts (Cohort A2 to Cohort H and Cohort J), scans are to be performed until RECIST 1.1 disease progression is identified by the investigator or notification by the Sponsor, or until the start of new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Cohort I:

For participants eligible for interval debulking surgery, the first on study imaging assessment should be performed at least 21 days after Day 1 of Cycle 2-5 and prior to the debulking surgery. An imaging assessment should be performed after debulking surgery and prior to dosing in the next cycle. Imaging assessments following surgery will be performed as detailed in Section 1.3.9. If surgery is not performed, the imaging assessment prior to the next cycle is not required and subsequent tumor imaging should be performed as detailed in Section 1.3.9. An imaging assessment to confirm eligibility (ie, non-PD) for the Maintenance Period will be performed as follows:

- A minimum of 21 days following Day 1 of Cycle 5 (for Q3W regimen) or a minimum of 7 days following C5D15 (for QW regimen); or
- A minimum of 21 days following Day 1 of the last cycle of chemotherapy for participants who cannot complete 6 treatment cycles (including lead-in) of chemotherapy due to toxicity but are deemed eligible for maintenance following Sponsor consultation

  Note: Imaging obtained within 4 weeks (28 days) prior to the planned start of maintenance, including postsurgery imaging, may be used as the maintenance eligibility scan following Sponsor approval.

When determining eligibility for the Maintenance Period, the imaging assessment obtained prior to starting the Maintenance Period should be compared with the baseline imaging assessment to assess non-PD. Subsequent tumor imaging should be performed every 9 weeks (63 days ± 7 days) from the maintenance eligibility assessment or more frequently if clinically indicated. After approximately 1 year (after Week 54), participants who remain on treatment will have imaging performed every 12 weeks (84 days ± 7 days). Week 54 is calculated from the date of allocation.

The maintenance eligibility scan submitted postsurgery will be used to establish a new baseline of tumor burden. Subsequent scans will be compared to this new baseline and the treatment responses will be limited to PD, non-PD, or NE.

Following debulking surgery, tumor may still be present. PD is defined as the growth of the primary tumor or appearance of any new tumors following debulking surgery as assessed by the investigator per RECIST 1.1 and iRECIST as outlined in Section 8.2.1.5 and Section 8.2.1.6, respectively. For those participants with NED following debulking surgery, progression is defined as the detection of new lesions on follow-up radiological assessments.

All cohorts:

For determination of OR, a PR or CR needs to be confirmed by a repeat scan at least 4 weeks after the initial response is observed. This may be performed at the next scheduled time point. If an additional scan is performed, participants will then return to the regular scan schedule at the next scheduled time point. Participants who receive additional scans for

confirmation do not need to undergo the next scheduled scan if it is fewer than 4 weeks later; scans may resume at the subsequent scheduled time point.

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

Clinically stable participants can continue on treatment after RECIST 1.1 PD with Sponsor approval. When RECIST 1.1 radiological disease progression is identified by the investigator in clinically stable participants, disease progression can be confirmed by another set of scans performed 4 to 8 weeks later, per iRECIST guidelines, if the investigator elects to implement iRECIST (Section 8.2.1.6).

If RECIST 1.1 disease progression is not confirmed participants are to return to their regular scan schedule. If the next scheduled scan will occur in less than 4 weeks, this scheduled scan may be skipped.

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

If participants discontinue study intervention, tumor scans should be performed at the time of discontinuation (±4-week window) unless previous scans were obtained within 4 weeks of discontinuation. For participants who discontinue study intervention due to documented RECIST 1.1 disease progression, this is the final required tumor imaging if the investigator elects to not implement iRECIST.

If participants discontinue study intervention without documented disease progression, every effort is to be made to monitor disease status by acquiring tumor scans using the same schedule calculated from the date of randomization/allocation (Cohort A1) or C1D1 (Cohorts A2-J), refer to Section 8.2.1.2.

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

- **Cohort A1**: Disease progression as defined by RECIST 1.1 and verified by BICR
- **Cohort A2 to Cohort J**: Disease progression as defined by RECIST 1.1 is identified by the investigator
- The start of a new anticancer treatment
- Pregnancy
- Death
- Withdrawal of consent
- The end of the study

Participants who are clinically stable and treated past RECIST 1.1 radiographic progression may continue to be assessed until progression is confirmed according to the rules of iRECIST, when clinically appropriate.

8.2.1.4 Second Course (Retreatment) Tumor Scans

Note: As of implementation of Amendment 11, Second Course will no longer be offered. Any participant receiving Second Course treatment prior to implementation of Amendment 11 will be able to complete treatment as planned.

Tumor scans must be performed within 28 days before restarting study intervention with either MK-7684A or pembrolizumab (**Cohort A1 only**):

- For Cohort A1, Second Course may be initiated if the participant qualifies (Section 6.1.2) and disease progression has been verified by BICR during First Course treatment.
- For Cohorts A2 to J, Second Course may be initiated if the participant qualifies (Section 6.1.2) and disease progression has been determined by investigator assessment.

Response assessments and progressive disease are determined by investigator assessment.

Second course imaging should not be sent to the iCRO.

8.2.1.5 RECIST 1.1 Assessment of Disease

8.2.1.5.1 Cohort A1

As of Amendment 11, participants who are still on study treatment will no longer have tumor response assessments by BICR. However, assessments of tumor response by imaging should continue as per local institutional guidelines.

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

Upon investigator-assessed RECIST 1.1 disease progression, the indicative scans are to be submitted immediately to iCRO for BICR verification of progression. After submission of scan(s), the iCRO will email the assessment to the site and Sponsor.

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

- If participant is clinically stable, continue study intervention per-protocol
  - resume imaging per-protocol schedule (≥4 weeks to next scan)
  - send scans to iCRO
  - continue local assessment
  - do not change investigator assessment of progression

  - if subsequent scan(s) indicate progression, submit scan(s) to iCRO to request verification

- If the participant is not clinically stable, best medical practice is to be applied

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

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

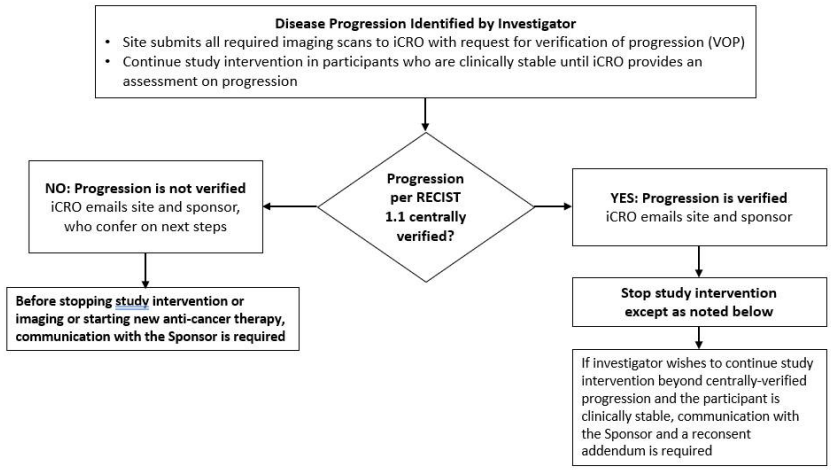
- investigator judgment will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed
- obtain scans locally per original protocol schedule
- do not send scans to iCRO

Figure 4 illustrates the study intervention decision process involving verification of disease progression for participants.

- For the purpose of this decision process, lack of clinical stability is defined as:
  - unacceptable toxicity
  - clinical signs or symptoms indicating clinically significant disease progression
  - decline in performance status
  - rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

Figure 4 BICR-verified Disease Progression

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



iCRO=imaging Contract Research Organization; VOP=verification of progression

8.2.1.5.2 Cohort A2 to Cohort J

As of Amendment 11, treatment beyond progression, unless previously approved, will no longer be available.

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

If disease progression is determined by the investigator, the process continues as follows:

- investigator judgment will determine action
- if the participant is clinically stable and study intervention is to continue, communication with the Sponsor is required and a reconsent addendum must be signed
- obtain scans per original protocol schedule
- RECIST 1.1 PD scans are the last required scans to be sent to the iCRO

For the purpose of this decision process, lack of clinical stability is defined as:

- unacceptable toxicity
- clinical signs or symptoms indicating clinically significant disease progression
- decline in performance status
- rapid disease progression or threat to vital organs or critical anatomical sites (eg, CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention

8.2.1.6 iRECIST Assessment of Disease

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression and make treatment decisions [Seymour, L., et al 2017]. When clinically stable, participants may continue study intervention beyond RECIST 1.1 progression with continued assessment of response according to the rules outlined in Appendix 12. iRECIST reflects that some participants can have a transient tumor flare after the start of immunotherapy then experience subsequent disease response. This data will be captured in the clinical database.

- If participant is clinically stable (refer to Section 8.2.1.5), continue study intervention per protocol
  - Perform scans 4 to 8 weeks after RECIST 1.1 progression
  - Continue investigator assessment per iRECIST

- If the participant is not clinically stable, best medical practice is to be applied

8.2.2 Patient-reported Outcomes (Cohort A only)

NOTE: As of Amendment 11, PRO assessments (EORTC QLQ-C30, EORTC QLQ-CX24, EQ-5D-5L) will no longer be performed.

The PRO questionnaires will be administered by trained site personnel and completed electronically by participants in Cohort A in the following order: EORTC QLQ-C30 first, then EORTC QLQ-CX24, and finally EuroQoL EQ-5D-5L. The questionnaires should be administered before dosing as detailed in Section 1.3.1. If Second Course is initiated, the PROs should be administered before dosing as detailed in Section 1.3.4.

It is best practice and strongly recommended that ePROs are administered to randomized participants before drug administration, AE evaluation, and disease status notification. If the participant does not complete the ePROs at a scheduled time point, the MISS_MODE form must be completed to capture the reason the assessment was not performed.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided. Refer to Appendix 7 for country-specific requirements.

The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in the laboratory manual.

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

8.3.1 Physical Examinations

A complete or directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standards. Height and weight will also be measured and recorded.

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

Cohort B2 and Cohort G only: The complete or directed physical examination must include an oral examination.

Cohort D2 and E: Refer to local regulations or local standard of practice for participant management regarding gemcitabine and/or 5-FU and cisplatin treatment (eg, requirements for baseline audiograms for cisplatin).

Cohort J only: Participants receiving capecitabine 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.

Capecitabine can induce severe skin reactions such as SJS and TEN. Capecitabine should be permanently discontinued in participants who experience a severe skin reaction during treatment.

After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

Refer to Appendix 7 for country-specific requirements.

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a full physical examination, including an oral examination for participants in Cohort B2 and Cohort G, during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for additional full physical examinations are described in Section 1.3. After the first

dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

8.3.1.2 Directed Physical Examination

For cycles that do not require a full physical examination as defined in Section 1.3, the investigator or qualified designee will perform a directed physical examination, including an oral examination for participants in Cohort B2 and Cohort G, as clinically indicated before study intervention administration. New clinically significant abnormal findings should be recorded as AEs.

8.3.2 Vital Signs

8.3.2.1 Vital Sign Measurements: Cohort A, Cohort B1, and Cohorts C to F, Cohort H, Cohort I, and Cohort J

The investigator or qualified designee will assess vital signs at Screening and as specified in the SoA (Section 1.3). Vital signs will include, temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

Cohort D2 only: Day 8 vital signs will not be assessed/performed when both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

Cohort I only: BP must be measured prior to the first administration of bevacizumab to ensure the participant does not have uncontrolled hypertension.

8.3.2.2 Vital Sign Measurements: Cohort B2 and Cohort G

Vital signs will include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate.

Vital sign measurements for participants who will receive lenvatinib in Cohort B2 and Cohort G should be performed as follows:

- BP and heart rate will be measured after the participant has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.
- Only 1 BP measurement is needed for participants with systolic BP <140 mm Hg and diastolic BP <90 mm Hg. If the participant's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) shows an elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

- At the C1D8 telephone visit and if required between clinic visits, participants will have BP measured. If the participant does not return to the study site for this BP measurement, BP may be measured, for example, at home or at a local pharmacy, and the results will be reviewed with the investigator or designee. The investigator/site may provide a diary as a tool to aid the participant in collecting BP evaluations between clinic visits. The Sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an on-site BP re-test, or other clinically appropriate intervention(s).

8.3.3 Electrocardiograms

8.3.3.1 Electrocardiograms: Cohort A, Cohort B1, Cohorts C to F, and Cohorts H to J

A standard 12-lead ECG will be obtained at Screening and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA (Section 1.3). Additional ECGs may be performed during the study as clinically indicated.

Note: A 6-lead ECG is allowed per institutional standard.

Refer to Appendix 7 for country-specific requirements.

8.3.3.2 Electrocardiograms: Cohort B2 and Cohort G

Electrocardiograms will be obtained as designated in the SoA (Section 1.3). Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Participants must be in the recumbent position for a period of 5 minutes before the ECG. The Fridericia correction method for calculating QTc will be used.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Appendix 3) and the eCRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the appropriate eCRF.

QTc prolongation has been seen in some lenvatinib studies. Monitor electrocardiograms every cycle (as specified in the SoA) in participants with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Refer to the lenvatinib IB.

8.3.4 Echocardiogram or Multiple-Gated Acquisition Scan (Cohort B2 and Cohort G Only)

A MUGA scan (using technetium-based tracer) or an echocardiogram will be performed to assess LVEF as designated in the SoA (Section 1.3). MUGA or echocardiogram scans should be performed locally in accordance with the institution’s standard practice. MUGA scans are

the preferred modality; however, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant. LVEFs as assessed by the institution will be entered onto the eCRF. Investigator assessment will be based upon institutional reports.

Refer to Appendix 7 for country-specific requirements.

8.3.5 Child-Pugh Score (Cohort G Only)

Originally developed in 1973, the Child-Pugh score was used to estimate the risk of operative mortality in participants with bleeding esophageal varices. It has since been modified, refined, and become a widely used tool to assess prognosis in patients with chronic liver disease and cirrhosis. The score considers 5 factors, 3 of which assess the synthetic function of the liver (ie, TBL level, serum albumin, and coagulation parameters [INR or PT]) and 2 of which are based on clinical assessment (ie, degree of ascites and degree of hepatic encephalopathy).

8.3.6 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual 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.
- **For Cohort B2 and Cohort G**: CBC with differential and clinical chemistry results must be reviewed before administration of study intervention. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all participants before starting study intervention.

- **For Cohort D2 only**: Day 8 hematology, chemistry and liver panel blood samples will not be collected after both chemotherapy agents (gemcitabine/cisplatin) are permanently discontinued.

8.3.7 Pregnancy Testing

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

- Pregnancy testing (urine and/or serum) should be conducted:
  - As clinically indicated during intervention (Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, and Cohort H)
  - Before each dose of study intervention (Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J)
- Pregnancy testing (urine and/or serum) should be conducted as per SoA for the time required to eliminate systemic exposure after the last dose of study intervention (ie, 120 days after the last dose of MK-7684A or pembrolizumab) and should correspond with the time frame for female participant contraception in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is:
  - MK-7684A: 120 days
  - Pembrolizumab: 120 days
  - Lenvatinib: 30 days
  - Chemotherapy: 180 days
  - Bevacizumab: 100 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.
- Refer to Appendix 7 for country-specific requirements.

8.3.8 Performance Assessment: Eastern Cooperative Oncology Group Performance Status

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

The investigator or qualified designee will assess ECOG status (see https://ecog-acrin.org/resources/ecog-performance-status) at Screening (within 7 days before starting study intervention) to determine eligibility, and at subsequent timepoints as specified in the SoA (Section 1.3).

For Cohort D2 only: Day 8 ECOG status will not be performed after both chemotherapy agents (gemcitabine/ cisplatin) are permanently discontinued.

For Cohort H only: An ECOG PS of 2 is allowed.

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

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

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

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

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

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

Adverse events will not be collected for participants during the prescreening period (for determination of archival tissue status) as long as that participant has not undergone any protocol-specified procedure or intervention. If the participant requires a blood draw, fresh tumor biopsy, etc, the participant is first required to provide consent to the main study, and AEs will be captured according to guidelines for standard AE reporting.

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 after cessation of study intervention must be reported by the investigator.
- All AEs meeting serious criteria, from the time of intervention allocation/randomization through 90 days after cessation of study intervention or 30 days after cessation of study intervention if the participant initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

- All pregnancies and exposure during breastfeeding, from the time of intervention allocation/randomization through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.7, or 30 days after cessation of study intervention if the participant initiates new anticancer therapy must be reported by the investigator.
- Additionally, any SAE brought to the attention of an investigator at any time outside the time specified above must be reported immediately to the Sponsor if the event is considered related to study intervention.

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

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 20.

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

Table 20 Reporting Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Period: Consent to Randomization/ Allocation**	**Reporting Period: Randomization/ Allocation Through Protocol-specified Follow-up Period**	**Reporting Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor**
NSAE	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines
SAE including Cancer and Overdose	Report if: – due to protocol-specified intervention – causes exclusion – participant is receiving placebo run-in or other run-in treatment	Report all	Report if: – drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event

Type of Event	**Reporting Period:** Consent to Randomization/ Allocation	**Reporting Period:** Randomization/ Allocation Through Protocol-specified Follow-up Period	**Reporting Period:** After the Protocol-specified Follow-up Period	Time Frame to Report Event and Follow-up Information to Sponsor
Pregnancy/Lactation Exposure	Report if: – participant has been exposed to any protocol-specified intervention (eg, procedure, washout, or run-in treatment including placebo run-in) Exception: A positive pregnancy test at the time of initial screening is not a reportable event.	Report all	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requiring regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – potential DILI – requiring regulatory reporting	Not required	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event

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

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

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

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

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

8.4.4 Regulatory Reporting Requirements for SAE

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

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

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

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

Note: To meet EU CTR requirements, the Sponsor will report SUSARs to the Eudravigilance database via E2B(R3) electronic ICSR form in compliance with CTR 536/2014.

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.

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

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

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

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

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as 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 ensure that unblinded aggregated efficacy endpoint events and safety data are monitored to safeguard the participants in the study.

8.4.7 Events of Clinical Interest

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

Events of clinical interest for this study include:

- An overdose of study intervention, as defined in Section 8.5. Lenvatinib overdose without an associated adverse event is not considered an ECI.
- Potential DILI events defined as an elevated AST or ALT laboratory value that is greater than or equal to 3X the ULN and an elevated total bilirubin laboratory value that is greater than or equal to 2X the ULN and, at the same time, an alkaline phosphatase laboratory value that is less than 2X the ULN, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

  Note: this does not apply to participants with HCC enrolled in Cohort G.

Cohort G Only: Hepatic ECIs include any of the following events if the events are considered not due to disease progression as judged by the investigator. All of these events (if not associated with disease progression under study) will require holding study treatment, notification of the event(s) to the Sponsor within 24 hours after awareness via electronic media or paper. For dose interval modification, refer to Section 6.6.2 and 6.6.3. For guidance related to the diagnosis and management of hepatic ECIs, refer to Section 6.6.3.5.2:

- ALT:
  a. Among participants with Baseline ALT <2 × ULN: ALT ≥5 × ULN
  b. Among participants with Baseline ALT ≥2 × ULN: ALT >3 × the Baseline level
  c. ALT >500 U/L regardless of baseline level

- Total Bilirubin:
  a. Total bilirubin >3.0 mg/dL

- Regardless of laboratory values, hepatic decompensation diagnosed clinically, including:
  a. New onset clinically detectable ascites requiring intervention for >3 days
  b. Hepatic Encephalopathy
  c. Gastrointestinal bleeding suggestive of portal hypertension (eg, esophageal or gastric varices)

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as follows:

- MK-7684A: ≥3 times the protocol-specified dose
- Pembrolizumab: 1000 mg or greater
- Lenvatinib: any dose above the protocol-prescribed dose if associated with an adverse event
- Chemotherapy: any dose ≥20% over the protocol-specified dose

No specific information is available on the treatment of overdose of MK-7684A, pembrolizumab, lenvatinib, or chemotherapy. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for differentiated thyroid cancer, RCC, and HCC.

All reports of MK-7684A, pembrolizumab, or chemotherapy overdose with and without an AE and all reports of lenvatinib overdose with an AE must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper.

Reports of either MK-7684A or pembrolizumab overdose without any associated clinical symptoms or abnormal laboratory results, should be reported using the terminology "accidental or intentional overdose without adverse effect."

8.6 Pharmacokinetics

NOTE: As of Amendment 11, PK and ADA samples will no longer be collected.

To further evaluate MK-7684A immunogenicity and exposure when administered alone and in combination with other anticancer therapies for the indications evaluated in this study, sample collections for analysis of ADA and PK are currently planned as shown in Section 1.3. Based on emerging data, if ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

To evaluate the exposure of lenvatinib when coadministered with MK-7684A, blood samples will be collected as specified in the SoA (Section 1.3) from all participants. Plasma concentrations of lenvatinib when coadministered with MK-7684A will be measured. Lenvatinib will be analyzed using a population PK approach. Lenvatinib will be quantified by use of validated High-Performance Liquid Chromatography-tandem mass spectroscopy method.

Study sites must have appropriately trained staff and adequate equipment for procuring and processing specimens. Instructions for the collection, handling, and shipping procedures of PK samples will be provided in the laboratory manual.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Biomarkers

As of Amendment 11, blood collections for ctDNA analysis and PBMC 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 in this study as specified in the SoA:

- Blood for genetic analysis
- Blood for ctDNA analysis
- Blood for PBMC analysis
- Newly obtained or Archival tumor specimen or tissue
- Cohort I only: Tumor tissue is required and should be obtained during interval debulking surgery and submitted to the central laboratory. This sample is not required if the participant is unable to undergo interval debulking.

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

Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites.

The planned genetic analysis sample should be obtained predose on Day 1 but may be collected at the next scheduled blood draw, if needed.

8.9 Future Biomedical Research Sample Collection

FBR samples will not be collected in this study.

8.10 Medical Resource Utilization and Health Economics

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

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

Documented informed consent must be obtained before performing any protocol-specific procedure. Results of a test performed before the participant provides documented informed consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days before the first dose of study intervention except for the following:

- Laboratory tests are to be performed within 10 days before randomization/allocation. An exception is hepatitis and HIV testing (if mandated by local health authority), which may be performed up to 28 days before randomization/allocation.
  Note: For Cohort I, Baseline imaging should be performed within 28 days prior to starting lead-in chemotherapy administration.
- Evaluation of ECOG is to be performed within 7 days before starting study intervention.
- For WOCBP, a pregnancy test will be performed within 24 hours to 72 hours before the first dose of study intervention as detailed in Section 5.1. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).
- Archival tumor sample collection is not required to be obtained within 28 days before the first dose of study intervention. Newly obtained tumor tissue may be obtained according to the laboratory manual.
  Note: For Cohort I, newly obtained tissue may be obtained no more than 8 weeks prior to the administration of systemic cytotoxic treatment for the treatment of current OC.

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

Refer to Appendix 7 for country-specific requirements.

8.11.2 Initial Treatment Phase

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.1 through Section 8.10.

8.11.3 Second Course Treatment Phase

See Section 6.1.2 for details concerning Second Course Treatment. Visit requirements are outlined in the SoA (Section 1.3).

8.11.4 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

Participants who discontinue study intervention due to disease recurrence or start of a new anticancer therapy will have Safety Follow-up and then proceed directly to Survival Follow up Phase as described in Section 8.11.5.

The Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study intervention, at the time of the mandatory Safety Follow-up Visit, the Discontinuation Visit procedures and any additional Safety Follow-up procedures should be performed.

8.11.5 Posttreatment Visit

8.11.5.1 Safety Follow-up Visit

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

Participants who are eligible for retreatment with either MK-7684A or pembrolizumab may have up to 2 safety follow-up visits: 1 after the Initial Treatment or First Course and 1 after the Second Course.

As of Amendment 11, once the Safety Follow-up Visit is completed, participants (except those in Cohort B1 and Cohort I) will be discontinued from the study.

8.11.5.2 Efficacy Follow-up Visits

As of Amendment 11, follow-up visits for assessment of efficacy will be discontinued for all participants. The section below is retained for reference.

Participants who complete the protocol-required cycles of study intervention or who discontinue study intervention for a reason other than disease progression will begin Efficacy Follow-up and should be assessed according to the on-treatment imaging schedule (Q9W [63 days ±7 days] through Week 54 and Q12W [84 days ±7 days] thereafter) 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, end of study or if the participant begins retreatment with either MK-7684A or pembrolizumab as detailed in Section 6.1.2. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who completed all efficacy assessments and/or will not have further efficacy assessments must enter Survival Follow-up.

Participants who are eligible to receive retreatment with either MK-7684A or pembrolizumab according to the criteria in Section 6.1.2 will move from Efficacy Follow-up to Second Course when they experience disease progression. Details are provided in the SoA (Section 1.3) for retreatment with either MK-7684A or pembrolizumab.

8.11.5.3 Survival Follow-up Contacts

As of Amendment 11, for all participants, survival follow-up visits will stop. Those participants remaining on active treatment at the time of Amendment 11 should continue to be monitored in the study through the AE reporting period (Section 8.4). The section below is retained for reference.

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

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

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

8.11.6 Vital Status

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

If a participant withdraws consent or is lost to follow-up, vital status (survival information) can be conducted by review of medical records or public records when vital status is in question in accordance with local regulations, unless the participant has specifically withdrawn consent for collection of vital status data.

9 STATISTICAL ANALYSIS PLAN

At implementation of Amendment 12 or upon receipt of investigator letter detailing discontinuation of the MK-7684A clinical program, the following changes apply. The changes listed below supersede any protocol content/instructions from previous amendments. Amendment 12 is adding to the updates implemented in Amendment 11.

- All cohorts are closed to enrollment. This study has enrolled 613 participants.
- Participants receiving MK-7684A will be transitioned to pembrolizumab monotherapy or in combination with another protocol-specified therapy.
- Pembrolizumab 200 mg will be administered IV q3w for all cohorts.
- Pembrolizumab can be sourced locally or centrally.
- Participants with access to approved SOC (eg, pembrolizumab alone or in combination with another protocol-defined therapy) should be considered for discontinuation from the study. Those benefiting from pembrolizumab alone or in combination with another protocol-defined therapy, but unable to access it as SOC outside the study, may continue on study and receive treatment until discontinuation criteria are met. The final required study visit will be the Safety Follow-up Visit.
- All assessments in the SoA will be done per local standard of care.
- Participants who complete study treatment or otherwise meet EOT criteria will be discontinued from the study after the EOT visit and any required safety follow-up visit. If currently receiving protocol-specified therapy that does not include pembrolizumab, the participants will be discontinued from the study.
- There will be no follow-up for survival status. Participants currently in imaging follow-up or survival follow-up are considered to have completed the study and therefore should obtain imaging and further oncological care as per local standard of care. However, standard safety reporting should continue, as applicable.
- Those participants remaining on study at the time of Amendment 12, should continue to be monitored in the study through the AE reporting period (Section 8.4).
- Participants may enroll in an extension study, if available.
  - Participation in this study is ended when the participant is consented for an extension study.
  - The overall study ends when the last participant completes the last study-related contact, withdraws consent, or is lost to follow-up (Section 7.3), or the last participant on active treatment is consented in an extension study.
  - For participants who enter an extension study, all AEs, SAEs, and other reportable safety events must be reported by the investigator in this protocol (parent study) from the time of intervention allocation up to the time of providing documented informed consent for an extension study. Note: Once consented to an extension study, safety events, including those considered related to study intervention, will be collected as instructed in the extension study.

Existing protocol content is retained for historical reference.

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but before the conduct of any analysis, will be documented in an sSAP and referenced in the CSR for the study. Other planned analyses (ie, PROs) will be documented in the sSAP.

9.1 Statistical Analysis Plan Summary

Key elements of the SAP are summarized below. The comprehensive plan is provided in Section 9.2 through Section 9.12.

Study Design Overview	A Multicenter, Open-label, Phase 2 Basket Study of MK-7684A, a Co-formation of Vibostolimab (MK-7684) with Pembrolizumab (MK-3475), With or Without Other Anticancer Therapies in Participants with Selected Solid Tumors (KEYVIBE-005)
Treatment Assignment	Participants in Cohort A1 will be randomly assigned in a 1:1 ratio to either MK-7684A (Arm 1) or pembrolizumab (Arm 2). Participants will be stratified by prior bevacizumab use (yes vs no). For all other cohorts, participants will be nonrandomly allocated to study intervention as detailed in Section 4.1. This is an open-label study.
Analysis Populations	Efficacy and safety analyses will be performed per tumor type. For the randomized cohort (ie, Cohort A1): • Efficacy: ITT • Safety: ApaT For the single-arm cohorts without the safety lead-in phase (Cohort A2, Cohort B1, Cohort C, Cohort D1, and Cohort H): • Efficacy: ApaT • Safety: ApaT For the single-arm cohorts with the safety lead-in phase (ie, Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J): • Efficacy: ApaT and received the RP2D • Safety: ApaT by dose levels • DLT-evaluable population for DLT analysis

Primary Endpoints	For Cohort A1: • ORR per RECIST 1.1 by BICR • PFS per RECIST 1.1 by BICR For Cohort A2 to Cohort H and Cohort J: • ORR per RECIST 1.1 by investigator For Cohort I: • PFS-9 and PFS-12 per RECIST 1.1 by investigator
Statistical Methods for Key Efficacy Analyses	For Cohort A1: • The stratified M&N method [Miettinen, O. and Nurminen, M. 1985] with strata weighted by sample size will be used for analysis of ORR. The primary hypothesis testing for PFS will be evaluated by comparing the experimental group to the control group using a stratified log-rank test. The hazard ratio of PFS and OS 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. For Cohort A2 to Cohort H and Cohort J: • The point estimate of ORR will be provided for each tumor type, together with 95% CI using exact binomial method proposed by Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934]. For Cohort I: • The PFS rates over time (ie, PFS-9 and PFS-12) will be estimated within each arm using the Kaplan-Meier method [Kaplan, E. L. and Meier, Paul 1958].
Statistical Methods for Key Safety Analyses	For Cohort A1: • For analyses in which 95% CIs will be provided for between-treatment differences in the percentage of participants with events, these analyses will be performed using the M&N method [Miettinen, O. and Nurminen, M. 1985]. For Cohort A2 to Cohort J: • Counts and percentages of participants with AEs will be provided per tumor type.
Interim Analyses	For the randomized Cohort A1, 1 efficacy interim analysis will be conducted for administrative purpose not related to any modification of current study. For cohorts with the safety lead-in phase (ie, Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J), data will be examined on a continuous basis using the mTPI design during the safety lead-in phase. Afterwards, safety data will be reviewed periodically by the siDMC for all cohorts in the study.

Multiplicity	For Cohort A1: • The overall type I error over the primary hypotheses is strongly controlled at 2.5% (1-sided), with 1.25% initially allocated to ORR (H1) and 1.25% to PFS (H2). • By using the graphical approach of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] [Maurer, W., et al 2011], if one hypothesis is rejected, the alpha will be shifted to other hypotheses. For Cohort A2 to Cohort J : • No multiplicity adjustment is planned.
Sample Size and Power	There will be 170 participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) randomized with at least 6 months of follow-up and ~147 PFS events at the analysis. The study has ~82% power for detecting a 20-percentage point difference between-treatment arms with an underlying 14% response rate in the control arm at an initially assigned 0.0125 (1-sided) significance level. It is estimated that there will be ~147 events at the PFS final analysis. With 147 PFS events, the study has ~80% power for detecting a HR of 0.6 at an initially assigned 0.0125 (1-sided) significance level. The planned sample size is approximately 30 participants for PD-L1 negative (CPS <1) cervical cancer; approximately 40 participants in each tumor type of dMMR endometrial cancer, pMMR endometrial cancer, HNSCC, 2L biliary cancer, esophageal cancer, TNBC, HCC, bladder cancer, and gastric cancer; and approximately 28 participants for ovarian cancer. Section 9.9 provides the precision of the ORR estimates. The study also includes approximately 10 participants with 1L biliary cancer for safety lead-in purpose.

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.

This study is being conducted as an open-label study, ie, participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is allocated and treatment is assigned.

The Sponsor will generate the randomization schedule for study intervention assignment for the randomized cohort (ie, participants with cervical cancer whose tumors express PD-L1 [CPS ≥1] in Cohort A1) and the randomization will be implemented in IVRS/IWRS.

Although the study is open-label, analyses by treatment arm for the randomized cohort (ie, participants with cervical cancer whose tumors express PD-L1 [CPS ≥1] in Cohort A1) will be limited and documented.

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

- **Objective Response Rate (Cohorts A1, A2 to H and J)**

For the randomized cohort (ie, Cohort A1), ORR is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by BICR.

For the single-arm cohorts except Cohort I (ie, Cohort A2 to Cohort H and Cohort J), ORR is defined as the percentage of participants who achieve a confirmed CR or PR per RECIST 1.1 as assessed by investigator.

- **Progression-free Survival (Cohorts A1 and I)**

For the randomized cohort (ie, Cohort A1), PFS is defined as the time from randomization to the first documented disease progression per RECIST 1.1 by BICR or death due to any cause, whichever occurs first.

For Cohort I, PFS-9 is defined as the proportion of participants free of documented progression per RECIST 1.1 by investigator or death due to any cause at 9 months from the first dose of study intervention. PFS-12 is defined as the proportion of participants free of documented progression per RECIST 1.1 by investigator or death due to any cause at 12 months from the first dose of study intervention.

Secondary

- **Progression-free Survival (Cohorts A2 to J)**

For the single-arm cohorts (ie, Cohort A2 to Cohort J), PFS is defined as the time from the first dose of study intervention to the first documented disease progression per RECIST 1.1 by investigator or death due to any cause, whichever occurs first.

- **Overall Survival (Cohorts A1, A2 to J)**

For the randomized cohort (ie, Cohort A1), OS is defined as the time from randomization to death due to any cause.

For the single-arm cohorts (ie, Cohort A2 to Cohort J), OS is defined as the time from the first dose of study intervention to death due to any cause.

- **Duration of Response (Cohorts A1, A2 to J)**

For participants in the randomized cohort (ie, Cohort A1) who demonstrate confirmed CR or PR per RECIST 1.1 assessed by BICR, duration of response is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

For participants in the single-arm cohorts (ie, Cohort A2 to Cohort J) who demonstrate confirmed CR or PR per RECIST 1.1 assessed by investigator, DOR is defined as the time from the first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

9.4.2 Safety Endpoints

The safety endpoints include AEs, SAEs, and study intervention discontinuation due to AEs. Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests and vital signs. For cohorts with the safety lead-in phase (ie, Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J), the safety endpoints also include the incidence of DLTs. Definition of DLTs are described in Section 6.6.1.

A description of safety measures is provided in Section 8.3.

9.4.3 Patient-reported Outcome Endpoints

The following PRO endpoints will be evaluated for Cohort A1.

- Mean change from baseline in EORTC QLQ-C30 global health status/quality-of-life scores (Items 29 and 30) and physical functioning score (Items 1-5)
- Mean change from baseline in the EQ-5D-5L visual analog scale (VAS)

Other exploratory PRO endpoints as described in Section 4.2.1.5 will be also evaluated. Details will be provided in the sSAP.

9.5 Analysis Populations

Both efficacy and safety analyses will be performed per tumor type.

9.5.1 Efficacy Analysis Populations

The ITT population will serve as the population for all efficacy endpoints other than DOR for the randomized cohort (ie, Cohort A1). All randomized participants will be included in this population. Participants will be analyzed in the treatment group to which they are randomized. The DOR analysis will be based on the population of responders (participants who achieved CR or PR).

The ApaT population will be used for all efficacy endpoints other than DOR for the single-arm cohorts (ie, Cohort A2 to Cohort J). Participants who received at least one dose of study intervention will be included in the ApaT population. For cohorts with the safety

lead-in phase (ie, Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J), this includes all participants from the safety lead-in phase and the efficacy phase on the same dose level. Participants will be analyzed according to the investigational treatment arm to which they were assigned. The DOR analysis will be based on the population of responders (participants who achieved CR or PR).

9.5.2 Safety Analysis Populations

Safety analyses will be conducted in the ApaT population, which consists of all randomized/allocated participants who received at least one dose of study intervention.

For cohorts with the safety lead-in phase (ie, Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J), participants will be analyzed separately by the dose received. For DLT evaluation, the DLT-evaluable population includes ApaT participants that meet the criteria for DLT evaluability (ie, finished DLT evaluation period without a DLT or experienced a DLT in the DLT evaluation period). See Section 4.3.5 and Section 6.6.1 for details.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study intervention 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 all randomized participants who have at least 1 PRO assessment available for the specific endpoint and have received at least 1 dose of the study intervention. Participants will be analyzed in the treatment arm to which they are randomized.

9.6 Statistical Methods

9.6.1 Statistical Methods for Efficacy Analysis

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

For the randomized cohort (ie, Cohort A1), the stratification factor used for randomization (see Section 6.3.2) will be applied to all stratified analyses, in particular, the stratified M&N method [Miettinen, O. and Nurminen, M. 1985], the stratified log-rank test, stratified Cox model. In the event that there are small strata, for the purpose of analysis, strata may be combined to ensure sufficient number of participants, responses, and events in each stratum. Details regarding the pooling strategy will be prespecified in the sSAP before the database lock, and decisions regarding the pooling will be based on a blinded review of response and event counts by stratum.

9.6.1.1 Objective Response Rate

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

For the randomized cohort (ie, Cohort A1), the stratified M&N method will be used for the comparison of ORR between 2 treatment groups. The difference in ORR and its 95% CI from the stratified M&N method with strata weighting by sample size will be reported. The stratification factor used for randomization (See Section 6.3.2) will be applied to the analysis.

9.6.1.2 Progression-free Survival

The nonparametric Kaplan-Meier method will be used to estimate the PFS curve in each tumor type and treatment group. For Cohort I, PFS-9, PFS-12, and their CIs will be estimated using nonparametric Kaplan-Meier method.

For the randomized cohort (ie, Cohort A1), the treatment difference in PFS will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factor used for randomization (See Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model.

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

For the primary analysis, any participant who experiences an event (PD or death) immediately after 2 or more missed disease assessments will be censored at the last disease assessment before the missed visits. In addition, any participant who initiates new anticancer therapy before documented progression will be censored at the last disease assessment before the initiation of new anticancer therapy. Participants who do not start new anticancer therapy and who do not experience an event will be censored at the last disease assessment. If a participant meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. Sensitivity analyses will be performed for comparison of PFS based on investigator's assessment.

To evaluate the robustness of the PFS endpoint per RECIST 1.1 by BICR, 2 sensitivity analyses with different sets of censoring rules will be performed. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anticancer therapy. The second sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to reasons other than CR, whichever occurs later, to be a PD event for participants without documented PD or death. If a participant meets multiple criteria for censoring, the censoring

criterion that occurs earliest will be applied. The censoring rules for the primary and sensitivity analyses are summarized in Table 21.

Table 21 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
Death or progression immediately after ≥ 2 consecutive missed disease assessments, or after new anticancer therapy	Censored at last disease assessment before the earlier date of ≥2 consecutive missed disease assessment and new anticancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment

PD=progressive disease; PFS=progression-free survival.

9.6.1.3 Overall Survival

The nonparametric Kaplan-Meier method will be used to estimate the survival curves in each tumor type and treatment group.

For the randomized cohort (ie, Cohort A1), 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 factor used for randomization (See Section 6.3.2) will be applied to both the stratified log-rank test and the stratified Cox model. Participants without documented death at the time of analysis will be censored at the date the participant was last known to be alive.

9.6.1.4 Duration of Response

If sample size permits, DOR will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of participants who show a confirmed CR or PR will be included in this analysis. Censoring rules for DOR are summarized in Table 22.

For each DOR analysis, a corresponding summary of the reasons responding participants are censored will also be provided. Responding participants who are alive, have not progressed, have not initiated new anticancer treatment, have not been determined to be lost to follow-up, and have had a disease assessment within ~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.

Table 22 Censoring Rules for DOR

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 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 before ≥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)

DOR=duration of response; PD=progressive disease.
Note: 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 Variables

A summary of the primary analysis strategy for the key efficacy endpoints is provided in Table 23.

Table 23 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Analyses			
ORR per RECIST 1.1 by BICR	Testing and estimation (for the randomized cohort): stratified M&N method	ITT (for the randomized cohort)	Participants with missing data are considered nonresponders
ORR per RECIST 1.1 by investigator	Summary statistics with 95% CI using Exact method based on binomial distribution	ApaT (for the single-arm cohorts except Cohort I)	Participants with missing data are considered nonresponders
PFS per RECIST 1.1 by BICR	Testing (for the randomized cohort): stratified log-rank test Estimation (for the randomized cohort): Stratified Cox model with Efron's tie handling method	ITT (for the randomized cohort)	Censored according to rules in Table 21
PFS-9 and PFS-12 per RECIST 1.1 by investigator	Estimation: nonparametric Kaplan-Meier method	ApaT (for Cohort I)	Censored according to rules in Table 21
Key Secondary Analyses			
PFS per RECIST 1.1 by investigator	Summary statistics using Kaplan-Meier method	ApaT (for the single-arm cohorts)	Censored according to rules in Table 21

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
OS	Summary statistics using Kaplan-Meier method Testing (for the randomized cohort): stratified log-rank test Estimation (for the randomized cohort): Stratified Cox model with Efron's tie handling method	ApaT (for the single-arm cohorts) ITT (for the randomized cohort)	Censored at the date participant last known to be alive
DOR per RECIST 1.1 by BICR	Summary statistics using Kaplan-Meier method	Responders in ITT population (for the randomized cohort)	Censored according to rules in Table 22
DOR per RECIST 1.1 by investigator	Summary statistics using Kaplan-Meier method	Responders in ApaT population (for the single-arm cohorts)	Censored according to rules in Table 22

ApaT=all-participants-as-treated; BICR=blinded independent central review; CI=confidence interval; DOR=duration of response; ITT=intent-to-treat; M&N method=Miettinen and Nurminen method; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; RECIST 1.1=Response Evaluation Criteria in Solid Tumors.

9.6.2 Statistical Methods for Safety Analysis

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

For the single-arm cohorts (ie, Cohort A2 to Cohort J), the broad AE categories consisting of the percentage of participants with any AE, a drug-related AE, a serious AE, an AE which is both drug-related and serious, a Grade 3 to 5 AE, a drug-related Grade 3 to 5 AE, and who discontinued due to an AE will be summarized. The number and percentage of participants with increased laboratory toxicity grade shift from baseline will also be provided.

For cohorts with the safety lead-in phase (ie, Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J), dose-limiting toxicities will be listed and summarized.

For the randomized cohort (ie, Cohort A1), the analysis of safety results will follow a tiered approach (Table 24). The tiers differ with respect to the analyses that will be performed. Adverse events (specific terms as well as system organ class terms) are either prespecified as "Tier 1" endpoints or will be classified as belonging to "Tier 2" or "Tier 3" based on observed proportions of participants with an event.

Tier 1 Events

Safety parameters or AEOSI that are identified a priori constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance. AEs that are immune-mediated or potentially immune-mediated are well documented and will be evaluated separately; however, these events have been characterized consistently throughout the pembrolizumab, vibostolimab, and MK-7684A clinical development programs, and determination of statistical significance is not expected to add value to the safety evaluation. Additionally, there are no known AEs associated with participants for which determination of a p-value is expected to impact the safety assessment. Therefore, there are no Tier 1 events in this study.

Tier 2 Events

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

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

Tier 3 Events

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

Table 24 Analysis Strategy for Safety Parameters

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

AE=adverse event; CI=confidence interval; SOC=system organ class.

9.6.3 Statistical Methods for Patient-Reported Outcome Analyses

This section describes the planned analyses for the PRO endpoints in Cohort A1. The time point for the mean change from baseline will be determined based on blinded data review before the database lock for any PRO analysis and documented in the sSAP.

To assess the treatment effects on the PRO score change from baseline in the EORTC QLQ-C30 global health status/quality-of-life scores, physical functioning score, and EQ-5D-5L VAS outcome, a cLDA model proposed by Liang and Zeger [Liang, K-Y. and Zeger, S. L. 2000] will be applied, with the PRO score as the response variable, and treatment, time, the treatment by time interaction, and stratification factor used for randomization (See Section 6.3.2) as a covariate. The treatment difference in terms of LS mean change from baseline will be estimated from this model together with 95% CI. Model-based LS mean with 95% CI will be provided by treatment group for PRO scores at baseline and post-baseline time point.

9.6.4 Demographic and Baseline Characteristics

The number and percentage of participants screened and allocated/randomized and the primary reasons for Screening failure and discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and

concomitant therapies will be summarized by tumor type and treatment either by descriptive statistics or categorical tables.

For the randomized cohort (ie, Cohort A1), 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.

9.7 Interim Analyses

For the randomized Cohort A1, one efficacy interim analysis will be conducted for administrative purpose not related to any modification of current study (eg., further program development planning). It will be conducted after approximately 80 participants are randomized (approximately 40 randomized to each arm) with a minimum of 6 months follow-up and approximately 60 PFS events have occurred. Enrollment will not pause for the IA. Two sets of efficacy bar will be evaluated based on the investigator assessment of ORR and PFS. The results of the interim analyses will be reviewed by siDMC.

- Efficacy Bar 1: ORR difference at least 15% favoring the MK-7684A arm or HR of PFS at least 0.7 favoring the MK-7684A arm.
- Efficacy Bar 2: ORR difference at least 10% favoring the MK-7684A arm or HR of PFS at least 0.8 favoring the MK-7684A arm.

Table 25 and Table 26 show the operating characteristics of the effficacy bars at IA for ORR and for PFS, respectively.

Table 25 Operating Characteristics of Efficacy Bars for ORR

Sample Size	True ORR	Probability of Observing ΔORR ≥ 15%	Probability of Observing ΔORR ≥ 10%
N=80 (40 each arm)	39% vs. 14%	0.87	0.95
N=80 (40 each arm)	34% vs. 14%	0.74	0.87
N=80 (40 each arm)	29% vs. 14%	0.55	0.74
N=80 (40 each arm)	24% vs. 14%	0.32	0.53
N=80 (40 each arm)	19% vs. 14%	0.14	0.29
N=80 (40 each arm)	14% vs. 14%	0.04	0.11
ΔORR=difference of objective response rate (MK-7684A Arm vs. Pembrolizumab Arm).			

Table 26 Operating Characteristics of Efficacy Bars for PFS

PFS Events	True PFS HR	Probability of Observing HR ≤ 0.7	Probability of Observing HR ≤ 0.8
60 (total)	0.55	0.82	0.93
60 (total)	0.60	0.72	0.87
60 (total)	0.65	0.61	0.79
60 (total)	0.70	0.50	0.70
60 (total)	0.80	0.30	0.50
60 (total)	0.90	0.17	0.32
60 (total)	1.00	0.08	0.19

HR=hazard ratio; PFS=progression-free survival.

The analyses planned, endpoints evaluated, and drivers of timing for the randomized Cohort A1 are summarized in Table 27.

Table 27 Summary of Interim and Final Analyses Strategy

Analyses	Key Endpoints	Timing	Estimated Time after First Participant Randomized	Primary Purpose of Analysis
Efficacy Interim Analysis	ORR by investigator PFS by investigator	At least 80 participants randomized with ~ 6 months of follow-up and ~ 60 PFS events has occurred	~ 12 months	Administrative purpose not related to any modification of current study (eg, further program development planning).
Final Analysis	ORR by BICR PFS by BICR	Both ~147 PFS events have occurred and ~6 months after last participant randomized (if the events accrue slower than expected, the Sponsor may conduct the analysis with up to an additional 6 months of follow-up)	~ 18 to 24 months	• Final ORR analysis • Final PFS analysis

BICR=blinded independent central review; ORR=objective response rate; PFS=progression-free survival.

For cohorts with the safety lead-in phase (ie, Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J), data will be examined on a continuous basis using the mTPI design during the safety lead-in phase. Afterwards, safety data will be reviewed periodically by the siDMC for all cohorts in the study (Appendix 1). Details will be specified the siDMC charter.

9.8 Multiplicity

No multiplicity adjustment is planned for the single-arm cohorts (ie, Cohort A2 to Cohort J).

For the randomized cohort (ie, Cohort A1), no multiplicity adjustment is planned for the administrative interim analysis. The study uses the graphical method of Maurer and Bretz [Maurer, W. and Bretz, F. 2013] [Maurer, W., et al 2011] to provide strong multiplicity control for multiple hypotheses. 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.

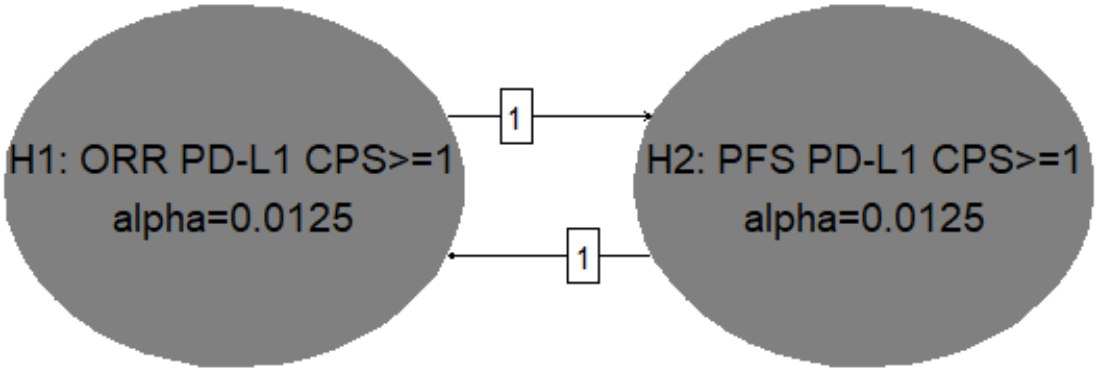
Figure 5 shows the initial 1-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for re-allocation from each hypothesis to the others are shown in the boxes on the lines connecting hypotheses.

The initial α assigned to ORR and PFS will be 0.0125 and 0.0125, respectively. If ORR hypothesis is rejected, the corresponding alpha can be reallocated to PFS. If the PFS hypothesis is rejected, the corresponding alpha can be reallocated to ORR.

Table 28 shows the possible α levels as well as the approximate treatment difference required to reach the bound (ΔORR), assuming underlying 14% and 34% response rates in the control and experimental groups, respectively.

Table 29 shows the efficacy boundaries and properties for the possible α levels for the PFS analysis.

Figure 5 Multiplicity Diagram for Type I Error Control



CPS=combined positive score; ORR=objective response rate; PD-L1=programmed cell death 1 ligand 1; PFS=progression-free survival.

Table 28 Possible α Levels and Approximate ORR Difference Required to Demonstrate Efficacy for Objective Response

α	~Δ Objective Response Rate (ORR)	Power (ΔORR=0.2)
0.0125	0.143	0.816
0.025	0.125	0.881
ORR=objective response rate.		

Table 29 Efficacy Boundaries and Properties for Progression-Free Survival Analyses

Analysis	Value	α=0.0125	α=0.025
N = 170 Events: 147 Month: 18	Z	2.2414	1.9600
	p (1-sided) [a]	0.0125	0.0250
	HR at bound[b]	0.6909	0.7237
	P(Cross) if HR=1[c]	0.0125	0.0250
	P(Cross) if HR=0.6[d]	0.8038	0.8722

HR=hazard ratio.
The number of events and timings are estimated.
[a] *p* (1-sided) is the nominal α for group sequential testing.
[b] HR at bound is the approximate HR required to reach an efficacy bound.
[c] P(Cross) if HR=1 is the probability of crossing a bound under the null hypothesis.
[d] P(Cross) if HR=0.6 is the probability of crossing a bound under the alternative hypothesis.

9.9 Sample Size and Power Calculations

The study will randomize approximately 170 participants with cervical cancer whose tumors express PD-L1 (CPS ≥1) in a 1:1 ratio into the MK-7684A and pembrolizumab arms. ORR and PFS are primary endpoints for this cohort, with OS and DOR as the secondary endpoints. The analysis will be performed after both criteria have been met: (1) at least 6 months of follow-up since last participant is randomized and (2) ~147 PFS events have been observed.

Based on the 170 participants with at least 6 months of follow-up, the power of the ORR testing at the initially allocated α=0.0125 (1-sided) approximately 81.6% to detect a 20-percentage point difference between an underlying 14% ORR in the pembrolizumab arm (based on data from KEYNOTE-158 Cohort E for participants with cervical cancer with PD-L1-positive tumors [CPS ≥1], [Chung, H. C., et al 2019]) and a 34% ORR in the MK-7684A arm.

For the PFS endpoint, based on a target number of 147 events at the PFS analysis, the study has approximately 80.4% power to detect a hazard ratio of 0.6 at the initially allocated α=0.0125 (1-sided). Note that the above power calculations are based on a constant hazard ratio assumption.

The above sample size and power calculations for PFS also assume the following:

- PFS follows an exponential distribution with a median of 2.1 months for the pembrolizumab group (based on data from KEYNOTE-158 Cohort E for participants with cervical cancer with PD-L1-positive tumors [CPS ≥1], [Chung, H. C., et al 2019]).
- Enrollment period of 12 months.
- Monthly dropout rate of 2% for PFS.
- A follow-up period of 6 months for PFS after the last participant is randomized.

The sample size and power calculations were performed using EAST 6.4.

The study will allocate approximately 30 participants with cervical cancer whose tumors do not express PD-L1 (CPS <1) to MK-7684A (Arm 1). In addition, the study will allocate approximately 40 participants to each of the following single-arm cohorts: Cohort B1 to Cohort H and Cohort J; and approximately 28 participants to Cohort I. Table 30 shows the 2-sided 95% confidence interval for ORR with 30 or 40 participants for different observed response rates based on the method of Clopper and Pearson (1934) [Clopper, C. J. and Pearson, E. S. 1934].

Table 30 2-sided 95% Confidence Interval for ORR with 30 or 40 Participants

Total Sample Size per Arm	Observed Number of Responses	Observed ORR	95% CI
30	6	20.0%	(7.7%, 38.6%)
30	8	26.7%	(12.3%, 45.9%)
30	9	30.0%	(14.7%, 49.4%)
30	12	40.0%	(22.7%, 59.4%)
40	8	20.0%	(9.1%, 35.6%)
40	10	25.0%	(12.7%, 41.2%)
40	12	30.0%	(16.6%, 46.5%)
40	14	35.0%	(20.6%, 51.7%)
40	16	40.0%	(24.9%, 56.7%)
40	18	45.0%	(29.3%, 61.5%)
40	20	50.0%	(33.8%, 66.2%)
40	22	55.0%	(38.5%, 70.7%)
40	24	60.0%	(43.3%, 75.1%)
40	26	65.0%	(48.3%,79.4%)
40	28	70.0%	(53.5%, 83.4%)
40	30	75.0%	(58.8%, 87.3%)
40	32	80.0%	(64.4%, 90.9%)

CI=confidence interval; ORR=objective response rate.

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the between-group treatment effect (for the randomized cohort) for ORR and PFS will be estimated and plotted within each category of the following subgroup variables:

- Geographic region (US, EU, ROW)
- ECOG performance status (0, 1)
- Age category (<65 years, ≥65 years)
- Race (white, all others)
- Brain metastasis at baseline (presence, absence)
- Liver metastasis at baseline (presence, absence)
- Prior bevacizumab use (yes vs no)
- HPV status (yes vs no)
- PD-L1 Status (CPS ≥10 vs CPS<10)

Details of subgroup analyses, if any, will be documented in the sSAP.

9.11 Compliance (Medication Adherence)

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

9.12 Extent of Exposure

Extent of Exposure for a participant is defined as the number of cycles in which the participant receives the study medication. 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)

I. Introduction

A. Purpose

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, planning, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with MSD's global standards, local and/or national regulations (including all applicable data protection laws and regulations), Regulation (EU) 536/2014, the International Council for Harmonisation Good Clinical Practice (ICH GCP) E6 and ICH General Considerations for Clinical Studies E8, 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 (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. Input may be considered from a broad range of stakeholders, including patient advocacy groups/patients representing the trial population, caregivers, and

healthcare providers to ensure operational feasibility. Trial design also includes proactive identification of critical to quality factors utilizing a risk-based approach. Plans are then developed to assess and mitigate risks to those factors as appropriate during the trial. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

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

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Participant Protection

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

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

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

B. Safety

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

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Trial designs include procedures and systems for the identification, monitoring, and reporting of safety concerns. 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.

During trial planning, the need for an independent Data Monitoring Committee (DMC) is assessed. DMC review of data accumulated during the conduct of the trial is integral to the well-being of trial participants.

C. Confidentiality

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

D. Genomic Research

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

E. Trial Results

At the time of providing informed consent and in accordance with local laws and regulations, participants should be informed about the plans for availability of trial results.

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 medical record review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

10.1.3 Data Protection

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

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

The participant must be informed that their 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 their 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.

The Sponsor has EU-approved Binding Corporate Rules since 2017, covering all aspects of its Global Privacy Program (Corporate Policy 20), and is self-certified pursuant to the EU-US Data Privacy Framework.

10.1.3.1 Confidentiality of Data

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

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this

process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked before transmission to the Sponsor.

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

10.1.3.3 Confidentiality of IRB/IEC Information

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

10.1.4 Committees Structure

10.1.4.1 Standing Internal Data Monitoring Committee

To supplement the routine monitoring outlined in this protocol, a separate siDMC will monitor the interim data from this study. The siDMC is comprised of members of Sponsor Senior Management, none of whom are directly associated with the conduct of this study. The siDMC will monitor the study at an appropriate frequency (as detailed in the charter) for evidence of adverse effects of study intervention and dose selection, as described in the detailed monitoring guidelines. The siDMC will determine whether the study should continue (or other modifications, prespecified or otherwise, should be made) according to the protocol, considering the overall risk and benefit to study participants. The siDMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both participant safety and the continued ethical integrity of the study.

Specific details regarding responsibilities of the siDMC will be described in a separate charter that is reviewed and approved by the siDMC.

10.1.5 Publication Policy

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

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

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

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the FDAAA of 2007 and the EMA clinical trials Regulation 536/2014, 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, https://euclinicaltrials.eu, or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trials Regulation 536/2014 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 Regulation 536/2014, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

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

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

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

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

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

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

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

10.1.8 Data Quality Assurance

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

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

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

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

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

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

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

Records and documents, including participants' documented informed consent, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period (eg, EU CTR: 25 years after the end of the study). No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

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

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

10.1.10 Study and Site Closure

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

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

10.2 Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 31 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Laboratory safety tests will be performed within 72 hours before dosing.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Refer to Appendix 7 for country-specific requirements.

Table 31 Protocol-required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**			
Hematology	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV[a] MCH[a]	WBC count with Differential: Neutrophils[b] Lymphocytes Monocytes Eosinophils Basophils	
Chemistry	BUN[c]	Potassium	AST/SGOT	Total bilirubin (and direct bilirubin, if total bilirubin is above the ULN)
	Albumin	Bicarbonate[a]	Chloride	Phosphorous[a]
	Creatinine clearance or GFR	Sodium	ALT/SGPT	Total Protein
	Glucose	Calcium	Alkaline phosphatase	Magnesium (**Cohort B2 and Cohort G only**)
	TSH[d]	T4 (FT4 is acceptable)	LDH	Amylase[e]
	Lipase[e]	T3 (FT3 is acceptable)	CO_2 (bicarbonate is acceptable)[a]	
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick[f] • Microscopic examination or other standard diagnostic evaluation (if blood or protein is abnormal)			
Pregnancy Testing	• Highly sensitive serum or urine hCG pregnancy test (as needed for WOCBP)			
Other Screening Tests	• FSH (as needed in WONCBP only) • PT/INR and aPTT/PTT[g] • Serology (HIV antibody, HbsAg, and hepatitis C virus antibody). Note: certain ex-US sites require testing for HIV, HBV, and HCV during Screening. Consult with regional health authorities and institutional standards to confirm if such testing is applicable.			

Laboratory Assessments	Parameters
Other Screening Tests (**Cohort I only**)	• CEA • Cortisol • CA-125 will be assessed at screening and then according to the same schedule as imaging (±14 days) by a local laboratory.
Other Tests (**Cohort I only**)	• Cortisol – to be collected within 7 days prior to interval debulking surgery and prior to administration of study treatment in the next 2 treatment cycles following surgery for participants undergoing interval debulking only.

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C1D1=Cycle 1 Day 1; CA-125=cancer antigen-125; CEA=carcinoembryonic antigen; CO2=carbon dioxide; FSH=follicle-stimulating hormone; FT3=free triiodothyronine; FT4=free thyroxine; GFR=glomerular filtration rate; HbsAg=hepatitis B surface antigen; HBV=hepatitis B virus; hCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; LDH=lactate dehydrogenase; MCH=mean corpuscular hemoglobin; MCV=mean corpuscular volume; PT=prothrombin time; PTT=partial thromboplastin time; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; ULN=upper limit of normal; WBC=white blood cell; WOCBP=women of childbearing potential; WONCBP=women of nonchildbearing potential.

[a] Performed only if considered local standard of care.

[b] Absolute, determined per institutional standard.

[c] Urea is acceptable if BUN is not available as per institutional standard.

[d] Participants may be dosed in subsequent cycles after C1D1 while thyroid function tests are pending.

[e] After Cycle 1 Day 1, retrospective review of lipase and amylase results is allowed when the results are not available prior to dosing.

[f] **Cohorts B2 and G only**: If urine protein is ≥2+ (first occurrence or a subsequent increase in severity of urine dipstick proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection should be done to quantify the 24-hour urine protein excretion.

[g] Performed as part of the Screening assessment and as clinically indicated for participants taking anticoagulants.

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 includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

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

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."
- Lenvatinib overdose without an associated adverse event is not reportable as an AE. Refer to Section 8.5 for the definition of overdose.
- Any new cancer (that is not a condition of the study). Progression of the cancer under study is not a reportable event. Refer to Section 8.4.6 for additional details.

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

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

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

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

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

10.3.4 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 study intervention cause the AE?

- The determination of the likelihood that the study intervention 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 study intervention and the AE; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study intervention caused the AE:**

  - **Exposure:** Is there evidence that the participant was actually exposed to the study intervention 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 study intervention? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with IMP)?

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

  - **Dechallenge:** Was the study intervention 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 study intervention; (3) the study is a single-dose drug study; or (4) study intervention(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the study intervention 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) study intervention(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 STUDY INTERVENTION, OR IF RE-EXPOSURE TO THE STUDY INTERVENTION 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 IRB/IEC.

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

- The assessment of relationship will be reported on the CRFs/worksheets by an investigator who is a qualified physician according to their 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 study intervention relationship).

  - Yes, there is a reasonable possibility of study intervention relationship:
    - There is evidence of exposure to the study intervention. The temporal sequence of the AE onset relative to the administration of the study intervention is reasonable. The AE is more likely explained by the study intervention than by another cause.
  - No, there is not a reasonable possibility of study intervention relationship:
    - Participant did not receive the study intervention OR temporal sequence of the AE onset relative to administration of the study intervention is not reasonable OR the AE is more likely explained by another cause than the study intervention. (Also entered for a participant with overdose without an associated AE.)

- The investigator must review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

- 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 their 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.

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

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

- The primary mechanism for reporting to the Sponsor will be the EDC tool.
  - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
  - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
  - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).

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

SAE reporting to the Sponsor via paper CRF

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

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

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with 2 FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraceptive Requirements

10.5.2.1 Cohort A1, Cohort A2, Cohort B1, Cohort C Cohort D1, and Cohort H (MK-7684A or Pembrolizumab Monotherapy)

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency[b] *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[c] • IUS[d] • 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.
Highly Effective Contraceptive Methods That Are User Dependent[b] *Failure rate of <1% per year when used consistently and correctly*.
• Combined (estrogen- and progestogen- containing) hormonal contraception[c] - Oral - Intravaginal - Transdermal - Injectable
• Progestogen-only hormonal contraception[c] - Oral - Injectable
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] Typical use failure rates are higher than perfect-use failure rates (ie, when used consistently and correctly). [c] If locally required, in accordance with CTFG guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation. [d] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.2.2 Cohort B2, Cohort D2, Cohort E, Cohort F, Cohort G, Cohort I, and Cohort J

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] • 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] IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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

Not applicable.

10.7 Appendix 7: Country-specific Requirements

10.7.1 Canada

Sites in Canada will not be participating in the new chemotherapy cohorts (D2, I, and J) added in Amendment 05.

10.7.2 France

Note: Data collection for race and ethnicity are not permitted per country regulations.

Inclusion Criteria

Cohort D2 and E (MK-7684A + Chemotherapy)

16. Male participants are eligible to participate if they agree to the following during the intervention period and for at least 120 days after the last dose of chemotherapy:

    - Refrain from donating sperm

    PLUS either:

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

    OR

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

Cohort D2 and E (MK-7684A + Chemotherapy)

19. 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

- Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:
  - MK-7684A: 120 days
  - Chemotherapy: 210 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 is more stringent than the requirements above, the local label requirements are to be followed.
- Has a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within either 24 hours (urine) or 72 hours (serum) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.7.
- Has had her medical history, menstrual history, and recent sexual activity reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

26. Has adequate organ function as defined in Table 5. Specimens must be collected within 10 days before the start of study intervention.

Table 5 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	>1500/µL
Platelets	>100,000/µL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine AND[b]/OR Measured or calculated[c] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN AND[b]/OR ≥30 mL/min for participants with creatinine levels >1.5 × institutional ULN ≥60 mL/min for participants with creatinine levels >1.5 × institutional ULN (**Cohort D2 and E only**)[d]
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)
Albumin (**Cohort J only**)	≥ 2.5 g/dL
Coagulation	
INR or PT aPTT/PTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) = alanine aminotransferase (serum glutamic-pyruvic transaminase); ANC=absolute neutrophil count; aPTT = activated partial thromboplastin time; AST (SGOT) = aspartate aminotransferase (serum glutamic-oxaloacetic transaminase); GFR=glomerular filtration rate; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; ULN=upper limit of normal.

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.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell transfusion within last 2 weeks.

[b] Applicable only when local guidelines require both assessments.

[c] CrCl should be calculated per institutional standard.

[d] The cisplatin product label should be followed for acceptable creatinine clearance rates.

Cohort I (MK-7684A + Chemotherapy)

Female participants:

19. A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least 1 of the following conditions applies:

a) Not a WOCBP as defined in Appendix 5

OR

b) A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the Treatment Period and for at least 120 days following the last dose of MK-7684A, and at least 210 days following the last dose of chemotherapy or bevacizumab.

Cohort J (MK-7684A + Chemotherapy)

Male participants:

16. In France, men participating in the study must use an effective method of contraception during study intervention and at least 6 months after stopping study intervention with oxaliplatin.

Exclusion Criteria

In addition to the criteria listed in Section 5.2, participants eligible for the following cohorts must be excluded if the participant:

Cohort D2 (MK-7684A + Chemotherapy)

61. Participants with Grade ≥2 audiometric hearing loss (25 decibels in 2 consecutive wave ranges) are not eligible for treatment with cisplatin.

Cohort E (MK-7684A + Chemotherapy)

62. Has a hearing impairment.

63. Has a pathology(ies) that is a contraindication to hyperhydration before chemotherapy administration.

64. Is unable to tolerate use of phenytoin.

65. DPD-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.

Cohort I (MK-7684A + Chemotherapy)

66. Participant has a hypersensitivity to Chinese hamster ovary (CHO) cell products or other recombinant human or humanized antibodies.

Note: This only applies to participants who will receive bevacizumab.

Cohort J (MK-7684A + Chemotherapy)

67. Participants with QT/QTc interval longer than 450 msec for men and longer than 470 msec for women on the inclusion ECG.

68. DPD-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.

Pregnancy Testing (**Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, and Cohort H only**)

Pregnancy testing (urine or serum as required by local regulations) should be conducted at least monthly intervals during treatment as well as at the end-of-study treatment.

Pregnancy Testing (**Cohort I only**)

WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to starting lead-in chemotherapy and again within either 24 hours (urine) or 72 hours (serum) prior to C1D1 as outlined in Appendix 5.

HIV testing and Hepatitis B/C Screening

HIV testing and hepatitis B/C screening are required evaluations for study entry and need to be performed to evaluate eligibility. This testing can be performed at any time during the Screening period.

Additional Requirements for Participants Enrolled in Cohort D2

Physical Examination

Audiogram to be completed at Screening. If any hearing issues arise, an additional audiogram will be performed.

Additional Requirements for Participants Enrolled in Cohort E

Safety Assessments

At least 1 oncogeriatric consultation should be obtained for study participants meeting the treatment center's age guidelines.

Physical Examination

Audiogram to be completed at Screening. If any hearing issues arise, an additional audiogram will be performed.

Additional Requirements for Participants Enrolled in Cohort J

For participants receiving oxaliplatin:

- A 12-lead ECG must be performed before and after intravenous administration of oxaliplatin.

For participants receiving capecitabine and oxaliplatin:

- Please refer to the updated SmPC for these marketed products or the website http://base-donnees-publique.medicaments.gouv.fr, which presents the updated version of the SmPC of the medicines.

10.7.3 Germany

Sites in Germany will not be participating in Cohort J.

Section 1.3 – Schedule of Activities (**Cohort E**)

DPD deficiency testing is required at screening for participants.

Pregnancy Testing (**Cohort A1, Cohort A2, Cohort B1, Cohort C, Cohort D1, and Cohort H only**)

Pregnancy testing (urine or serum as required by local regulations) should be conducted at least monthly intervals during treatment as well as at the end-of-study intervention.

Pregnancy Testing (**Cohort I only**):

WOCBP require a negative pregnancy test within either 24 hours (urine) or 72 hours (serum) prior to starting lead-in chemotherapy and again within either 24 hours (urine) or 72 hours (serum) prior to C1D1 as outlined in Appendix 2.

More frequent pregnancy testing may be performed if required by local regulations or clinically indicated.

HIV testing and Hepatitis B/C Screening

HIV testing and hepatitis B/C screening are required evaluations for study entry and need to be performed to evaluate eligibility. This testing can be performed at any time during the Screening period.

Section 5.2 – Exclusion Criteria (**Cohort E**)

DPD-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 (**Cohort I only**)

Laboratory tests are to be performed within 7 days prior to the initiating chemotherapy in the Lead-in Period. An exception is HIV and hepatitis testing which may be done up to 56-day Screening Period prior to randomization.

LVEF Assessment (**Cohort B2 and Cohort G only**)

In Germany, MUGA is not permitted for LVEF assessment, and ECHO should be the method of choice.

Legally Acceptable Representative

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

10.7.4 Italy

Section 1.3 – Schedule of Activities (**All Cohorts**)

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

Section 1.3 – Schedule of Activities (**Cohort E and Cohort J only**)

DPD deficiency testing is required at screening for participants.

Pregnancy Testing (**All Cohorts**)

Pregnancy testing (urine or serum as required by local regulations) should be conducted at least monthly intervals during treatment, at the time of study intervention discontinuation, and 1 month after the last dose of study intervention.

Section 5.2 – Exclusion Criteria (**All Cohorts**)

- Known history of HIV infection
- History of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as detectable HCV RNA [qualitative]) infection

Section 5.2 – Exclusion Criteria (**Cohort E and Cohort J only**)

DPD-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.

Additional Requirements for Participants Enrolled in Cohort J

Participants with significant cardiovascular impairment, including myocardial infarction, within 6 months of the first dose of study intervention should be excluded.

10.7.5 Japan

Carboplatin/paclitaxel regimen for Cohort I

In Japan, the following regimen is not used in this study:

- Carboplatin AUC2 or AUC2.7 QW plus paclitaxel 60 mg/m^2 QW

Section 6.1 Study Intervention(s) Administered

Table 6 Study Interventions

Pembrolizumab and gemcitabine used in this study are categorized as “test product(s)” in Japan.

10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
1L	first-line
2L	second-line
5-FU	5-fluorouracil
5-HT3	5-hydroxytryptamine
AASLD	American Association for the Study of Liver Diseases
Ab	antibody
ADA	antidrug antibodies
ADL	activities of daily living
ADR	adverse drug reaction
AE	adverse event
AEOSI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ApaT	All-Participants-as-Treated
ART	anti-retroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the curve
AxMP	auxiliary medicinal product
BCLC	Barcelona Clinical Liver Cancer
BICR	blinded independent central review
BP	blood pressure
BRCA	breast cancer susceptibility gene
BRCAm	breast cancer susceptibility gene mutated
BSA	body surface area
BTC	bile tract cancer
BW	body weight
C1	Cycle 1

Abbreviation	Expanded Term
C2	Cycle 2
CAP	College of American Pathologists
CAPOX	capecitabine and oxaliplatin
CBC	complete blood count
CCA	cholangiocarcinoma
CD137	cluster of differentiation 137
CD155	cluster of differentiation 155
CD28	cluster of differentiation 28
CD3ζ	cluster of differentiation 3 zeta
CD4	cluster of differentiation 4
CD8	cluster of differentiation 8
CEA	carcinoembryonic antigen
CEP17	chromosome 17 centromere
CG	Cockcroft-Gault
CI	confidence interval
CISH	chromogenic in situ hybridization
CL	clearance
cLDA	constrained longitudinal data analysis
CL/F	apparent total body clearance
Cmax	maximum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COPD	chronic obstructive pulmonary disorder
CPS	combined positive score
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
CRU	clinical research unit
CSR	clinical study report

Abbreviation	Expanded Term
CT	computed tomography
CTCAE 5.0	Common Terminology Criteria for Adverse Events, Version 5.0
ctDNA	circulating tumor DNA
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
Ctrough	concentration at the end of the dosing period
CYP	cytochrome P450
D1	Day 1
D15	Day 15
D5	Day 5
D8	Day 8
DCR	disease control rate
DDI	drug-drug interaction
DILI	drug-induced liver injury
DISH	dual in situ hybridization
DLT	dose-limiting toxicity
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DNAM-1	DNAX accessory molecule-1
DOR	duration of response
DPD	dihydropyrimidine dehydrogenase
DVT	deep vein thrombosis
ECG	electrocardiogram
ECHO	echocardiogram
ECI	event of clinical interest
ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic Case Report Form
EDC	electronic data collection
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate

Abbreviation	Expanded Term
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOC	epithelial ovarian cancer
EORTC	European Organisation for Research and Treatment of Cancer
ePROs	electronic patient-reported outcomes
EQ-5D-5L	EuroQoL 5-dimension 5-level
ER	estrogen receptor
ESCC	squamous cell carcinoma of the esophagus
EU CTR	European Union Clinical Trial Regulation
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	formalin-fixed, paraffin embedded
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FIGO	International Federation of Gynecology and Obstetrics
FISH	fluorescent in situ hybridization
FoxP3	forkhead box protein P3
FP	cisplatin and 5-FU treatment regimen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor
GEJ	gastroesophageal junction
GFR	glomerular filtration rate
GI	gastrointestinal
GM CSF	granulocyte macrophage colony-stimulating factor
HbcAb	hepatitis B core antibody
HbsAb	hepatitis B surface antibody
HbsAg	hepatitis B surface antigen

Abbreviation	Expanded Term
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
hCG	human chorionic gonadotropin
HCV	hepatitis C virus
HECI	hepatic events of clinical interest
HER2/neu	human epidermal growth factor receptor-2/neu
HGSC	high grade serous carcinoma
HIV	human immunodeficiency virus
HNSCC	head and neck squamous cell carcinoma
HPV	human papilloma virus
HR	hazard ratio
HRD	homologous recombination repair deficient
HRCT	high-resolution computed tomography
HRQoL	health-related quality-of-life
HRR	homologous recombination repair
HRT	hormone replacement therapy
HUVEC	human umbilical vein endothelial cell
IA	Interim analysis
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
iCPD	confirmed progressive disease by iRECIST
iCR	complete response by iRECIST
iCRO	imaging CRO
ID	identification
IDO1	indoleamine-pyrrole 2,3 dioxygenase-1
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma

Abbreviation	Expanded Term
Ig	immunoglobulin
IgG1	immunoglobulin G1
IgG4	immunoglobulin G4
IgV	immunoglobulin-variable
IHC	immunohistochemistry
IIR	independent imaging review
IL-10	interleukin-10
ILD	interstitial lung disease
IMP	investigational medicinal product
IND	Investigational New Drug
INR	international normalized ratio
IO	immune-oncology
iPR	partial response by iRECIST
irAEs	immune-related AEs
IRB	Institutional Review Board
iRECIST	Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics
IRT	interactive response technology
iSD	stable disease by iRECIST
ITT	intent-to-treat
IUD	intrauterine device
IUO	Investigational Use Only
iUPD	unconfirmed progressive disease by iRECIST
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
IVD	in vitro diagnostic
IVRS	interactive voice response system
IWRS	integrated web response system
Ki	inhibitor constant; concentration required to produce half-maximal inhibition
KIT	mast/stem cell growth factor receptor Kit

Abbreviation	Expanded Term
KM	Kaplan-Meier
LAM	lactational amenorrhea method
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
LS	least squares
LVEF	left ventricular ejection fraction
M&N	Miettinen and Nurminen method
mAb	monoclonal antibody
MAPK	mitogen-activated protein kinase
MASCC	Multinational Association of Supportive Care in Cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MIDS	mononuclear immune cell density score
mm Hg	millimeters of mercury
MMR	mismatch repair
mRECIST	modified Response Evaluation Criteria in Solid Tumors
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
mTPI	modified toxicity probability interval
MUGA	multiple-gated acquisition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	nonevaluable
NED	no evidence of disease
NIMP	noninvestigational medicinal product

Abbreviation	Expanded Term
NSCLC	non–small cell lung cancer
NDA	New Drug Application
NK	natural killer
NKT	natural killer T
NYHA	New York Heart Association
OC	ovarian cancer
ONJ	osteonecrosis of the jaw
OR	objective response
ORR	objective response rate
ORRWk24	objective response rate at Week 24
OS	overall survival
OTC	over-the-counter
PARP	poly(adenosine-ribose) polymerase
PBMC	peripheral blood mononuclear cell
PBPK	physiologically based PK
pCR	pathological complete response
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death 1 ligand 1
PD-L2	programmed cell death 1 ligand 2
PDGFRα	platelet-derived growth factor receptor alpha
PET	positron emission tomography
PFS	progression-free survival
Pgp	P-glycoprotein
PgR	progesterone receptor
PK	pharmacokinetic(s)
PKCθ	protein kinase C-theta
pMMR	mismatch repair proficient
po	orally

Abbreviation	Expanded Term
PR	partial response
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome
PSA	prostate-specific antigen
PT	prothrombin time
PVR	poliovirus receptor
PVRL-2	poliovirus receptor-related 2
Q2W	every 2 weeks
Q3W	every 3 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
qd	once daily
QW	once weekly
QoL	Quality-of-life
QLQ-C30	Quality-of-life questionnaire core 30
QLQ-CX24	cervical cancer-specific quality-of-life questionnaire
QTc	corrected QT interval
QTcF	corrected QT interval by Fridericia
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RET	proto-oncogene tyrosine-protein kinase receptor RET
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RPLS	reversible posterior leukoencephalopathy syndrome
S6	ribosomal protein S6
S6K	ribosomal protein S6 kinase
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease

Abbreviation	Expanded Term
SGCTG	Scottish Gynaecological Cancer Trials Group
SGOT	serum glutamic-oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SHP-1	Src homology 2 domain-containing protein tyrosine phosphatase 1
SHP-2	Src homology 2 domain-containing protein tyrosine phosphatase 2
siDMC	Standing Internal Data Monitoring Committee
SIM	Site Imaging Manual
SJS	Stevens-Johnson Syndrome
SLAB	supplemental laboratory test(s)
SmPC	Summary of Product Characteristics
SNP	single nucleotide polymorphism
SoA	schedule of activities
SOC	standard of care
SOP	Standard Operating Procedures
sSAP	supplemental Statistical Analysis Plan
SUSAR	suspected unexpected serious adverse reaction
TACE	transarterial chemoembolization
TBL	total bilirubin
TEN	toxic epidermal necrolysis
TIDM	type I diabetes mellitus
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIL	tumor-infiltrating lymphocyte
Tim-3	T-cell immunoglobulin and mucin domain-containing-3
TNM	Classification of Malignant Tumors
TNBC	triple-negative breast cancer
TNF	tumor necrosis factor
TPS	tumor proportion score
Tregs	regulatory T-cells
TTD	time to deterioration
TTP	time to progression

Abbreviation	Expanded Term
TTR	time to response
UC	urothelial carcinoma
ULN	upper limit of normal
UPCR	urine protein-to-creatinine ratio
US	United States
Vc	volume of the central compartment
VAS	Visual Analog Scale
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
WBC	white blood cell
WOCBP	woman/women of childbearing potential
WONCBP	woman/women of nonchildbearing potential
XP	cisplatin and capecitabine treatment regimen
ZAP70	zeta-chain-associated protein kinase

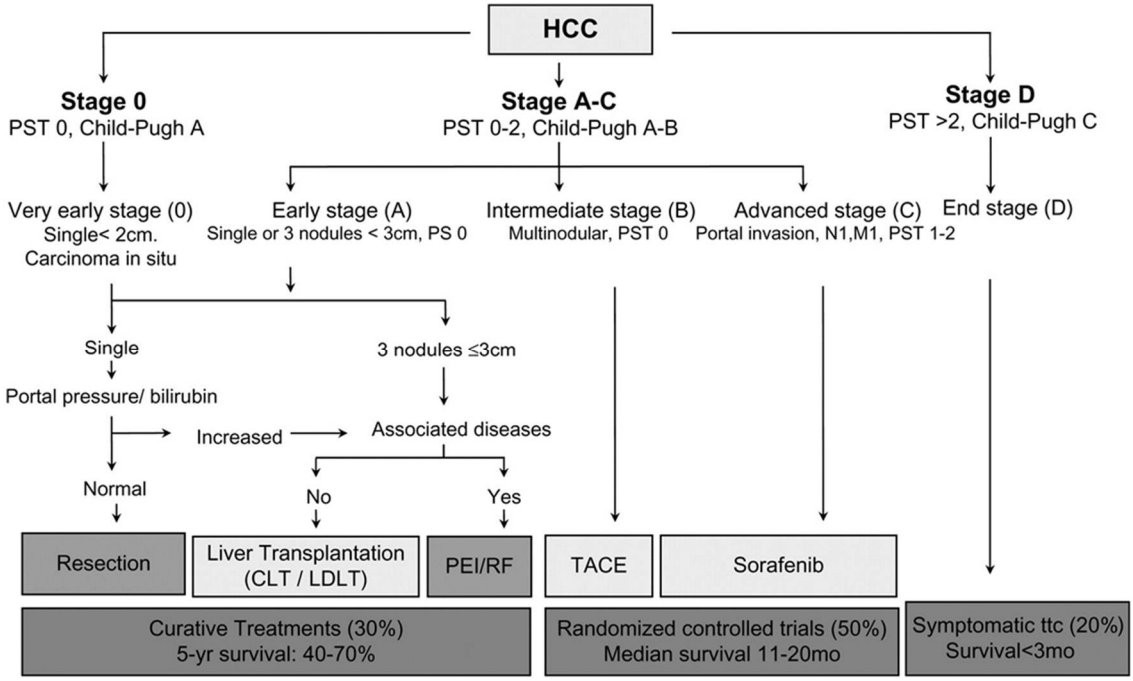
10.9 Appendix 9: New York Heart Association Cardiac Disease Classification

The New York Heart Association (NYHA) Cardiac Disease Classification provides a functional and therapeutic classification for the prescription of physical activity for cardiac participants. On the basis of NYHA definitions, participants are to be classified as follows:

Class	Definition
Class I	Participants with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Participants with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Participants with marked limitation of activity; they are comfortable only at rest.
Class IV	Participants who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.
Adapted from The Criteria Committee of the New York Heart Association, 1994 [Dolgin, M., et al 1994] [Dolgin, M., et al 1994a].	

10.10 Appendix 10: Barcelona Clinic Liver Cancer Staging System

The BCLC staging system is shown below:



CLT = cadaveric liver transplantation; HCC = hepatocellular carcinoma; LDLT = living donor liver transplantation; PEI = percutaneous ethanol injection; PST = performance status test; RF = radio frequency (ablation); TACE = transarterial chemoembolization.

[Llovet, J. M., et al 2008]

10.11 Appendix 11: Child-Pugh Score

The Child-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation.

Scoring

The score employs 5 clinical measures of liver disease. Each measure is scored from 1 to 3, with 3 indicating most severe derangement.

Measure	1 point	2 points	3 points
Total bilirubin[a] (mg/dL)	<2.0	2.0 to 3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
INR[b,c] Or Prothrombin time, prolongation (seconds)	<1.7 <4.0 above ULN	1.7 to 2.3 4.0-6.0 above ULN	>2.3 >6.0 above ULN
Ascites	None	Mild (easily controlled by medication)	Moderate to Severe (poorly controlled)
Hepatic encephalopathy[d]	None	Grade I-II (mild or moderate)	Grade III-IV (severe or coma)

[a] In primary sclerosing cholangitis and primary biliary cirrhosis, the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 µmol/L (4 mg/dL) and the upper limit for 2 points is 170 µmol/L (10 mg/dL).

[b] Different textbooks and publications use different measures. Some older reference works substitute PT prolongation for INR

[c] For patients on anticoagulants (eg, Coumadin), only 1 point is assigned irrespective of the patient's INR and PT value.

[d] Hepatic encephalopathy graded according to West Haven Criteria for Semi-quantitative Grading of Mental Status: *Adapted from: Conn H, Lieberthal M. The hepatic coma syndromes and lactulose. Baltimore: Williams & Wilkins; 1979.*

- Grade I: Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- Grade II: Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behavior

- Grade III: Somnolence to semi-stupor, but responsive to verbal stimuli; Confusion; Gross disorientation
- Grade IV: Coma (unresponsive to verbal or noxious stimuli)

Interpretation

Chronic liver disease is classified into Child-Pugh class A to C, employing the added score from above.

Points	Class	One-year Survival	2-year Survival
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

10.12 Appendix 12: Description of the iRECIST Process for Assessment of Disease Progression

iRECIST is based on RECIST 1.1 but adapted to account for the unique tumor response seen with immunotherapeutic drugs. iRECIST will be used by the investigator to assess tumor response and progression, and to guide decisions about changes in management.

Assessment at Screening and Before RECIST 1.1 Progression

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

Assessment and Decision at RECIST 1.1 Progression

For participants who show radiological disease progression by RECIST 1.1, the investigator will decide whether to continue a participant on study intervention until repeat scans 4 to 8 weeks later are obtained, as described in Section 8.2.1.6.

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

- Increase in the sum of diameters of target lesion(s) identified at baseline to ≥20% and ≥5 mm from nadir

  Note: The iRECIST publication uses the terminology "sum of measurements," but "sum of diameters" will be used in this protocol, consistent with the original RECIST 1.1 terminology.

- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit showing progression according to RECIST 1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST 1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST 1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of diameters of these lesions will be calculated and kept distinct from the sum of diameters for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Nontarget.

Assessment at the Confirmatory Scans

On the confirmatory scans, the participant will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (iSD/iPR/iCR).

Confirmation of Progression

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

- Any of the factors that were the basis for the iUPD at the previous visit show worsening
  - For target lesions, worsening is a further increase in the sum of diameters of ≥5 mm, compared with any prior iUPD time point
  - For nontarget lesions, worsening is any significant growth in lesions overall, compared with a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST 1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of diameters by ≥5 mm from a prior iUPD time point
    - Visible growth of new nontarget lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered disease progression by RECIST 1.1

Persistent iUPD

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

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

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

Resolution of iUPD

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

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

The response is classified as iSD or iPR (depending on the sum of diameters of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudoprogression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management After the Confirmatory Scan

If repeat scans do not confirm disease progression, and the participant continues to be clinically stable, study intervention is to continue. The regular scan schedule is to be followed. If disease progression is confirmed, participants may be discontinued from study intervention.

Note: If a participant has confirmed radiographic progression (iCPD) and clinically meaningful benefit, study intervention may be continued after consultation with the Sponsor. If study intervention is continued, tumor scans are to be performed after the intervals as outlined in Section 1.3.

Detection of Progression at Visits After Pseudoprogression Resolves

After resolution of pseudoprogression (ie, after iSD/iPR/iCR), another instance of progression (another iUPD) is indicated by any of the following events:

- Target lesions
  - Sum of diameters reaches the disease progression threshold (≥20% and ≥5 mm increase from nadir) either for the first time, or after resolution of previous pseudoprogression. The nadir is always the smallest sum of diameters seen during the entire study, either before or after an instance of pseudoprogression.
- Nontarget lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - Previously identified new target lesions show an increase of ≥5 mm in the new lesion sum of diameters, from the nadir value of that sum
  - Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Scan above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process on the subsequent iUPD is identical to the iUPD confirmation process for the initial disease progression, with one exception, which can occur if new lesions had occurred at a prior instance of iUPD, had not resolved, then worsened (increase in size or number) leading to the second iUPD. If new lesion worsening has not resolved at the confirmatory scan, then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until new or worsening cause of progression indicates iCPD.

Additional details about iRECIST are provided in the iRECIST publication [Seymour, L., et al 2017].

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