TITLE PAGE

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Protocol Title: Phase 1/2 Study of Intravesical MK-3120 in BCG-Naïve or BCG-Exposed High-Risk Non-muscle Invasive Bladder Cancer

Study Number: 003-00

Compound Code(s): MK-3120

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

Legal Registered Address:

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

Regulatory Agency Identifying Number(s):

NCT	Pending
EU CT	2025-520467-40
jRCT	Not applicable
WHO/UTN	U1111-1317-2687
IND	176216

Approval Date: 18 July 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
Original Protocol	18-JUL-2025	Not applicable

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: Phase 1/2 Study of Intravesical MK-3120 in BCG-Naïve or BCG-Exposed High-Risk Non-muscle Invasive Bladder Cancer

Short Title: Phase 1/2 Study of Intravesical MK-3120 in HR NMIBC

Acronym: Not applicable.

Hypotheses, Objectives, and Endpoints:

There are no hypotheses for this study.

In BCG-naïve or BCG-exposed individuals with HR NMIBC:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of I-VESIC MK-3120 monotherapy	-DLT -AEs -Discontinuation of study intervention due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of I-VESIC MK-3120 with respect to CRR at 3 months based on local assessment	CR at 3 months, where CR is defined as the absence of all of the following as determined by local assessment using urine cytology, cystoscopy, biopsy and radiology assessments as applicable: • High-risk non-muscle invasive UC (defined as HG Ta, CIS, or any T1 disease of the bladder, urethra, or upper tract [ureters, renal pelvis]) • Any T2 or greater in the bladder, including transurethral prostate stromal invasion of UC, or in the upper tract (ureters, renal pelvis) • Metastatic UC, defined as: - Regional lymph node metastasis of UC (N1 or greater) - Distant lymph node or visceral metastasis of UC (M1)

Overall Design:

Study Phase	Phase 1/2
Primary Purpose	Treatment
Indication	Bladder cancer
Population	Participants with BCG-naïve or BCG-exposed HR NMIBC with CIS (+/- papillary tumors)
Study Type	Interventional
Intervention Model	Single Group This is a multi site study.
Type of Control	No Control
Study Blinding	Open Label
Blinding Roles	Not Applicable
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 38 months from the time the first participant (or their legally acceptable representative) provides documented informed consent until the last participant's last study-related contact.

Number of Participants:

Approximately 45 participants will be enrolled in Part 1 of the study.

Intervention Groups and Duration:

Arm Name	Intervention Name	Unit Dose Strength(s)	Dosage Level(s)	Route of Administration	Regimen/ Treatment Period/ Vaccination Regimen	Use
Part 1	MK-3120	100 mg/vial	300 mg 600 mg 900 mg	Intravesical	Induction: qw for 6 weeks Maintenance: q1month for 9 months	Test Product

qw=once weekly; q1month=once per month.

Other current or former names or aliases for MK-3120 are as follows: SKB410.

Total Number of Intervention Groups/Arms	1
Duration of Participation	Each participant will participate in the study for approximately 2 years from the time the participant provides documented informed consent through the final protocol-specified contact. After a screening period of up to 28 days, each participant will receive the assigned study intervention for approximately 1 year. After the end of treatment, each participant will continue to be followed for efficacy and/or survival for a total study participation period of approximately 2 years. After the end of treatment, each participant will be followed for the occurrence of AEs, SAEs, and other reportable safety events. All participants will be followed for overall survival until death, withdrawal of consent, end of the study, or until they have completed the approximately 2-year study period.

Study Governance Committees:

Executive Oversight Committee	No
External Data Monitoring Committee	No
Clinical Adjudication Committee	No

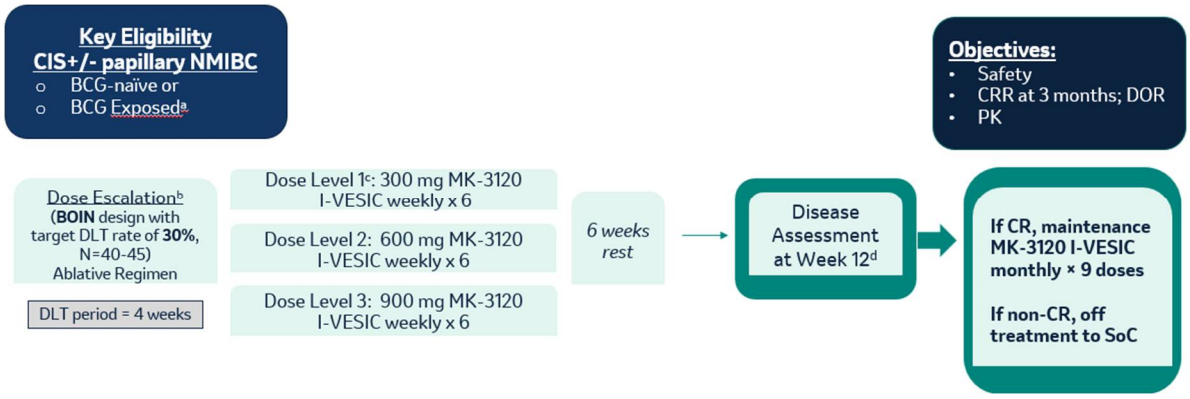
There are no governance committees in this study. Regulatory, ethical, and study oversight considerations are outlined in Appendix 1.

Study Accepts Healthy Participants: No

A list of abbreviations is in Appendix 9.

1.2 Schema

Figure 1 Study Design



BCG=Bacillus Calmette-Guérin; BOIN=Bayesian Optimal Interval Design; CIS=carcinoma in situ; CR=complete response; CRR=complete response rate; DL=dose level; DLT=dose-limiting toxicity; DOR=duration of response; HR NMIBC=high-risk non-muscle invasive bladder cancer; I-VESIC=intravesical; MRU=magnetic resonance urography; PK=pharmacokinetics; RDE=recommended dose for expansion; SOC=standard of care.

[a] BCG-exposed is defined as recurrence of CIS +/- papillary HR NMIBC >12 months but ≤24 months after completion of adequate BCG therapy. Adequate BCG therapy is defined as either at least 5 of 6 doses from an initial induction course, plus at least 2 doses from a maintenance therapy course; or at least 5 of 6 doses from an initial induction, plus at least 2 of 6 doses from a second induction.

[b] Plan for backfilling dose levels (to a maximum of 15 at each dose level) to enable determination of RDE.

[c] Participants will deescalate to 150 mg (DL-1) if the decision to deescalate from DL1 is made.

[d] Based on urine cytology, cystoscopy, biopsy, and radiology assessments as applicable.

1.3 Schedule of Activities

Any visits that do not require participants to be on site (concomitant medication review, AE review, etc) can be done via a telephone contact or a telehealth visit, at the discretion of the investigator.

1.3.1 Screening, Rescreening, and Study Intervention Period Schedule

Table 1 Study Schedule of Activities: Screening, Rescreening, and Study Intervention Periods

Study Period:			**Induction (6 Weeks)**							**Maintenance (9 Months)**									**Notes**
Dose Week:	**Screening**	**Rescreening* (if applicable)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	
Week Day:			**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	* If needed, the rescreening window starts after the full screening window has elapsed. If a screening activity/test is performed within 28 days before W1D1 (unless stated otherwise), then it does not need to be repeated during rescreening.
Visit Window (Days):	**28**	**28**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Administrative Procedures																			
Informed Consent	X																		Including optional Additional Research consent, see Section 8.1.1.2.
Participant Identification Card	X		X																Add the allocation number at the time of allocation. See Section 8.1.8 for details.
Inclusion/ Exclusion Criteria	X	X																	
Demographics and Medical History	X	X																	Including evaluation of tobacco use

Study Period:			**Induction (6 Weeks)**							**Maintenance (9 Months)**									**Notes**
Dose Week:	**Screening**	**Rescreening* (if applicable)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	
Week Day:			**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	* If needed, the rescreening window starts after the full screening window has elapsed. If a screening activity/test is performed within 28 days before W1D1 (unless stated otherwise), then it does not need to be repeated during rescreening.
Visit Window (Days):	**28**	**28**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Prior Cystoscopy/ TURBT History	X	X																	Must have undergone TURBT/biopsy to remove all resectable disease within 12 weeks before allocation. These procedures should be recorded as part of the prior treatments for NMIBC as described in Section 8.1.6.1.
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	All prior medications, including: all prior cancer treatments, medications taken within 28 days before first dose of study intervention, and concomitant medications taken during the study up to 30 days after the last dose should be recorded (refer to Section 8.1.6). All medications taken for AEs should be recorded as defined in Section 8.4.
Intervention Allocation			X																

Study Period:			**Induction (6 Weeks)**							**Maintenance (9 Months)**									**Notes**
Dose Week:	**Screening**	**Rescreening* (if applicable)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	
Week Day:			**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	* If needed, the rescreening window starts after the full screening window has elapsed. If a screening activity/test is performed within 28 days before W1D1 (unless stated otherwise), then it does not need to be repeated during rescreening.
Visit Window (Days):	**28**	**28**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
MK-3120 I-VESIC Administration			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	Refer to Section 6.6.3 for recommended premedication (starting 1.5 hours [±30 min]) for the first 4 administrations (all participants) and for participants who have a hypersensitivity reaction. Refer to Section 6.5.1 for recommended prophylactic treatment for nausea and vomiting and to mitigate the onset and severity of stomatitis/oral mucositis. MK-3120 should be retained in the bladder for 2 hours and then voided. Participants unable to retain the study intervention for 2 hours should be allowed to void sooner, if necessary. Participants must be monitored for possible hypersensitivity reactions for at least 60 minutes post-void for the first 4 instillations. After subsequent instillations, participants must be monitored in the clinic until they void.

Study Period:			**Induction (6 Weeks)**							**Maintenance (9 Months)**								**Notes**
Dose Week:	**Screening**	**Rescreening* (if applicable)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	
Week Day:			**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	* If needed, the rescreening window starts after the full screening window has elapsed. If a screening activity/test is performed within 28 days before W1D1 (unless stated otherwise), then it does not need to be repeated during rescreening.
Visit Window (Days):	**28**	**28**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Vital Status and Bladder Status			←															→	Sponsor may request vital status and bladder status updates at any time during the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their vital status and bladder status.
Efficacy Assessments																			
Cystoscopy (with TURBT/biopsy if applicable)	X†	X†								X			X			X			†Must have undergone TURBT/biopsy to remove all resectable disease within 12 weeks before allocation. Perform q12w (±14 days) from the time of first dose of study intervention or more frequently as clinically indicated. Use the same cystoscopy technique for all evaluations when clinically feasible. Biopsies are to be performed as detailed in Section 8.2.3. Pathology assessment will be performed locally. See Sections 8.2.2 and 8.2.3 for details.

Study Period:			**Induction (6 Weeks)**							**Maintenance (9 Months)**									**Notes**
Dose Week:	**Screening**	**Rescreening* (if applicable)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	
Week Day:			**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	* If needed, the rescreening window starts after the full screening window has elapsed. If a screening activity/test is performed within 28 days before W1D1 (unless stated otherwise), then it does not need to be repeated during rescreening.
Visit Window (Days):	**28**	**28**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Urine cytology (local)	X	X								X			X			X			Results per Paris criteria system (refer to Section 8.2.1 and Appendix 8). Perform q12w (±14 days) from the time of the first dose of study intervention.
Evaluation of Extravesical Disease by CTU/MRU	X†	X†								X††			X††			X††			†Baseline imaging must be done within 6 months before the first dose. Evaluation of imaging to be performed locally. ††Imaging is only required if the criteria in Section 8.2 are met.
Safety Procedures																			
AE/SAE Monitoring	X	X	←															→	AEs and laboratory measurements will be graded per NCI CTCAE version 5.0 and evaluated for seriousness. Refer to Section 8.4 for details.
Full Physical Examination	X	X																	
Directed Physical Examination			X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	Including oral examination
Height	X	X																	
Weight	X†	X†				X				X	X	X	X	X	X	X	X	X	†Within 14 days before first dose.
Vital Signs	X†	X†	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	†Within 14 days before first dose. Include temperature, pulse/heart rate, respiratory rate, and blood pressure.

Study Period:			**Induction (6 Weeks)**							**Maintenance (9 Months)**									**Notes**
Dose Week:	**Screening**	**Rescreening* (if applicable)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	
Week Day:			**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	* If needed, the rescreening window starts after the full screening window has elapsed. If a screening activity/test is performed within 28 days before W1D1 (unless stated otherwise), then it does not need to be repeated during rescreening.
Visit Window (Days):	**28**	**28**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
12-lead ECG	X	X†																	†If procedure was performed during full screening, it is not required to repeat during rescreening. Performed at baseline, repeat as clinically indicated.
ECHO/MUGA	X	X†																	†If procedure was performed during full screening, it is not required to repeat during rescreening. Additional measurements to be taken as clinically indicated.
ECOG Performance Status	X	X				X				X	X	X	X	X	X	X	X	X	
Local Laboratory Procedures/Assessments																			
HIV, hepatitis B and C screen (per site SOP)	X	X																	Acceptable to be based on history unless testing is required by local regulation.
Pregnancy Test in WOCBP	X†	X†				X			X††	X	X	X	X	X	X	X	X	X	†A negative pregnancy test is required before the start of study intervention (within 24 hours for urine or within 72 hours for serum). ††Week 8 pregnancy test may be performed at home as per local standard of care. Refer to Sections 8.3.6 and 5.1 for additional details. Refer to Appendix 7 for country-specific requirements.

Study Period:			**Induction (6 Weeks)**							**Maintenance (9 Months)**									**Notes**
Dose Week:	**Screening**	**Rescreening* (if applicable)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	
Week Day:			**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	* If needed, the rescreening window starts after the full screening window has elapsed. If a screening activity/test is performed within 28 days before W1D1 (unless stated otherwise), then it does not need to be repeated during rescreening.
Visit Window (Days):	**28**	**28**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Urinalysis	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	Urine dipstick, plus urine microscopy if indicated by dipstick, should be performed prior to each dose. I-VESIC treatment should not be administered if concurrent gross hematuria or symptomatic UTI is present.
Urine creatinine	X	X†								X									†If a sample was obtained during full screening, an additional sample is not required during rescreening.
Hematology	X†	X†		X		X		X		X	X	X	X	X	X	X	X	X	†Must be performed within 14 days before starting study intervention. Additional measurements to be taken as clinically indicated.
Chemistry Panel	X†	X†		X		X		X		X	X	X	X	X	X	X	X	X	†Must be performed within 14 days before starting study intervention. Additional measurements to be taken as clinically indicated.
PT/INR and aPTT	X	X																	Must be performed within 14 days before starting study intervention. Consider ongoing testing for participants on routine anticoagulant treatment as per local SOC.
Biomarkers																			
Blood for Genetic Analysis			X																Collect from enrolled participants only. See Section 8.8.1 for additional details.

Study Period:			**Induction (6 Weeks)**							**Maintenance (9 Months)**									**Notes**
Dose Week:	**Screening**	**Rescreening* (if applicable)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	
Week Day:			**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	* If needed, the rescreening window starts after the full screening window has elapsed. If a screening activity/test is performed within 28 days before W1D1 (unless stated otherwise), then it does not need to be repeated during rescreening.
Visit Window (Days):	**28**	**28**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Plasma for ctDNA	X	X†								X									Collect predose. †If a sample was obtained during full Screening, an additional sample is not required during Rescreening. Refer to the Laboratory Manual for details pertaining to blood sample collection.
Urine for Biomarkers	X	X†								X									Collect predose. †If a sample was obtained during full Screening, an additional sample is not required during Rescreening. Refer to the Laboratory Manual for details pertaining to urine sample collection.
Urine for utDNA	X	X†								X									Collect predose. †If a sample was obtained during full Screening, an additional sample is not required during Rescreening. Refer to the Laboratory Manual for details pertaining to urine sample collection.

Study Period:			**Induction (6 Weeks)**							**Maintenance (9 Months)**									**Notes**
Dose Week:	**Screening**	**Rescreening* (if applicable)**	**Week 1**	**Week 2**	**Week 3**	**Week 4**	**Week 5**	**Week 6**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 24**	**Week 28**	**Week 32**	**Week 36**	**Week 40**	**Week 44**	
Week Day:			**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	* If needed, the rescreening window starts after the full screening window has elapsed. If a screening activity/test is performed within 28 days before W1D1 (unless stated otherwise), then it does not need to be repeated during rescreening.
Visit Window (Days):	**28**	**28**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
Tissue for Biomarkers	X	X†	X††																†An additional sample is not required during Rescreening if a sample was previously submitted. ††If tissue is collected per the disease assessment guidelines and shows progression, persistence, or relapse locally, it should be submitted for biomarker analysis (refer to Section 8.8) unless otherwise discussed with the Sponsor. Refer to the Laboratory Manual for details.

AE=adverse event; aPTT=activated partial thromboplastin time; CBC=complete blood count; CTCAE=Common Terminology Criteria for Adverse Events; ctDNA=circulating tumor DNA; CTU=computed tomography urography; D=day; DC=discontinuation; ECG=electrocardiogram; ECHO/MUGA=echocardiogram/multiple-gated acquisition scan; ECOG=Eastern Cooperative Oncology Group; EFU=efficacy follow-up; EOT=end of treatment; FU=follow-up; HIV=human immunodeficiency virus; I-VESIC=intravesical(ly); MRU=magnetic resonance urography; NCI=National Cancer Institute; NMIBC= non-muscle invasive bladder cancer; PT/INR=prothrombin time/ international normalized ratio; q12w=every 12 weeks; SOP=standard operating procedures; TURBT=transurethral resection of bladder tumor; utDNA=urine tumor DNA; UTI=urinary tract infection; W1D1=Week 1 Day 1; WOCBP=woman/women of childbearing potential.

1.3.2 End-of-Treatment Visit and Posttreatment Schedule

Table 2 Study Schedule of Activities: End of Treatment Visit and Posttreatment Period

Study Period:	**EOT/DC**	**Safety FU**	**Efficacy FU**	**Survival FU**	**Notes**
Week Day:	**At time of treatment DC[a]**	**14 days post last dose***	**Continue q12w from the first dose of study intervention until Week 108 (~2 years)**	**q12w for max 2 years from the first dose of study intervention**	*** If EOT/DC visit happens 7 or more days post last dose, the EOT/DC and Safety FU visits should be combined. Participants will continue to be followed for AEs as per Section 8.4.1.**
Visit Window (Days):	**+7**	**±7**	**±14**	**±14**	
Administrative Procedures					
Prior and Concomitant Medication Review	X	X			Concomitant medications taken during the study up to 30 days after the last dose should be recorded (refer to Section 8.1.6). All medications taken for AEs should be recorded as defined in Section 8.4.
Subsequent Anticancer Therapy and Oncologic Surgery Status	X	X	X	X	
Vital Status and Bladder Status	◄———	———	———	———►	Sponsor may request vital status and bladder status updates at any time during the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their vital status and bladder status.

Study Period:	EOT/DC	Safety FU	Efficacy FU	Survival FU	Notes
Week Day:	**At time of treatment DC[a]**	**14 days post last dose***	**Continue q12w from the first dose of study intervention until Week 108 (~2 years)**	**q12w for max 2 years from the first dose of study intervention**	*** If EOT/DC visit happens 7 or more days post last dose, the EOT/DC and Safety FU visits should be combined. Participants will continue to be followed for AEs as per Section 8.4.1.**
Visit Window (Days):	**+7**	**±7**	**±14**	**±14**	
Efficacy Procedures					
Cystoscopy (with TURBT/biopsy if applicable)			X		Use the same cystoscopy technique for all evaluations when clinically feasible. Perform q12w (±14 days) from the time of the first dose of study intervention to the final study assessment at Week 108. Biopsies are to be performed as detailed in Section 8.2.3. Pathology assessment will be performed locally. Perform more frequently as clinically indicated. See Sections 8.2.2 and 8.2.3 for details.
Urine cytology (local)			X		Results per Paris criteria system (refer to Section 8.2.1 and Appendix 8). Perform q12w (±14 days) from the time of the first dose of study intervention to the final study assessment at Week 108.
Evaluation of Extravesical Disease by CTU/MRU			X		Evaluation of imaging to be performed locally. Imaging to be done as clinically indicated and as per disease assessment guidelines; refer to Section 8.2 for details. A surveillance CTU/MRU will occur at Week 48 (±14 days). Surveillance imaging not required if CTU/MRU was performed within the past 36 weeks and is not required per disease assessment guidelines or otherwise clinically indicated.

Study Period:	EOT/DC	Safety FU	Efficacy FU	Survival FU	Notes
Week Day:	**At time of treatment DC[a]**	**14 days post last dose***	**Continue q12w from the first dose of study intervention until Week 108 (~2 years)**	**q12w for max 2 years from the first dose of study intervention**	*** If EOT/DC visit happens 7 or more days post last dose, the EOT/DC and Safety FU visits should be combined. Participants will continue to be followed for AEs as per Section 8.4.1.**
Visit Window (Days):	**+7**	**±7**	**±14**	**±14**	
Safety Procedures					****If performed at the EOT/DC visit, then the assessment does not need to be repeated at the Safety FU visit.**
AE/SAE Monitoring	X	X			AEs and laboratory measurements will be graded per NCI CTCAE version 5.0 and evaluated for seriousness. Refer to Section 8.4 for details.
Directed Physical Examination**	X	X			Including oral examination
Weight**	X	X			
Vital Signs**	X	X			Include temperature, pulse/heart rate, respiratory rate, and blood pressure.
ECOG Performance Status**	X	X			
Local Laboratory Procedures/Assessments					****If performed at the EOT/DC visit, then the assessment does not need to be repeated at the Safety FU visit.**
Pregnancy Test in WOCBP		X			Refer to Sections 8.3.6 and 5.1 for additional details.
Urinalysis	X	X			Urine dipstick, plus urine microscopy if indicated by dipstick.
Urine creatinine			X[†]		[†]Collected on Week 12 visit only.
Hematology**	X	X			
Chemistry Panel**	X	X			
Biomarkers					
Urine for Biomarkers			X[†]		[†]Collected on Week 12 visit only. Refer to the Laboratory Manual for details pertaining to urine sample collection.

Study Period:	**EOT/DC**	**Safety FU**	**Efficacy FU**	**Survival FU**	**Notes**
Week Day:	**At time of treatment DC[a]**	**14 days post last dose***	**Continue q12w from the first dose of study intervention until Week 108 (~2 years)**	**q12w for max 2 years from the first dose of study intervention**	*** If EOT/DC visit happens 7 or more days post last dose, the EOT/DC and Safety FU visits should be combined. Participants will continue to be followed for AEs as per Section 8.4.1.**
Visit Window (Days):	**+7**	**±7**	**±14**	**±14**	
Plasma for ctDNA			X†		†Collected on Week 12 visit only. Refer to the Laboratory Manual for details pertaining to blood sample collection.
Urine for utDNA			X†		†Collected on Week 12 visit only. Refer to the Laboratory Manual for details pertaining to urine sample collection.
Tissue for Biomarkers			X†		†If tissue is collected per the disease assessment guidelines that shows progression, persistence, or relapse locally, it should be submitted for biomarker analysis (refer to Section 8.8) unless otherwise discussed with the Sponsor. Refer to the Laboratory Manual for details.

AE=adverse event; CBC=complete blood count; CTCAE=Common Terminology Criteria for Adverse Events; ctDNA=circulating tumor DNA; CTU=computed tomography urography; D=day; DC=discontinuation; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ECHO/MUGA=echocardiogram/multiple-gated acquisition scan; EFU=efficacy follow-up; EOT=end of treatment; FU=follow-up; HIV=human immunodeficiency virus; I-VESIC=intravesical(ly); max=maximum; MRU=magnetic resonance urography; NCI=National Cancer Institute; q12w=every 12 weeks; SAE=serious adverse event; SFU=survival follow-up; SOP=standard operating procedure; TURBT=transurethral resection of bladder tumor; utDNA=urine tumor DNA; UTI=urinary tract infection; WOCBP=woman/women of childbearing potential.

[a] The EOT visit is performed at the time of study intervention discontinuation when treatment is discontinued before completion; it is not performed when the study intervention period is completed.

1.3.3 Pharmacokinetics and Antidrug Antibodies Schedule

Table 3 Schedule of Activities: Pharmacokinetics and Antidrug Antibodies

Study Period:	**Induction (6 Weeks)[a]**									**Maintenance (9 Months)[a]**
Dose Week:	**Week 1 and Week 4**						**Weeks 2, 3, 5, and 6**			**Weeks 12, 20, 28, 36, 44**
Week Day:	**1**	**1**	**1**	**1**	**1**	**2 (Week 1 only)**	**1**	**1**	**1**	**1**
Time from Instillation:	**Prior to instillation**	**30 min post-instillation (during bladder retention of dose)**	**First bladder voiding post-instillation**	**4 h post-instillation**	**6 h post-instillation**	**Any time during visit**	**Prior to instillation**	**30 min post-instillation (during bladder retention of dose)**	**First bladder voiding post-instillation**	**Prior to instillation**
Window:	**0-3 h**	**±15 min**	**+15 min**	**±1 h**	**±1 h**	**+1 day**	**0-3 h**	**±15 min**	**+15 min**	**0-3 h**
Blood for serum MK-3120 PK of ADC and TAb	X	X	X	X	X	X	X	X	X	X
Blood for plasma MK-3120 PK of payload	X	X	X	X	X	X	X	X	X	X
Urine for MK-3120 payload PK[b]	X		X	X[c]	X[c]	X	X		X	
Blood for serum ADA to MK-3120[d]	X						X			X

ADA=antidrug antibodies; ADC=antibody-drug conjugate; h=hours; min=minute(s); PK=pharmacokinetic(s); TAb=total antibody

[a] No PK samples will be collected after the end of treatment.

[b] Participant should void bladder completely.

[c] If samples could not be obtained at specific 4h (±1 h) and 6h (±1 h) post-instillation timepoints (ie, due to urinary urgency), at least 2 additional urine samples should be obtained following first bladder voiding post-instillation.

[d] ADA blood sample for MK-3120 should be collected prior to instillation (0-3 h before dosing).

2 INTRODUCTION

This is a dose-escalation and dose-finding study to assess the safety, tolerability, PK, efficacy, and immunogenicity/ADA of I-VESIC delivery of MK-3120 as monotherapy in participants with CIS +/- papillary HR NMIBC.

2.1 Study Rationale

In humans, Nectin-4 is normally expressed in keratinocytes of transitional epithelium of the bladder, as well as the skin, sweat glands, hair follicles, salivary gland ducts, esophagus, breast, and stomach. Nectin-4 is also expressed in multiple cancers, particularly those of epithelial origin, including UC [Challita-Eid, P. M., et al 2016].

MK-3120 binds to Nectin-4 on the surface of tumor cells by a humanized anti-Nectin-4 antibody. ADCs like MK-3120 are novel immunoconjugates that use the specificity of mAbs to target antigens such as Nectin-4 expressed on cancer cells for the delivery of a potent cytotoxic payload. This provides an opportunity to deliver a chemotherapeutic drug to tumor cells while reducing off-target toxicity [Chau, C. H., et al 2019]. For MK-3120, the cytotoxic payload is KL610023, a topoisomerase 1 inhibitor.

This study will evaluate the safety, tolerability, preliminary efficacy, PK, and immunogenicity/ADA of I-VESIC MK-3120 in participants with CIS +/- papillary HR NMIBC who are BCG-naïve or exposed with relapse between 12 and 24 months following adequate BCG therapy. Due to the known expression of high levels of Nectin-4 in NMIBC, as well as in MIBC, participants on this study may benefit from MK-3120 administered by an I-VESIC route, affording direct binding locally to CIS tumor cells within the bladder urothelium.

Refer to the IB for detailed background information on MK-3120.

2.2 Background

2.2.1 Background on Study Population

Bladder cancer is a common malignancy with an annual incidence of 613,791 worldwide, with more than 60% of new cases combined occurring in Europe and Asia, while the annual incidence of 83,190 in the US accounts for just over 15% of worldwide cases [Bray, F., et al 2024] [Siegel, R. L., et al 2024]. The incidence is known to increase with increasing age, with a median age of 73 years at diagnosis [National Cancer Institute 2024]. Notably, bladder cancer is associated with the highest cost per patient (total Medicare Payments) from diagnosis to death of all malignancies, largely owing to the frequent procedures required for disease monitoring and treatment [Botteman, M. F., et al 2003].

NMIBC comprises 70% to 80% of bladder cancer [Abugomaa, A., et al 2020]. NMIBC includes Ta (noninvasive papillary), T1 (submucosal invasive) tumors, and CIS, which account for approximately 70%, 20%, and 10% of non-muscle invasive cancers, respectively [Batista, R., et al 2020] [Kirkali, Z., et al 2005]. NMIBC is a heterogenous disease characterized by frequent recurrence and high morbidity, but a low risk of mortality. Muscle-

invasive bladder cancer represents approximately 20% of primary diagnoses and is potentially lethal in approximately 50% of those patients [National Comprehensive Cancer Network 2024]; approximately 5% of new diagnoses of bladder cancer involve metastatic disease.

NMIBC is further classified into low-, intermediate-, and high-risk disease based on stage, grade, additional clinical features such as number and size of tumors, frequency of recurrence, and time to recurrence [Holzbeierlein, J. M., et al 2024] [Babjuk, M., et al 2022] [National Comprehensive Cancer Network 2024]. Low-risk NMIBC is defined as a solitary low-grade Ta, <3 cm. High-risk is defined as the presence of any T1, high-grade Ta, or CIS [Holmang, S., et al 1999]. Intermediate risk includes anything that does not fulfill the criteria for the low- or high-risk groups. Standard therapy for NMIBC is TURBT followed by, if applicable, I-VESIC therapy. The choice of I-VESIC agent (chemotherapy, BCG) and duration is based on the patient's risk stratification [Holzbeierlein, J. M., et al 2024] [Babjuk, M., et al 2022] [National Comprehensive Cancer Network 2024].

I-VESIC instillation of BCG is the current SOC for treating patients with high-risk NMIBC with a goal of reducing the risk of recurrence and/or progression to MIBC and death from bladder cancer. Despite this therapy, approximately 50% of patients with high-risk tumors ultimately become BCG-unresponsive or experience stage progression. Metastatic disease occurs in 20% to 30% of these individuals who progress to muscle-invasive disease, with death due to bladder cancer in nearly all of these patients [Cookson, M. S., et al 1997] [Millan-Rodriguez, F., et al 2000]. While the NCCN guidelines suggest that pembrolizumab, I-VESIC chemotherapy, nadofaragene firadenovec, or combination therapy with nogapendekin alfa inbakicept and BCG could be used for select patients who are BCG-intolerant or unresponsive, the only preferred treatment option for patients who develop BCG-unresponsive NMIBC is radical cystectomy [National Comprehensive Cancer Network 2025] [Babjuk, M., et al 2017] [Chang, S. S., et al 2016]. Although curative, this surgery is associated with significant morbidity/mortality, high hospital readmission rates, and a decrease in quality of life/body image [Kanno, T., et al 2019] [Shabsigh, A., et al 2009] [Stimson, C. J., et al 2010] [Singer, S., et al 2013]. Many patients either decline radical cystectomy or are considered medically ineligible due to the presence of comorbidities [Chang, S. S., et al 2017].

The FDA defines adequate I-VESIC BCG therapy as either at least 5 of 6 doses from an initial induction course, plus at least 2 doses from a maintenance therapy course; or at least 5 of 6 doses from an initial induction plus at least 2 of 6 doses from a second induction [U.S. Prescribing Information 2022]. The American Urological Association/Society for Urologic Oncology guidelines further advocate for patients to receive a longer BCG maintenance course of 3 years [Holzbeierlein, J. M., et al 2024]. BCG is highly effective initially but ultimately fails to provide durable efficacy, due in part to poor compliance related to the prolonged treatment schedule and significant local toxicity. A recent study examining BCG adherence in patients with NMIBC found that, of patients with CIS who received BCG with at least 1 year of follow-up (n = 615), only 1.6% (n = 10) completed BCG induction (at least 5 BCG doses) and 1 year of maintenance therapy (at least 2 BCG doses at 3/6/12 months) [Gaylis, F. D., et al 2024]. Of CIS patients with at least 36 months of follow-up (n = 315), none completed 3 years of BCG maintenance.

There is a significant need for novel I-VESIC therapies that favorably balance efficacy and toxicity in this early-stage disease setting. There is robust clinical evidence of efficacy using systemic Nectin-4-targeting ADC in UC. Early clinical evidence indicates antitumor efficacy via I-VESIC administration may occur without significant systemic exposure [Kamat, A. M., et al 2023]. The potential for I-VESIC MK-3120 therapy to effectively treat HR NMIBC would represent a significant advancement in the current treatment paradigm.

2.2.2 Pharmaceutical and Therapeutic Background

2.2.2.1 MK-3120

MK-3120 is an ADC comprising 3 major components: a recombinant anti-Nectin-4 humanized mAb (SKB410mAb), a linker containing a 2-(methylsulfonyl) pyrimidine; and a cytotoxin molecule, KL610023. KL610023 is a topoisomerase 1 inhibitor that can block cell cycle progression, inhibit cell proliferation, and induce tumor cell apoptosis. MK-3120 also mediates and enhances the killing of nontarget cells around target cells through a bystander effect.

MK-3120 has shown significant tumor inhibition in a variety of tumor cell xenograft models (eg, UC, TNBC, and NSCLC). Refer to the IB for detailed background information on MK-3120.

2.2.2.2 Nectin-4 Targeted Therapies

EV was the first Nectin-4 targeted therapy approved for the treatment of locally advanced/metastatic UC. EV is an ADC made up of a fully human anti-Nectin-4 IgG1 kappa mAb conjugated to the small molecule microtubule disrupting agent, MMAE, via a protease-cleavable maleimidocaproyl VC linker [U.S. Prescribing information 2023]. EV binds to the V domain of Nectin-4 protein [Challita-Eid, P. M., et al 2016]. In the presumed mechanism of action, the drug binds to the Nectin-4 protein on the cell surface and is internalized, causing proteolytic cleavage of the VC linker and intracellular release of MMAE. Free MMAE subsequently disrupts tubulin polymerization and leads to mitotic arrest [U.S. Prescribing information 2023].

EV-201 was a single-arm, multicohort, multicenter clinical study evaluating EV monotherapy in participants with locally advanced/metastatic UC who had received prior PD-1 or PD-L1 inhibitors [U.S. Prescribing information 2023]. Participants in Cohort 1 had also received prior platinum-based chemotherapy; participants in Cohort 2 were cisplatin-ineligible. Cohort 1 results showed an ORR of 44% (95% CI: 35.1, 53.2) and a median DOR of 7.6 months (95% CI: 6.3, not estimable). Cohort 2 results showed an ORR of 51% (95% CI: 39.8, 61.3) and a median DOR (95% CI) of 13.8 months (6.4, not estimable). EV-301, a Phase 3 open-label, randomized, multicenter, confirmatory study evaluated EV as a single agent in participants with locally advanced/metastatic UC who had received prior PD-1 or PD-L1 inhibitors and platinum-based chemotherapy. Participants were randomized 1:1 to receive either EV or investigator's choice of chemotherapy. The results showed a median OS of 12.9 months (95% CI: 10.6, 15.2) for EV versus 9.0 months (95% CI: 8.1, 10.7) for chemotherapy (Hazard Ratio: 0.70 [95% CI: 0.56, 0.89]; p=0.0014); median PFS of

5.6 months (95% CI: 5.3, 5.8) for EV versus 3.7 months (95% CI: 3.5, 3.9) for chemotherapy (Hazard Ratio: 0.62 [95% CI: 0.51, 0.75]; $p<0.0001$); and ORR of 40.6% (95% CI: 34.9, 46.5) for EV versus 17.9% (95% CI: 13.7, 22.8; $p<0.0001$) for chemotherapy [U.S. Prescribing information 2023]. These results led to the approval of EV in patients with locally advanced or metastatic UC who had previously received treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy or patients who were ineligible for cisplatin-based chemotherapy and had received 1 or more lines of therapy.

EV-302 is an ongoing, open-label, randomized, Phase 3 study evaluating the combination of EV plus pembrolizumab versus platinum-based chemotherapy in participants with previously untreated, locally advanced/metastatic UC. Results as of the data cutoff (median follow-up of 17.2 months) showed a median PFS of 12.5 months in the EV plus pembrolizumab arm compared with 6.3 months in the chemotherapy arm (Hazard Ratio: 0.45 [95% CI: 0.38, 0.54]; $p<0.001$). Similarly, median OS in the EV plus pembrolizumab arm was 31.5 months compared with 16.1 months in the chemotherapy arm (Hazard Ratio: 0.47 [95% CI: 0.38, 0.58], $p<0.001$). Confirmed ORRs of 67.7% and 44.4% were observed in the EV plus pembrolizumab and chemotherapy arm, respectively ($p<0.001$) [Powles, T. B., et al 2024]. These results led to the approval of EV plus pembrolizumab as first-line treatment for adults with locally advanced or metastatic UC.

The safety and tolerability of EV as a single agent was evaluated in clinical studies. In the pivotal study EV-301, SARs occurred in 47% of treated participants. The most common SARs (≥2%) were urinary tract infection (7%), acute kidney injury (7%), and pneumonia (5%). ADRs leading to discontinuation occurred in 17% of participants; the most common of these ADRs (≥2%) were peripheral neuropathy (5%) and rash (4%) [U.S. Prescribing information 2023]. A boxed warning for PADCEV® includes severe skin reactions.

For more details refer to the approved labeling for PADCEV.

Several other Nectin-4 targeting ADC/PDC with various payloads (9MW2821, CRB-701/SYS6002, and BT8009) are being evaluated in early-phase clinical studies, and early safety and efficacy results are emerging [Zhang, J., et al 2024] [Ye, D. W., et al 2024] [Torras, O. R., et al 2024].

2.2.3 Preclinical Studies

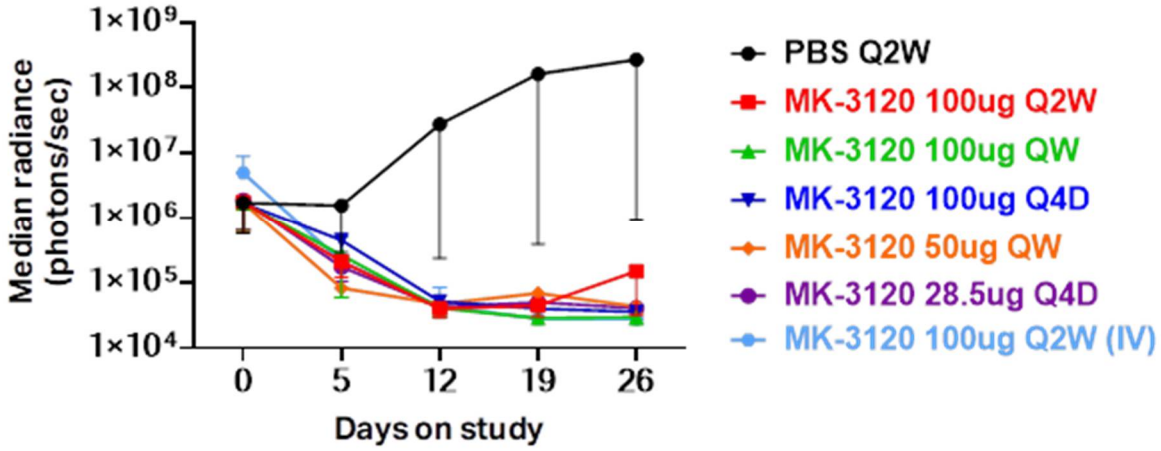
In vitro data indicate that MK-3120 binds to Nectin-4 with high affinity, is endocytosed by target-expressing cells, and effectively inhibits cell proliferation and induces tumor cell apoptosis. The effect of MK-3120 is primarily attributed to the intracellular release of a conjugated toxin payload (denoted “KL610023”), a topoisomerase 1 inhibitor that blocks cell cycle progression and activates apoptotic cell signaling pathways. A variety of in vivo tumor models show that MK-3120 inhibits tumor growth. In addition to the direct cytotoxicity, MK-3120 also mediates and enhances killing of nearby nontarget cells through a bystander effect.

I-VESIC MK-3120 has a favorable nonclinical profile. The antitumor activity of MK-3120 was evaluated in an orthotopic UM-UC-3-luc-TROP2-Nectin-4 NMIBC xenograft tumor

model after I-VESIC dosing. The UM-UC-3 cell line, a urothelial bladder cancer cell line, was engineered to express TROP2 and Nectin-4 at high levels; expression was confirmed by flow cytometry and immunohistochemistry. The study was designed to determine if dose regimen affects antitumor activity and is summarized below.

I-VESIC MK-3120 is efficacious in NMIBC in vivo mouse models with minimal systemic levels of MK-3120 and unconjugated payload KL610023. Mice bearing orthotopic tumors were randomized into 7 groups, 10 mice per group, with I-VESIC administration using a 1-hour dwell time. One group was systemically dosed MK-3120 using an IV delivery. MK-3120 was administered utilizing the IV formulation for all groups. The treatment groups included vehicle q2w I-VESIC, 100 µg MK-3120 q2w I-VESIC, 100 µg MK-3120 qw I-VESIC, 100 µg MK-3120 q4d I-VESIC, 50 µg MK-3120 qw I-VESIC, 28.5 µg MK-3120 q4d I-VESIC, and 100 MK-3120 q2w IV. The dosing groups were chosen to evaluate the dosing frequency at the same dose level (100 µg q2w, 100 µg qw and 100 µg q4d) as well as the same "total dose" spread across different dosing regimens (100 µg q2w, 50 µg qw and 28.5 µg q4d). The dose of 100 µg in mice is equivalent to the weight-based dose of 5 mg/kg (assuming mouse reference body weight of 0.02 kg). Due to the local I-VESIC route of administration and expected minimal systemic exposure, correction based on body surface area was not accounted for in human or animal equivalent dose calculations. All MK-3120 treatment groups showed robust antitumor activity (Figure 2). MK-3120 was well tolerated by the tumor-bearing mice in all dosing groups. Bioanalysis of bladder tumor tissue and serum samples taken 1 hour after the final dose showed that while MK-3120 and unconjugated payload KL610023 were detected in tumor-bearing bladder tissue, minimal systemic exposure after I-VESIC dosing was observed with serum levels several hundred-fold lower for I-VESIC-dosed animals compared with the IV group.

Figure 2 Antitumor Activity of MK-3120 after I-VESIC Administration (1-Hour Dwell Time) in the Orthotopic UM-UC-3-luc-TROP2-NECTIN-4 NMIBC Mouse Tumor Model



PBS=phosphate-buffered saline; q2w=every 2 weeks; q4d=once every 4 days; qw=once weekly.

A GLP I-VESIC local tolerability study in humanized Nectin-4 KI mice evaluated the bladder histopathology after I-VESIC MK-3120 instillation at doses exceeding the maximum proposed human clinical dose on both a mg/kg basis and normalized bladder tissue surface area calculation. After twice-weekly (total of 4 doses) I-VESIC instillation of MK-3120, no MK-3120-related histopathologic changes were observed at either dose level (data on file).

2.2.4 Clinical Studies

This is the first clinical study with MK-3120 administered via I-VESIC route.

As of 07-AUG-2024, 27 participants with advanced solid tumors were enrolled and treated in the ongoing Phase 1 study in China (SKB410-I-01 [MK-3120-001]) to evaluate the safety, tolerability, PK, and preliminary efficacy of IV MK-3120 (SKB410). Of these, 25 participants (92.6.%) had at least 1 AE that was considered related to MK-3120 by the investigator. The most frequently reported drug-related AEs (in >30% of participants) were anemia, WBC count decreased, neutrophil count decreased, nausea, asthenia, platelet count decreased, and vomiting. Drug-related SAEs were reported for 1 participant each in the 4 mg/kg group (Grade 3 ileus) and 5 mg/kg group (Grade 3 asthenia), and 1 participant in the 6 mg/kg group discontinued study intervention because of a DLT (Grade 4 neutrophil count decreased). There were no deaths considered related to MK-3120 by the investigator, and no DLTs were observed at dose levels up to 5 mg/kg. The MTD for IV MK-3120 was determined to be 6 mg/kg q2w. Please refer to the MK-3120 IB for more details about MK-3120-001.

MK-3120-002 is a Phase 1/2 open-label expansion cohort study to evaluate the safety and efficacy of IV MK-3120 in participants with advanced solid tumors including UC, head and neck squamous cell carcinoma, cervical cancer, endometrial cancer, and TNBC. Two dose levels will be tested, including 4 mg/kg and 5 mg/kg administered intravenously every 2 weeks. The primary endpoint in MK-3120-002 is safety and tolerability, with secondary endpoints evaluating efficacy, including OR, DOR, PFS, and OS; PK will also be evaluated.

The proposed starting dose for the current study is 300 mg, which is the fixed dose equivalent of the weight-based 4 mg/kg dose for MK-3120.

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.

There is a considerable unmet need to improve outcomes for patients with high-risk NMIBC, given that 50% to 70% of patients will relapse despite initial response with BCG therapy [Siddiqui, M. R., et al 2017]. Evaluating MK-3120 in participants with CIS +/- HR NMIBC represents an opportunity to study the benefits of this agent, which could provide increased durability of responses and improved quality of life in these patients.

Although there are no clinical data available for MK-3120 given via the I-VESIC route, preliminary results from a Phase 1 Study of I-VESIC EV, a Nectin-4 ADC, demonstrate the

feasibility of administering a systemic ADC via the I-VESIC route with observed antitumor efficacy and limited systemic exposure [Kamat, A. M., et al 2023]. Due to the limited exposure time of MK-3120 in the bladder (approximately 1 to 2 hours following each I-VESIC dose), it is anticipated that toxicities will be minimized compared with those observed with systemic administration. Consequently, I-VESIC administration of MK-3120 may offer a favorable benefit/risk profile for patients with NMIBC.

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

There are no hypotheses for this study.

In BCG-naïve or BCG-exposed individuals with HR NMIBC:

Primary Objective	**Primary Endpoint**
To evaluate the safety and tolerability of I-VESIC MK-3120 monotherapy	-DLT -AEs -Discontinuation of study intervention due to AEs
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of I-VESIC MK-3120 with respect to CRR at 3 months based on local assessment	CR at 3 months, where CR is defined as the absence of all of the following as determined by local assessment using urine cytology, cystoscopy, biopsy and radiology assessments as applicable: • High-risk non-muscle invasive UC (defined as HG Ta, CIS, or any T1 disease of the bladder, urethra, or upper tract [ureters, renal pelvis]) • Any T2 or greater in the bladder, including transurethral prostate stromal invasion of UC, or in the upper tract (ureters, renal pelvis) • Metastatic UC, defined as: - Regional lymph node metastasis of UC (N1 or greater) - Distant lymph node or visceral metastasis of UC (M1)
Tertiary/Exploratory Objectives	**Tertiary/Exploratory Endpoints**
To evaluate the efficacy of I-VESIC MK-3120 with respect to overall CRR based on local assessment	CR for the overall study period
To evaluate the efficacy of I-VESIC MK-3120 with respect to the duration of CR based on local assessment	Duration of CR: defined as the time from the first documented evidence of CR until the occurrence of high-risk non-muscle invasive UC, any T2 or greater in the bladder, metastatic UC, or death due to any cause, whichever occurs first
To evaluate efficacy of I-VESIC MK-3120 with respect to OS	OS: defined as time from allocation to death due to any cause

To characterize the systemic PK profile of MK-3120	Blood levels of MK-3120 ADC, TAb, and payload
To characterize the urine PK of payload for I-VESIC MK-3120 monotherapy	Urine levels of payload
To characterize the immunogenicity of I-VESIC MK-3120	Incidence of ADA formation to I-VESIC MK-3120
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-3120 and other treatments	Molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to treatments, using biospecimens

4 STUDY DESIGN

4.1 Overall Design

This is an open-label, multicenter, Phase 1/2 study to evaluate the safety and efficacy of I-VESIC MK-3120. The study will be conducted in 2 parts.

In Part 1, MK-3120 dose escalation and RDE will be assessed at the following dose levels:

- DL1: 300 mg MK-3120 I-VESIC qw for 6 weeks
- DL2: 600 mg MK-3120 I-VESIC qw for 6 weeks
- DL3: 900 mg MK-3120 I-VESIC qw for 6 weeks

During dose escalation, the dose level that has been cleared may be expanded ("backfilled") to enroll up to a maximum of 10 participants. Once dose escalation has completed, selected dose level(s) may undergo extended backfilling to approximately 15 participants to collect additional data (ie, safety, efficacy, PK, and pharmacodynamics [if applicable]). Refer to Section 4.3.1.4 for details regarding backfilling.

Intraparticipant dose escalation will not be permitted.

Upon completion of dose escalation (Part 1) and achievement of an RDE, Part 2 (Phase 2 dose expansion) will be initiated by protocol amendment to further evaluate I-VESIC MK-3120. The totality of the data generated in Part 1, including safety, efficacy, and PK will be used to guide the design of Part 2. The criteria for dose modification of MK-3120 and definition of DLTs are outlined in Section 6.6.

All participants will have cystoscopy, urine cytology, and, if applicable, biopsy and radiologic imaging every 12 weeks from the first dose of study intervention and continuing for approximately 2 years for assessment of disease. Participants with abnormal cystoscopy will undergo directed biopsy of any target/suspicious lesion(s). A biopsy confirmed locally as HG Ta, T1, or CIS of the bladder, urethra, prostatic urethra, or upper tract (ureters, renal pelvis), or disease progression to T2 or worse at any time will warrant a CTU or MRU, as appropriate.

Participants without malignant or suspicious lesions on cystoscopy, but whose urine cytology is confirmed as, or suspicious for, HG UC, will undergo serial biopsies of the normal-looking mucosa (random biopsies or R-biopsies). These participants will also undergo evaluation for extravesical disease by CTU or MRU, as appropriate.

Participants with CR observed locally at the 12-week assessment will receive maintenance I-VESIC MK-3120 monthly for up to 9 months at the same dose level. Participants with locally confirmed HG Ta, T1, or CIS in the bladder, urethra, prostatic urethra, or upper tract (ureters, renal pelvis), or disease progression to T2 or worse will be discontinued from study intervention. Development of extravesical disease verified by radiologic imaging will constitute progressive disease necessitating discontinuation of study intervention.

Participants with LG Ta will be permitted to undergo a TURBT to fully resect the LG Ta and are permitted to remain on study intervention. If all the LG Ta was removed at the initial biopsy, a repeat TURBT is not required.

Preliminary efficacy will be evaluated using CRR as assessed by local cystoscopy, urine cytology, and biopsy/imaging (when indicated) as a secondary endpoint (Part 1). Additional efficacy endpoints include duration of CR. After locally confirmed disease progression, relapse, persistence, and/or initiation of a subsequent anticancer treatment, all participants will be followed for survival (by phone contact or clinic visit) until death, withdrawal of consent, loss to follow-up, or until the study is concluded or terminated early, whichever occurs first, for a maximum of 2 years.

AEs and SAEs will be reported for participants for the time periods specified in Section 8.4.1 and will be graded for severity according to the guidelines outlined in the NCI CTCAE version 5.0.

The study design is summarized in Figure 1. See Appendix 7 for country-specific requirements.

Part 1: Dose Escalation

Part 1 is designed to demonstrate a tolerable safety profile and confirm tolerable dose(s) for dose expansion (Part 2). Approximately 15 participants are planned for each intended study dose level. The BOIN design with a target DLT rate of 30% will be used to determine an acceptable dose level for Part 2.

For the definition of DLT, see Section 6.6.1. The initial planned doses for each of the investigational dose levels are shown in Table 4.

Table 4 Part 1 MK-3120 Dose Levels

Intervention Group	Dose Level
DL1[a]	300 mg MK-3120 I-VESIC × qw for 6 weeks
DL2	600 mg MK-3120 I-VESIC × qw for 6 weeks
DL3	900 mg MK-3120 I-VESIC × qw for 6 weeks

DL=dose level; qw=weekly; I-VESIC=intravesical

[a] Participants will deescalate to 150 mg (DL-1) if the decision to deescalate from DL1 is made.

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.

Participants will be enrolled and allocated via IRT according to the dose escalation and dose confirmation BOIN design guidelines outlined in Section 4.3.1.3. The dose level will be specified via IRT. Dose levels will be opened or closed through IRT to ensure correct dosing.

Safety data from individual participants will be closely followed by the investigators and the Sponsor on an ongoing basis and shared at regular safety teleconferences. The safety and

tolerability of MK-3120 for all participants, including those undergoing and who have completed DLT evaluation, will be reviewed at dose-escalation/dose-decision meetings. The Sponsor and investigators will jointly assess the appropriateness of the protocol-defined dose-escalation rules (refer to Section 4.3.1.3) based on safety and tolerability data before opening enrollment for the next dose level.

Each dose-escalation decision will occur after at least 3 evaluable participants have completed the DLT evaluation period of the previous dose level.

Dose-escalation decisions will be based on key safety variables, with summary statistics as needed, including AEs, vital signs, laboratory tests, and protocol-specific parameters. PK and immunogenicity/ADA data may be included in the dose-escalation decisions if available.

If, as judged by the Sponsor and investigator, the safety and tolerability data do not justify dose escalation, the dose will not be increased as planned. Instead, participants may:

- Receive the same dose level to further explore safety and tolerability at that level,
- Receive a lower dose of the study intervention, or
- Dosing may be stopped.

Participant discontinuation criteria are outlined in Section 7.

4.2 Scientific Rationale for Study Design

This study is designed to assess the safety, tolerability, PK, preliminary efficacy, and immunogenicity/ADA of I-VESIC MK-3120. The direct antitumor effect of I-VESIC MK-3120 will also be explored. There is clinical evidence of efficacy with systemic Nectin-4-targeting ADC in UC, but no mature efficacy data when given via the I-VESIC route [Sridhar, S., et al 2023] [Rosenberg, J. E., et al 2023]. Early clinical evidence indicates antitumor efficacy via I-VESIC delivery may occur without significant systemic exposure (EV-104) [Kamat, A. M., et al 2023]. Given the limited duration of exposure within the bladder following each I-VESIC dose and potential for minimal systemic exposure, larger doses of MK-3120 may be tolerated via I-VESIC administration.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The efficacy endpoint of this study is to evaluate the antitumor activity of MK-3120 in participants with CIS +/- papillary high-risk NMIBC. In Part 1, the rate of CR at 3 months, as assessed by local cystoscopy, urine cytology, pathology (when indicated) and radiology review (when indicated), will be used as the efficacy endpoint. The duration and overall CRR will also be evaluated. CR is considered an important endpoint in patients with CIS+/- papillary high-risk NMIBC who have a high unmet medical need and a relative lack of nonsurgical treatment options. Also, CR is an acceptable measure of clinical benefit for the

study as it represents direct evidence of the ablative antitumor effect of MK-3120 measured at an early timepoint and provides a signal of I-VESIC MK-3120 activity.

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

An exploratory objective of this study is to characterize the PK profile of MK-3120 after I-VESIC administration as a single agent. Levels of MK-3120 ADC, TAb, and payload will serve as the primary readout for blood PK. Furthermore, urine PK of MK-3120 payload will also be characterized. The results of these analyses will be used in conjunction with efficacy, safety, and other exploratory endpoint data to help assess future dosing strategies for MK-3120.

4.2.1.4 Antidrug Antibodies

The incidence of ADA will be evaluated and summarized over time by dose.

4.2.1.5 Exploratory Biomarker and Pharmacodynamic 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. 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 (eg, blood components, tumor material, etc) 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 the following:

Germline 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, 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.

Genetic (DNA) tumor analyses

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify important tumor-specific DNA changes (eg, mutations,

methylation status, microsatellite instability, etc). Key molecular changes of interest to oncology drug development may also include the mutational burden of tumors and the tumor microenvironment. Microsatellite instability may also be evaluated as this is an important biomarker for some cancers (eg, colorectal cancer). 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. Circulating tumor DNA may also be evaluated from biospecimens (eg, blood, urine, etc).

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 might correlate to clinical response to treatment with antitumor therapies. Specific gene sets (eg, those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Expression of individual genes may also be evaluated. MicroRNA profiling may also be pursued as well as exosomal profiling. Circulating tumor RNA may also be evaluated from biospecimens (eg, blood, urine, etc).

Immunohistochemical (IHC) and/or proteomic analyses using tumor

Tumor samples from this study may undergo histopathological, proteomic, and/or immunological analyses. These approaches could identify novel protein biomarkers that could aid in patient selection for antitumor therapy.

Other biomarkers

In addition to expression on the tumor tissue, tumor-derived proteins can be shed from tumor and released into the blood. Assays such as ELISA may be used to measure such proteins in serum, plasma, and/or urine. 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.

Furthermore, when applicable, cell populations may be also separated by either flow cytometry or mass cytometry-based sorting. These approaches may be used to quantify cell- and/or tissue-based analytes to further elucidate mechanism of action and/or assess disease-related parameters.

4.2.1.6 Additional Research Rationale

Additional Research will be conducted by the Sponsor on specimens for which consent was provided during this clinical study.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol and will only be conducted on specimens from appropriately consented participants. The objective of collecting/retaining specimens for these purposes is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer,

more effective drugs/vaccines, and/or to ensure participants receive the correct dose of the correct drug/vaccine at the correct time.

4.3 Justification for Dose

4.3.1 Starting Dose for This Study

Enrollment will begin at MK-3120 DL1 (300 mg) and escalate to MK-3120 DL2 (600 mg) and MK-3120 DL3 (900 mg) through the DLT evaluation window. A deescalation dose of 150 mg (DL-1) will be evaluated if the decision is made to deescalate from DL1. The deescalation dose was chosen such that it is sufficiently distinct in terms of dosing concentration from the starting dose of 300 mg in case unacceptable toxicities are observed.

The first 3 participants at each dose level will undergo an observation period of 24 hours before the next participant is dosed. Subsequent participants will not undergo a staggered enrollment.

4.3.1.1 Rationale for Starting and Maximum Dose of MK-3120

Due to minimal systemic absorption, I-VESIC treatment is expected to afford higher doses than IV due to reduced systemic toxicity. The local toxicity is to be evaluated. There was no measurable systemic ADC and payload exposure at the EV I-VESIC Phase 1 starting dose (125 mg; EV-104) [Kamat, A. M., et al 2023]. Additionally, there was minimal systemic ADC and payload exposure in the preclinical I-VESIC study of MK-3120 in mice (Section 2.2.3).

I-VESIC chemotherapy doses are similar to the IV doses [McKiernan, J. M., et al 2006] [Tan, W. S., et al 2023] [Arends, T. J. H., et al 2016] [Medscape 2024] [Medscape 2024a] [Medscape 2024b] and historically have a lower frequency of Grade ≥3 local or systemic toxicities [Laufer, M., et al 2003] [Tan, W. S., et al 2022] [Schmidt, S., et al 2020] than IV administration. The EV I-VESIC Phase 1 starting dose was the maximal IV RP2D, and the first 2 dose levels (125 and 250 mg) were well tolerated with no DLTs or treatment-related Grade ≥3 AEs or SAEs [Kamat, A. M., et al 2023]. Fixed I-VESIC doses are feasible as there are minimal differences in bladder size, and these differences are not expected to affect PK. Thus, the proposed starting dose for MK-3120-003 is 300 mg, which is the fixed dose equivalent of the weight-based 4 mg/kg dose for MK-3120, the lower of the 2 IV doses being tested in MK-3120-002. This starting dose is expected to be well tolerated via the I-VESIC route with minimal or no systemic absorption. Preclinical PK data in mice showed limited systemic exposure of the ADC and free payload in the MK-3120 100 µg (fixed dose equivalent of 5 mg/kg) I-VESIC cohorts, which was more than 100-fold lower than the MK-3120 100 µg IV cohort (Section 2.2.3). The MK-3120 IV clinical program will include dose expansion with 4 mg/kg q2w and 5 mg/kg q2w doses for determination of the IV RP2D (MK-3120-002). No DLTs were reported in the Phase 1 IV study (MK-3120-001/SLB410-I-01) at doses up to 5 mg/kg q2w.

An MTD is not expected to be attained for I-VESIC administration due to minimal systemic absorption and a lower rate of systemic toxicities compared with IV dosing; thus, the number of dose levels in this study has been limited to 3. The second dose level in this study will be

600 mg (2-fold of the starting dose), and the third dose level will be 900 mg (3-fold of the starting dose). These higher dose levels could potentially provide greater local tumor uptake compared with the starting dose and allow evaluation of dose-response between the 3 dose levels.

The totality of data for PK, efficacy, safety, and tolerability will be used to assess future dosing strategies of I-VESIC MK-3120.

4.3.1.2 Rationale for Dose Intervals

Typical dosing intervals used in I-VESIC studies from literature have been considered for deciding the intervals for I-VESIC MK-3120.

A typical I-VESIC induction regimen is weekly dosing for 6 weeks [Kamat, A. M., et al 2023][Dalbagni, G., et al 2006][Steinberg, R. L., et al 2015][Arends, T. J. H., et al 2016][Laufer, M., et al 2003][Tan, W. S., et al 2022][Schmidt, S., et al 2020] followed by disease assessment at Week 12 (recommended timing for first follow-up).

For participants with high-risk NMIBC, maintenance treatment is expected to provide durable efficacy responses [Gontero, P., et al 2024] [Holzbeierlein, J. M., et al 2024]. Monthly maintenance treatment for I-VESIC chemotherapies has been shown to be beneficial for patients with high-risk NMIBC [McElree, I. M., et al 2023] [Steinberg, R. L., et al 2015], and it was also used for the Phase 1 study for an I-VESIC ADC [Kamat, A. M., et al 2023]. However, the duration and frequency of maintenance treatment has varied across literature [Arends, T. J. H., et al 2016] [Witjes, J. A., et al 1998], and it may be further optimized for I-VESIC MK-3120 in future studies.

MK-3120 should be retained in the bladder for 2 hours and then voided. Participants unable to retain the study intervention for 2 hours should be allowed to void sooner, if necessary.

4.3.1.3 Dose Finding Using a Bayesian Optimal Interval Design

Dose finding will follow the BOIN design [Yuan, Y., et al 2016] with a target DLT rate of 30%. Dose-escalation and deescalation decisions are based on the BOIN design and depend on the number of participants enrolled and number of participants with at least 1 DLT observed at the current dose level.

A minimum of 3 participants are required at each dose. However, depending on the accrual rate, 3, 4, 5, or 6 participants may be enrolled within 7 to 14 days of the opening of a dose cohort. In Table 5, the columns indicate the numbers of participants treated at the current dose level, and the rows indicate the numbers of participants experiencing 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, deescalating the dose, and excluding the dose from the study due to unacceptable toxicity, respectively. For example, if 0 of 3 participants at a given dose level develop a DLT, then the dose can escalate to the next level. If 2 of 3 participants develop a DLT, the dose will be deescalated to the next lower dose level. If 3 of 3 participants develop a DLT, this indicates an unacceptable toxicity at this dose. The dose should be deescalated and the current dose will not be explored further. If 1 of 3 participants at a given dose level

develop a DLT, then additional participants should be enrolled at that dose level following the rules below. The totality of the data and BOIN table will be considered in making the next dose decision. For example, if a DLT rate of 33% is repeatedly observed (2 of 6, 3 of 9, etc), the review of data may lead to a dose de-escalation decision even if the BOIN design suggests a "Stay" decision.

When adding participants to a dose level, the number of additional participants to be enrolled is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 5). To determine how many more participants can be enrolled at the dose level, one can count steps in diagonal direction (down and to the right) from the current cell to the first cell marked DU. For example, if 1 of 3 participants have experienced a DLT at a given dose level, no more than an additional 3 participants should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 3 of the additional participants experience a DLT (ie, 4/6 participants with DLT in Table 5).

A D or DU decision at the lowest dose level will stop the study. An E decision at the highest dose level will result in staying at that level. During dose finding, it may be acceptable to deescalate or escalate to an intermediate dose that was not predefined and not previously studied if evaluation of toxicity at such a dose is desired. If this approach is taken, 3 to 6 new participants may be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.

After 10 participants have been enrolled at any of the tested doses (including intermediate doses), dose finding will stop if the BOIN table indicates "S" for staying at current dose.

After the dose-finding stops, the dose with an estimated DLT rate closest to 30% will be treated as a preliminary MTD. However, the totality of the data will be considered before deciding on the dose(s) to carry forward to dose expansion and the escalation schedule may be adjusted based on data emerging throughout the study.

Note that although 30% was the target DLT rate used to generate the guidelines in Table 5, the observed rates of participants with DLTs at the MTD may be slightly above or below 30%.

Table 5 Dose-finding Rules per BOIN Design With Target DLT Rate 30%

Number of Participants With At Least 1 DLT	**Number of Participants Evaluable for DLT at Current Dose**							
	3	**4**	**5**	**6**	**7**	**8**	**9**	**10**
0	E	E	E	E	E	E	E	E
1	S	S	E	E	E	E	E	E
2	D	D	D	S	S	S	E	E
3	DU	DU	D	D	D	D	S	S
4		DU	DU	DU	D	D	D	D
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

BOIN=Bayesian optimal design; 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; S=Stay at the current dose.

4.3.1.4 Backfilling Dose Levels

Dose Escalation and Backfilling

Once the participants have completed the DLT evaluation period at a given dose level and an escalation decision to a higher dose level based on the BOIN design is made (Table 5), the dose level that has been cleared may be expanded ("backfilled") to enroll up to a maximum of 10 participants, including those previously enrolled during dose escalation, to collect additional data (ie, safety, efficacy, PK, pharmacodynamic [if applicable]):

- Up to 2 dose levels immediately below the dose level under evaluation by the BOIN design may be open simultaneously for backfilling.

- If 2 dose levels are open for backfilling, alternating allocation will be employed to assign participants to a dose cohort.

Whenever there is a conflict in the dose escalation decision between a backfill dose and the current dose, the more conservative decision may be taken. For example, if the decision from the current dose is "E" and from the backfill dose is "S", the decision may be "Stay" at the current dose.

Extended Backfilling

Once the BOIN dose escalation has completed (Section 4.3.1.3), additional participants may be enrolled at the preliminary recommended dose and lower dose levels (ie, extended backfilling). Extended backfilling may continue until a maximum of 15 participants have been enrolled in each of the selected dose levels, including those participants previously enrolled during dose escalation and backfilling. Whenever 2 or more doses are open for

extended backfilling, alternating allocation will be employed to assign participants to a dose cohort.

The totality of the data from dose finding, backfilling, and extended backfilling will be included in the evaluation of the RDE.

4.4 Beginning and End-of-Study Definition

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

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

4.4.1 Clinical Criteria for Early Study Termination

Recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements, procedure-related problems, or if the number of discontinuations for administrative reasons is too high.

If >25% of study participants who have completed the prespecified DLT period experience Grade ≥4 drug-related AEs, as determined by the investigator, and if the totality of the data does not support a favorable risk-benefit ratio for the study intervention under evaluation, enrollment may be paused, and all available safety data will be reviewed to inform further decisions on study conduct. If treatment is discontinued, participants will continue in follow-up.

Early study termination will be the result of the criteria specified below:

1. Incidence or severity of adverse drug reactions in this or other studies suggest a potential health hazard to participants
2. Plans to modify or discontinue the development of the study drug

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-3120.

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.

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

1. Has histologically confirmed CIS +/- papillary HR NMIBC, confirmed locally
   Note: Individuals who have HG Ta or T1 without CIS are not eligible.
   Note: Individuals with tumors of mixed histology are eligible provided the conventional urothelial component is ≥50%.
   Note: Individuals whose tumors contain any neuroendocrine or small cell component are not eligible.
2. Is an individual whose most recent TURBT was performed within 12 weeks before allocation and showed high-risk NMIBC histology as detailed in Inclusion Criterion #1. For individuals with papillary tumors (Ta and T1), a complete TURBT must have been performed, as characterized by attainment of a visually complete resection of all papillary tumors (Ta and T1).
   Note: Individuals with residual CIS not amenable to complete resection are eligible.
   Note: Individuals with T1 disease must have undergone a restaging TURBT procedure confirming complete resection and that the individual continues to meet eligibility criteria. Individuals who undergo restaging TURBT of T1 lesion(s) are still eligible if the restaging TURBT:

- Is performed within 12 weeks before allocation even if the previous TURBT was performed >12 weeks before allocation
- Is absent of muscle-invasive tumor (≥T2).

3. Is either:

- BCG-naïve, defined as either having never received BCG or having received BCG more than 2 years before CIS +/- papillary HR NMIBC recurrence. Recurrence must be at least 24 months from the last exposure to BCG with evidence of complete response during the 2-year period post-BCG.

OR

- BCG-exposed and received adequate BCG therapy and had recurrence of CIS +/- papillary HR NMIBC >12 months but ≤24 months after the last BCG dose. Adequate BCG therapy is defined as at least:
  - 5 of 6 doses of initial induction BCG plus at least
    - 2 doses of subsequent maintenance OR
    - 2 of 6 doses of a second induction.

  Note: Participants should be disease-free after BCG induction and subsequently have a CIS +/- papillary recurrence outside the BCG-unresponsive window (>6 months for Ta/T1 and >12 months for CIS), but within 24 months.

Demographics

4. Is an individual of any sex/gender, ≥18 years of age at the time of providing the informed consent. Follow local regulatory requirements if the legal age of consent for participation is >18 years of age.

Assigned Male Sex at Birth

5. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for study intervention is: 120 days.

- Refrains from donating sperm
- Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method (refer to Section 10.5.3), as a condom may break or leak

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

Note: If the participant is 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), no contraception is required.

Assigned Female Sex at Birth

6. A participant assigned female sex at birth is eligible to participate if not breastfeeding during the study intervention period and for at least 14 days after the last dose of study intervention.

7. A WOCBP is eligible to participate if not pregnant and if a negative highly sensitive pregnancy test (urine or serum), as required by local regulations, has been obtained within 24 hours (for a urine test) or 72 hours (for a serum test) 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. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.6.
8. A WOCBP is eligible to participate if they use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or if they adhere to penile-vaginal intercourse abstinence 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 the study intervention after the last dose of study intervention. In addition, the participant agrees not to donate eggs (ova, oocytes) to others or freeze/store eggs during this period for the purpose of reproduction. The length of time required to continue contraception for the study intervention is: 210 days

- Note: The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recent initiation) in relationship to the first dose of study intervention. Contraceptive use by WOCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the local contraception requirements for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed. Medical history, menstrual history, and recent sexual activity should be reviewed by the investigator to decrease the risk for inclusion of a WOCBP with an early undetected pregnancy.

Informed Consent

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

Additional Categories

10. Able to provide a tissue sample for biomarker research from the diagnostic TURBT/biopsy procedure.
11. Participants who have AEs due to previous anticancer therapies must have recovered to ≤Grade 1 or baseline. Participants with endocrine-related AEs who are adequately treated with hormone replacement or participants who have ≤Grade 2 neuropathy are eligible.
12. Participants must agree to avoid donating blood or blood products for the duration of the study treatment period.
13. Participants must agree to avoid any penile or vaginal sexual contact for 2 days after drug instillation to prevent sharing of drug.
14. HIV-infected participants must have well controlled HIV on ART, defined as:
    a. Participants on ART must have a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening

b. 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
c. It is advised that participants must not have had any AIDS-defining opportunistic infections within the past 12 months
d. 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 (Day 1) and agree to continue ART throughout the study
e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)

15. 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 prior to 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 guidelines

16. 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 prior to allocation.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local guidelines

17. An ECOG performance status of 0, 1, or 2 assessed within 14 days before allocation.
18. Adequate organ function as defined in the following table (Table 6). Specimens must be collected within 14 days before the start of study intervention.

Table 6 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL
Platelets	≥100,000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L [a]
Renal	
eGFR per local institutional standard	≥60 mL/min/1.73 m^2
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 involvement)
Coagulation	
International normalized ratio (INR)/prothrombin time (PT), or activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); eGFR=estimated glomerular filtration rate; ULN=upper limit of normal.

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

5.2 Exclusion Criteria

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

Medical Conditions

1. History of or current locally advanced (ie, T2, T3, T4) or metastatic UC.
2. Has concurrent extravesical (ie, urethra, ureter, renal pelvis) non-muscle invasive UC or history of extravesical non-muscle invasive UC that recurred within the last 2 years.

   Note: Individuals with concurrent LG Ta of the prostatic urethra are eligible.

   Note: Individuals with prostatic ductal invasion regardless of histology are not eligible.
3. Has active total bladder incontinence, active UTI, neurogenic bladder, or urethral stricture
4. Has a condition that would prohibit normal voiding (or holding bladder voiding for 1 to 2 hours)
5. Has uncontrolled, significant cardiovascular disease or cerebrovascular disease, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, uncontrolled symptomatic arrhythmia, prolongation of QTcF interval to >470 ms, and/or other serious cardiovascular and cerebrovascular diseases within the 6 months preceding study intervention.
6. Has history of documented severe dry eye syndrome, severe Meibomian gland disease and/or blepharitis, or severe corneal disease that prevents/delays corneal healing.

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

Prior/Concomitant Therapy

8. Received prior treatment with a Nectin-4-targeted ADC or a topoisomerase 1 inhibitor, including ADCs.
9. Received strong CYP3A4 inhibitors, inducers, or substrates within 2 weeks before the first dose of study intervention or within 5 half-lives of drug elimination, whichever is longer.
   Note: A list of strong inhibitors or inducers of CYP3A4 can be found at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.
10. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of killed vaccines is allowed.
11. Received prior systemic and/or I-VESIC anticancer therapy within 4 weeks or 5 half-lives (whichever is shorter) and has not recovered to grade ≤ 1 or baseline from AE associated with anticancer therapy before allocation.
    Note: A single dose of I-VESIC chemotherapy following TURBT/biopsy is permitted without a washout.

Prior/Concurrent Clinical Study Experience

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

Diagnostic Assessments

13. Known additional malignancy that is progressing or has required active treatment within the past 3 years.
    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, that have undergone potentially curative therapy are not excluded. Participants with low-risk early-stage prostate cancer (T1-T2a, Gleason score ≤6, and PSA <10 ng/mL) either treated with definitive intent or untreated in active surveillance with stable disease are not excluded.
14. Known active CNS metastases and/or carcinomatous meningitis.
15. Active infection requiring systemic therapy other than those permitted in Section 5.1.
16. History of (noninfectious) pneumonitis/ILD that required steroids or has current pneumonitis/ILD.
17. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's ability to cooperate with the requirements of the study, such that it is not in the best interest of the participant to participate, in the opinion of the treating investigator.
18. A known severe hypersensitivity reaction to MK-3120 and/or any of its excipients

Other Exclusions

19. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.
20. Participants who are incapacitated are not eligible for this study.

See Appendix 7 for country-specific requirements.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Foods or alternative supplements that affect CYP3A4 activity should be avoided while receiving study intervention (Section 6.5).

Participants should be advised to modify their diet to avoid foods that may cause damage to the mucosa (eg, pretzels and chips) and foods that are acidic.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study and are deemed ineligible or are not subsequently 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.

Retesting may be performed only within the screening/rescreening periods; see Section 8.11.1 for details. Participants who are retested will retain their original screening number.

Individuals who fail screening may be rescreened one time for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management; see Section 8.11.1.

5.5 Participant Replacement Strategy

For safety monitoring in Part 1, all enrolled participants are required to meet safety evaluation criteria during the DLT evaluation window (first I-VESIC dose to the fourth I-VESIC dose +1 week). Replacement of a nonevaluable participant will occur if the participant is:

- Allocated, but not treated with study intervention
- Discontinued from study treatment without completing required DLT safety evaluations (excluding treatment-related AE discontinuations)

- Did not receive all 4 doses of study intervention during the DLT evaluation window (excluding treatment-related AE delays or discontinuations)

Nonevaluable participants in Part 1 will not count toward total participant numbers for DLT assessment in a particular dose level/cohort.

If a participant discontinues from study intervention or withdraws from the study, a replacement participant may be enrolled if deemed appropriate by the investigator and Sponsor. The replacement participant will generally receive the same intervention as the participant being replaced. The replacement participant will be assigned a unique allocation number. The study site should contact the Sponsor for the replacement participant's allocation number.

6 STUDY INTERVENTION

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

Clinical supplies provided by the Sponsor (MK-3120) will be packaged to support enrollment and replacement participants as required. When a replacement participant is required, the Sponsor or designee needs to be contacted before dosing the replacement participant. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Global clinical supply complaints and/or temperature excursions are to be reported as soon as possible upon first becoming aware of the issue by completing the Online Form at www.csincident.msd.com or via email to clinical.complaints.intake@MSD.com in case of system downtime or technical issues with the online form.

6.1 Study Intervention(s) Administered

The study intervention to be used in this study is outlined in Table 7.

Table 7 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
Part 1	Experimental	MK-3120	Biological/Vaccine	Powder, For Solution	100 mg/vial	300 mg 600 mg 900 mg	Intravesical	Induction: qw for 6 weeks Maintenance: q1month for 9 months	Test Product	IMP	Central

EEA=European Economic Area; IMP=investigational medicinal product; NIMP/AxMP=noninvestigational/auxiliary medicinal product; qw=once weekly; q1month=once per month.

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

MK-3120 will be provided centrally by the Sponsor (Table 7).

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

6.1.1 Treatment

Study treatment with MK-3120 consists of an induction period of 6 I-VESIC instillations given on a weekly basis, followed by a maintenance period of 1 instillation per month for a total of 9 months (9 instillations). Treatment with MK-3120 will be initiated on Day 1 of Week 1 and should continue as described in the SoA (Table 1) until any of the criteria for discontinuation of study intervention are met (Section 7.1).

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

All MK-3120 dose levels will be administered with an instillation volume of 50 mL. Details on preparation and administration of MK-3120 are provided in the pharmacy manual.

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 will occur centrally using IRT.

In Part 1 of the study, participants will be allocated by nonrandom assignment. The first 3 participants at each dose level will undergo an observation period of 24 hours before the next participant is dosed. Subsequent participants will not undergo a staggered enrollment.

The next dose level will open for enrollment without delay once the DLT observation period for the previous dose level is completed and a dose-escalation decision is made. If more than 1 dose level is open, alternating allocation will be employed to assign participants to a dose cohort.

6.3.2 Stratification

No stratification based on age, sex, or other characteristics will be used in this study.

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 instillation was stopped, the details of and reason for any interruption or instillation cessation of study intervention will be documented in the participant's medical record.

Interruptions from the protocol-specified treatment for >14 days from the next scheduled dose (except as permitted per the guidelines for dose modification due to AEs in Section 6.6) require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

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 to the assigned study participant.

6.5 Concomitant Therapy

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

The following medications and vaccinations are prohibited during the study treatment period:

- Strong inhibitors, inducers, or substrates of CYP3A4 (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)
- I-VESIC anticancer therapy not specified in this protocol is prohibited during the study treatment and efficacy follow-up periods.

If the investigator determines that a participant requires any of the following prohibited medications and vaccinations for any reason during the study, study intervention must be discontinued:

- Systemic antineoplastic chemotherapy, immunotherapy, or biological therapy not specified in this protocol
- Investigational agents other than those specified in this protocol
- Radiation therapy
  Note: Radiation therapy for curative intent to an early-stage second primary malignancy may be allowed at the investigator's discretion after the DLT observation period.
- Investigational vaccines (ie, those not licensed or approved for Emergency Use) are not allowed.

Study treatment should be held for 7 days before concomitant, nononcology surgery and may be restarted once any associated AEs have resolved to Grade ≤1 and the participant is clinically stable per the investigator's assessment.

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 medications will be recorded on the eCRF including all prescriptions, 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.

6.5.1 Rescue Medications and Supportive Care

Medications required to treat AEs or concurrent illnesses other than those prohibited in Section 6.5 are allowed during the study.

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

Suggested supportive care measures for the management of AEs associated with study intervention are outlined along with the dose modification guidelines in Section 6.6.

Appropriate resuscitation equipment should be available and a physician readily available during the period of drug administration.

Prophylactic dosing for nausea and vomiting is recommended before initial and subsequent study intervention administration. One or more of the following combinations may be selected based on previous response of participants to antiemetic medications and individual factors: 5-HT3 receptor antagonists, dexamethasone, NK-1 receptor antagonists, etc. Prophylactic dosing regimens may be adjusted if accompanied by other risk factors or in participants who have failed prophylaxis.

Before treatment with MK-3120, it is recommended that participants receive prophylactic treatment to mitigate the onset and severity of stomatitis/oral mucositis in accordance with published ASCO and MASCC/ISOO guidelines [Brown, T. J. and Gupta, A. 2020] [Elad, S., et al 2020]. Refer to Section 6.6.3 for information regarding recommended premedication to prevent hypersensitivity and/or infusion reactions.

If a steroid-containing mouthwash is not considered SOC per local/institutional guidelines, investigators can opt to use a non-steroid-containing prophylactic measure, including but not limited to:

- Rinsing with bland solutions (eg, normal saline, sodium bicarbonate, or tap water) at least 4 times per day or mucoadhesive hydrogel (eg, MuGard) or calcium phosphate rinses (eg, Caphosol) are recommended.
- Oral nystatin suspension or other topical antifungal agent can be used following the steroid-containing mouthwash per investigator discretion and following institutional guidelines.

6.6 Dose Modification

All toxicities will be graded using NCI CTCAE version 5.0 based on the investigator assessment.

6.6.1 Definition of Dose-limiting Toxicity

The DLT window of observation will be from the first I-VESIC dose to the fourth I-VESIC dose + 1 week.

The occurrence of any of the following toxicities during this window will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study intervention administration.

- Clinically significant hematuria leading to clot or obstruction
- Grade 4 thrombocytopenia

- Grade 3 thrombocytopenia associated with clinically significant bleeding
- Febrile neutropenia, defined as absolute neutrophil count <1000/mm3 with a single temperature >38.3°C (101°F) or a sustained temperature ≥38°C (100.4°F) for more than 1 hour
- Any other Grade ≥3 hematologic toxicity not listed above lasting >7 days
- Any nonhematologic (nonlaboratory) AE ≥Grade 3 should be considered a DLT, with the following exceptions:
  - Grade 3 diarrhea, nausea, or vomiting without use of antiemetics or antidiarrheals per SOC
  - Grade 3 fatigue lasting less than 7 days
  - Grade 3 rash without use of corticosteroids or anti-inflammatory agents per SOC
- ≥Grade 2 pneumonitis/ILD
- Any ≥Grade 3 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 >7 days, or
  - The abnormality results in a DILI (see Section 8.4.7 for criteria), or
  - Any AST or ALT elevation >8 × ULN regardless of duration and AST or ALT elevation 5 × to 8 × ULN that persists for greater than 2 weeks.
  - Exceptions:
    - Clinically nonsignificant, treatable, or reversible (resolved within 7 days to Grade 1 or baseline) laboratory abnormalities including liver function tests, uric acid, etc.
    - Grade 3 or higher electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.
    - Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.
- Any recurrent Grade 2 AE resulting in a prolonged delay (>2 weeks) in receiving the next treatment dose due to intervention-related toxicity.
- Any intervention-related toxicity that causes the participant to discontinue study intervention.
- Any Grade 5 toxicity or AE not due to underlying disease or extraneous causes.

6.6.2 Guidelines for Dose Modification due to Adverse Events for MK-3120

The CTCAE version 5.0 must be used to grade the severity of AEs. If a dose modification for toxicity occurs with MK-3120, the dose may not be reescalated to the dose that preceded the dose modification.

Recommended dose modification guidelines for MK-3120 are provided in Table 8. Dosing delays due to an AE should not exceed 14 days during the induction period or 28 days during the maintenance period unless otherwise discussed with the Sponsor.

If a participant experiences a DLT, the decision to continue the participant on study intervention with a dose reduction requires the mutual agreement of the investigator and the Sponsor.

Participants may have 1 dose reduction of MK-3120 over the course of the study, as described in Table 8. If the participant experiences an AE that requires a second dose reduction but the participant is deriving clinical benefit, the decision to reduce the dose and continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

MK-3120 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. Study intervention is to be restarted within 14 days of the next scheduled dose unless otherwise discussed with the Sponsor. The reason for study intervention interruption is to be documented in the participant's study record.

Exceptional circumstances to following the dose modification table below may be considered after consultation with the Sponsor.

Table 8 MK-3120 Dose Modification and Treatment Discontinuation Guidelines for Drug-related Adverse Events

Event(s)	**Toxicity grade (CTCAE 5.0) / result**	**Dose delay or modification[a]**	**Management and treatment**
Hematologic toxicities[b]			
Anemia	Grade 3	• First occurrence, delay until Grade ≤1 or baseline • Recurrent Grade 3, delay until Grade ≤1 or baseline and reduce dose by 1 dose level	• Consider transfusion, as appropriate
	Grade 4	• First occurrence, delay until Grade ≤1 or baseline and reduce dose by 1 dose level • Recurrent Grade 4, permanently discontinue	

Event(s)	Toxicity grade (CTCAE 5.0) / result	Dose delay or modification[a]	Management and treatment
Neutropenia	Grade 1	• Maintain current dose	• Consider administering growth factors (eg, G-CSF). During the initial induction phase, clinically evaluate the need for growth factors prior to subsequent weekly instillations. If growth factors are clinically indicated, the next instillation during induction must be delayed by at least 7 days. Administer growth factors for all subsequent monthly maintenance instillations per the ASCO guidelines and/or institutional standards.
	Grade 2	• Maintain current dose or delay until resolved to Grade ≤1 at the investigator's discretion	
	Grade 3 or 4	• First occurrence, delay until resolved to Grade ≤1 or baseline • Recurrent Grade 3, delay until Grade ≤1 or baseline and reduce dose by 1 dose level • Recurrent Grade 4, permanently discontinue	• First occurrence, administer growth factors (eg, G-CSF) • During the initial induction phase, clinically evaluate the need for growth factors prior to subsequent weekly instillations. If growth factors are clinically indicated, the next instillation during induction must be delayed by at least 7 days. Administer growth factors for all subsequent monthly maintenance instillations per the ASCO guidelines and/or institutional standards.
	Grade 3 or 4 febrile neutropenia	• First occurrence, delay until resolved and reduce dose by 1 dose level • Recurrent Grade 3, permanently discontinue • Recurrent Grade 4, permanently discontinue	
Thrombocytopenia	Grade 1 or 2	• Maintain current dose	• Monitor per institutional standards
	Grade 3 or 4 without clinically significant hemorrhage	• First occurrence, delay until resolved to Grade ≤1 or baseline and reduce dose by 1 dose level • Recurrent Grade 3 or 4, permanently discontinue	• Consider transfusion, as appropriate
	Grade 3 or 4 with clinically significant hemorrhage, or any spontaneous hemorrhage in vital organs	• Permanently discontinue	

Event(s)	Toxicity grade (CTCAE 5.0) / result	Dose delay or modification[a]	Management and treatment
Nonhematologic toxicities			
Diarrhea	Grade 1 or 2	• Maintain current dose and schedule	• Evaluate for infectious or other causes of diarrhea and treat, as appropriate • Provide antidiarrheal support
	Grade 3	• First occurrence, delay until resolved to Grade ≤2 • Recurrent Grade 3, reduce dose by 1 dose level	
	Grade 4	• Permanently discontinue	
Local bladder toxicity[c]	Grade 2	• Delay next scheduled treatment pending the resolution of symptoms to Grade ≤1 or baseline • Any participant that must delay treatment for more than 2 consecutive weeks during the initial 6 weeks of treatment will discontinue study intervention unless discussed with the Sponsor.	• Treat per the investigator's discretion or following local/institutional standards.
	Grade 3	• Delay next scheduled treatment pending the resolution of symptoms to Grade ≤1 or baseline and reduce dose by 1 dose level • Any participant that must delay treatment for more than 2 consecutive weeks during the initial 6 weeks of treatment will discontinue study intervention unless discussed with the Sponsor.	
	Grade 4	• Permanently discontinue	

Event(s)	Toxicity grade (CTCAE 5.0) / result	Dose delay or modification[a]	Management and treatment
Neurological toxicities (including peripheral neuropathy)	Grade 1	• Monitor closely and maintain current dose and schedule	• Ensure adequate evaluation to confirm etiology and/or exclude other causes • Provide supportive care, as needed, per institutional guidelines
	Grade 2	• Delay until resolved to Grade ≤1	
	Grade 3	• First occurrence, delay until resolved to Grade ≤1 and reduce dose by 1 dose level • Recurrent Grade 3, permanently discontinue	
	Grade 4	• Permanently discontinue	
Nonhematologic toxicity not otherwise specified	Grade 1 or 2	• Maintain current dose and schedule	• Ensure adequate evaluation to confirm etiology and/or exclude other causes • Provide supportive care, as needed, per institutional guidelines
	Grade 3	• First occurrence, delay until Grade ≤ 1 or baseline • Recurrent Grade 3, delay until Grade ≤1 or baseline and reduce dose by 1 dose level	
	Grade 4	• Permanently discontinue	
Pneumonitis/ILD	Grade 2	• First occurrence, delay until resolved to Grade ≤1 and reduce dose by 1 dose level • Recurrent Grade 2, permanently discontinue	• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Consider prophylactic antibiotics for opportunistic infections • Consider pulmonology consultation and additional workup including bronchoscopy, PFTs, etc.
	Grade 3 or 4	• Permanently discontinue	• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper • Administer prophylactic antibiotics for opportunistic infections • Consider pulmonology consultation and additional workup including bronchoscopy, PFTs, etc.

Event(s)	Toxicity grade (CTCAE 5.0) / result	Dose delay or modification[a]	Management and treatment
Stomatitis/Oral mucositis	Grade 1	• Maintain dose	• Provide supportive treatment (Section 6.5.1) and pain management as soon as the participant complains of a sore mouth per the ASCO/MASCC/ISOO guidelines [Brown, T. J. and Gupta, A. 2020] [Elad, S., et al 2020] or institutional standards • Evaluate for secondary infections
	Grade 2	• Delay until resolved to Grade ≤1	• Use formulated mouthwashes which contain mixtures of steroids, topical anesthetics, and other agents as needed. (eg, 50 mL saline plus 10 mg dexamethasone plus 0.2 g lidocaine), or other mixture per local guidelines (see Section 6.5.1) • Provide additional supportive treatment (Section 6.5.1) and pain management per the ASCO/MASCC/ISOO guidelines [Brown, T. J. and Gupta, A. 2020] [Elad, S., et al 2020] or institutional standards • Evaluate for secondary infections
	Grade 3	• First occurrence, delay until Grade ≤1 • Recurrent Grade 3, reduce dose by 1 dose level	• Use formulated mouthwashes which contain mixtures of steroids, topical anesthetics, and other agents as needed. (eg, 50 mL saline plus 10 mg dexamethasone plus 0.2 g lidocaine) or other mixture per local guidelines (see Section 6.5.1) • Administer analgesics (eg, morphine) • Provide additional supportive treatment (Section 6.5.1) and pain management per the ASCO/MASCC/ISOO guidelines [Brown, T. J. and Gupta, A. 2020] [Elad, S., et al 2020] or institutional standards • Evaluate for secondary infections
	Grade 4	• Permanently discontinue	• Use formulated mouthwashes which contain mixtures of steroids, topical anesthetics, and other agents as needed (eg, 50 mL saline plus 10 mg dexamethasone plus 0.2 g lidocaine) or other mixture per local guidelines (see Section 6.5.1) • Administer analgesics (eg, morphine) • Provide additional supportive treatment (Section 6.5.1) and pain

Event(s)	Toxicity grade (CTCAE 5.0) / result	Dose delay or modification[a]	Management and treatment
			management per the ASCO/MASCC/ISOO guidelines [Brown, T. J. and Gupta, A. 2020] [Elad, S., et al 2020]or institutional standards • Evaluate for secondary infections
Rash[d]	Grade 3	• First occurrence, delay until Grade ≤2 • Recurrent Grade 3, reduce dose by 1 dose level	• Ensure adequate evaluation to confirm etiology and/or exclude other causes • Based on severity of AE, administer corticosteroids per institutional guidelines
	Grade 4	• Permanently discontinue	
QTcF prolongation	≥500 msec	• For any QTcF prolongation ≥500 msec, including recurrent, withhold treatment until QTcF is <470 msec or returns to baseline	• Monitor potassium, calcium, and magnesium, and replenish as appropriate

AE=adverse event; ASCO=American Society of Clinical Oncology; CTCAE 5.0=Common Terminology Criteria for Adverse Events, version 5.0; DRESS=drug reaction with eosinophilia and systemic symptoms; G-CSF=granulocyte colony-stimulating factor; ILD=interstitial lung disease; ISOO=International Society of Oral Oncology; MASCC=Multinational Association of Supportive Care in Cancer; PFT=pulmonary function test; QTcF=corrected QT interval by Fridericia; SJS=Stevens-Johnson syndrome; TEN=toxic epidermal necrolysis.

Note: Appropriate resuscitation equipment should be available and a physician readily available during the period of drug administration.

[a] One dose reduction is allowed (ie, from 300 mg to 150 mg, from 600 mg to 300 mg, or from 900 mg to 600 mg). If the participant experiences an AE that requires a second dose reduction but the participant is deriving clinical benefit, the decision to reduce and continue the participant on study intervention requires the mutual agreement of the investigator and the Sponsor.

[b] Dosing decisions should be based on laboratory values obtained before the scheduled dosing visit (Section 1.3).

[c] Examples of local bladder toxicity include dysuria, urgency, frequency, cystitis, and cramping/pain.

[d] Participants should be permanently discontinued for confirmed SJS, confirmed TEN, or confirmed DRESS.

For further information, please refer to the CTCAE 5.0 at http://ctep.cancer.gov.

After any Grade 4 drug-related AE, participants should not restart study intervention without consultation with the Sponsor. Toxicity must have resolved to Grade 0 to 1 or baseline before restarting.

6.6.3 Prevention and Management of MK-3120 Hypersensitivity Reactions

Systemically administered ADCs such as MK-3120 may cause severe or fatal infusion-related reactions, including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after IV drug infusion and generally resolve completely within 24 hours of completion of infusion.

It is unknown whether I-VESIC administration of MK-3120 may cause hypersensitivity reactions related to instillation. Systemic absorption following I-VESIC administration is expected to be minimal. However, given the risk with systemic ADCs, participants must be monitored while retaining MK-3120 within their bladder and for at least 60 minutes post-

void for the first 4 instillations of MK-3120. After subsequent instillations, participants must be monitored in the clinic until they void; post-void monitoring will be at the discretion of the investigator.

Premedication to prevent hypersensitivity and/or instillation reactions may be given before each dose of MK-3120. Premedication should be administered starting 1.5 hours (±30 min) before instillation of MK-3120. Suggested premedication for the first 4 administrations includes diphenhydramine (50 mg po [or equivalent dose of antihistamine]) and acetaminophen (500 to 1000 mg po [or equivalent dose of analgesic]). Additionally, a corticosteroid (dexamethasone 8 mg to 10 mg IV, po, or IM [or equivalent]) may be added. After the fourth instillation, in the absence of prior instillation-related or hypersensitivity AEs, participants should be premedicated at the discretion of the investigator.

Dose modification and toxicity management of instillation reactions following MK-3120 administration are provided in Table 9.

Refer to Section 6.5.1 for information regarding recommended antiemetic premedication.

Table 9 Instillation Hypersensitivity Reaction Dose Modification and Treatment Guidelines for MK-3120

NCI CTCAE 5.0 Grade	**Treatment**	**Premedication at subsequent dosing**
Grade 1 Mild reaction; intervention not indicated	Encourage voiding in cases where clinically feasible Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator	Participants are required to be premedicated starting 1.5 h (±30 min) before instillation of study intervention with: • Diphenhydramine (or equivalent H1 receptor antagonist [per approved product label]) • H2 receptor antagonist (if available, per approved product label) • Acetaminophen (or equivalent [per approved product label]) • Dexamethasone 8 mg to 10 mg IV (or equivalent [per approved product label]) Instillation-related AEs will be monitored for all subsequent dosing.
Grade 2 Responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	Encourage voiding in cases where clinically feasible. 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. Participant should be premedicated for the next scheduled dose. Participants who develop recurrent Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study intervention.	

NCI CTCAE 5.0 Grade	Treatment	Premedication at subsequent dosing
Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication); recurrence of symptoms after initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Encourage voiding in cases where clinically feasible. Additional appropriate medical therapy may include but is not limited to: • Epinephrine (used immediately in the case of anaphylaxis) • 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. Participant is permanently discontinued from further study intervention.	No subsequent dosing
AEs=adverse event(s); CTCAE 5.0=Common Terminology Criteria for Adverse Events, version 5.0; h=hour(s); IV=intravenous; min=minute(s); NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs. Note: Appropriate resuscitation equipment should be available and a physician readily available during the period of drug administration. For further information, please refer to the CTCAE 5.0 at http://ctep.cancer.gov.		

6.7 Intervention After the End of the Study

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

All study-related procedures and data collection as defined per protocol will be terminated at study completion. In addition, 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

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

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

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention before completion of the protocol-specified treatment period will still continue to be monitored in this study and participate in the study visits and procedures as specified in Section 1.3 and Section 8.11.3 unless the participant has withdrawn from the study as specified in 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 as noted in Section 6.6.2, requires 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, places the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Any progression or recurrence of malignancy or any occurrence of another malignancy that requires systemic treatment.
  Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (excluding carcinoma in situ of the bladder) who have undergone potentially curative resection do not have to discontinue study intervention.
  Note: Participants who receive curative intent radiation or surgery for a second primary malignancy outside of the DLT period do not have to discontinue study intervention.
- 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.

- Side effects and/or concomitant medications required for treatment of HIV and/or its complications that are incompatible with continued study treatment (exceptions are permissible, but should be discussed with the Sponsor).

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

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

7.2 Participant Withdrawal From the Study

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

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

Specific details regarding procedures to be performed at the time of withdrawal from the study, as well as specific details regarding withdrawal from Additional Research, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified (by education, training, and experience) staff. Delegation of study-site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).
- All study-related medical (or dental) decisions must be made by an investigator who is a qualified physician.
- 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.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

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

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 their legally acceptable representative) and of the person conducting the consent discussion.

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

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, age of majority requirements or health), the investigator or medically qualified designee must ensure the appropriate documented informed consent from the participant (or their legally acceptable representative) is in place.

8.1.1.1 Full Informed Consent

Specifics about the study and the study population are to be included in the ICF.

The participant (or their 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.

8.1.1.2 Consent for Additional Research

The investigator or medically qualified designee will explain the optional Additional Research to the participant, or the participant's legally acceptable representative, answer all their questions, and obtain documented informed consent before performing any procedure related to Additional Research. A copy of the informed consent will be given to the participant before performing any procedure related to this research.

The original full consent including Additional Research, any subsequent revised version, and any written information provided to the participant must receive the IRB/IEC's approval/favorable opinion in advance of use. If new information becomes available, which may be relevant to the participant's willingness to continue participation in this research, the participant or their legally acceptable representative should be informed in a timely manner.

If the IRB/IEC does not provide approval, the study may proceed without Additional Research and participants will not be consented for this research.

If the Additional Research consent is under review or unavailable, then the FBR consent is to be used.

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, site personnel will add the treatment/allocation 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 Tobacco Use Assessment

Definitions for cigarette use are as follows [Land, S. R., et al 2016]:

- Current smokers: persons who report smoking ≥100 cigarettes during their lifetime and who, at the time of screening, reported smoking every day or some days within the last year.
- Former smokers: persons who report smoking ≥100 cigarettes during their lifetime and who, at the time of screening, had stopped smoking for at least 1 year prior.
- Never smokers: persons who report smoking <100 cigarettes during their lifetime.

8.1.5 Prior Cystoscopy/TURBT History

A history of cystoscopy/TURBT procedures the participant has received will be obtained by the investigator or qualified designee. The most recent of these procedures must have been performed within 12 weeks before allocation. These procedures should be recorded as part of the prior treatments for NMIBC as described in Section 8.1.6.1.

8.1.6 Prior and Concomitant Medications Review

8.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 28 days before the first dose of study intervention.

Treatment for the disease for which the participant has enrolled in this study will be recorded separately and not listed as a prior medication. The investigator or qualified designee will record all prior cancer treatments including systemic treatments, radiation, and surgeries the participant has received for their NMIBC. This will include detailed information about any disease persistence or recurrence. Reasons for participant ineligibility will also be recorded in the eCRF.

8.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study through 30 days after the last dose of study intervention. All medications taken for SAEs or ECIs should be recorded as described in Section 6.5.

8.1.7 Assignment of Screening Number

All consented participants will be given a unique participant identification code that will be used to identify the participant for all procedures that occur before intervention allocation. Each participant will be assigned only 1 participation identification code. Participation identification codes must not be reused for different participants.

Any participant who is rescreened will retain the original participant identification code assigned at the Screening Visit. Specific details on the screening/rescreening visit requirements are in Section 8.11.1. Pre-trial screening logs may be collected for review by the Sponsor. If applicable, any information that would make the participant identifiable will be removed.

8.1.8 Assignment of Treatment/Allocation Number

All eligible participants will be allocated, by nonrandom assignment, and will receive an allocation number. The assigned participant identification code will become the participant's allocation number. Once an allocation number is assigned to a participant, it can never be reassigned to another participant.

A single participant cannot be assigned more than 1 allocation number.

8.1.9 Study Intervention Administration

Study intervention(s) will be administered by the investigator and/or an appropriately qualified designee as outlined in the SoA (Section 1.3) and the pharmacy manual.

Study intervention should begin within 3 days of intervention allocation/assignment.

8.1.9.1 Timing of Dose Administration

MK-3120 will be administered as an I-VESIC instillation once per week for 6 consecutive weeks during the induction period, followed by a maintenance period of 1 instillation per month for a total of 9 months (9 instillations) as outlined in the SoA (Section 1.3). The reason for any variability in administration of MK-3120 outside the protocol-specified window should be documented in the participant's medical record and recorded on the eCRFs.

Every effort should be made to begin the first dose of study intervention on the day of allocation, but if this is not achieved, study intervention should be initiated no later than 3 days from the date of allocation. During the induction period, study intervention may be administered up to 3 days before or 3 days after the scheduled Day 1 of each week due to administrative reasons per the investigator's judgment. During the maintenance period, study intervention may be administered up to 7 days before or 7 days after the scheduled Day 1 of each week due to administrative reasons per the investigator's judgment. All study interventions will begin after all predose study procedures and assessments have been completed as detailed in the SoA (Section 1.3).

Dose modification guidelines are in Section 6.6. After dosing delays, treatment with MK-3120 should be resumed as soon as possible rather than waiting for the next scheduled protocol timepoint. Subsequent administrations will be adjusted to maintain the protocol schedule of planned time between treatment administrations.

The pharmacy manual contains specific instructions for MK-3120 preparation and administration.

MK-3120 should be retained in the bladder for 2 hours and then voided. Participants unable to retain the study intervention for 2 hours should be allowed to void sooner, if necessary. Participants must be monitored while retaining MK-3120 within their bladder and for at least 60 minutes post-void for the first 4 instillations of MK-3120. This includes monitoring of vital signs per local/institutional procedures so that immediate intervention can occur in response to symptoms of an untoward reaction. If clinically feasible, the participant should void the bladder if an instillation reaction occurs. After subsequent instillations, participants must be monitored in the clinic until they void; post-void monitoring will be at the discretion of the investigator.

Emergency rescue medications, appropriate resuscitation equipment, and a physician should be readily available during the period of drug administration and monitoring.

Refer to premedication guidelines in Section 6.6.3.

8.1.10 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 8.11.3.

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

8.1.10.1 Withdrawal From Additional Research

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

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

8.1.11 Procedures for Negative Studies Without Safety Concerns

If the study or one study intervention group discontinues due to futility or the study does not demonstrate statistically significant efficacy results per protocol specified analyses without any urgent safety issues, one or more of the following actions may occur:

- cessation of recruitment
- discontinuing participants assigned to a specific control group (see Sections 7.1 and 8.1.9) or study intervention group unless participants are deriving clinical benefit

The investigator or medically qualified designee must rapidly inform each participant of these results and discuss treatment options. Additionally, the protocol is to be amended to reflect any change in the study conduct (eg, cohort changes and follow-up).

8.1.12 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.

8.1.13 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.

8.1.14 Biospecimens for Biomarker Eligibility or Stratification

No biomarker biospecimens are used for eligibility or stratification in this study.

Details pertaining to exploratory biomarker specimens collected in this study can be found in Section 8.8 and the Central Laboratory Manual.

8.1.15 Elevated Transaminases With Treated HBV or HCV

Participants who were treated for HBV or HCV, enrolled in the study, and present with elevated transaminases according to the criteria below should be evaluated for viral hepatitis exacerbation/reactivation.

- If baseline AST/ALT <2 × ULN and an increase of AST/ALT ≥5 × ULN
- If baseline AST/ALT ≥2 × ULN and an increase of AST/ALT >3 × baseline level
- AST/ALT >500 U/L regardless of baseline
- Viral load testing and additional hepatitis serologies should be included as required.

8.1.16 Participants With Treated HIV

Participants with HIV should continue ongoing management by their health care provider(s), including monitoring of HIV viral load, CD4+ T-cell count, and additional supportive care measures.

8.2 Efficacy Assessments

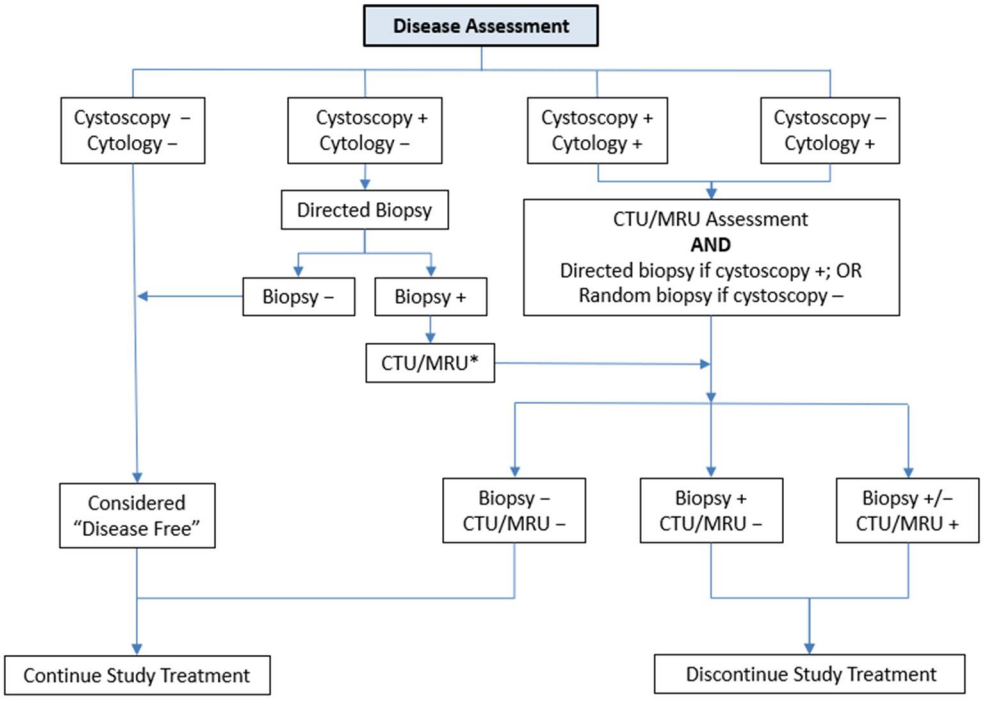
Disease will be assessed based on the integrated evaluation of urine cytology and cystoscopy with or without biopsies and/or CTU/MRU when applicable (Figure 3). All assessments will be evaluated locally. Tissue will be submitted for biomarker analysis as described in Section 8.8.

Participants who need to undergo TURBT/biopsy or CTU/MRU may receive study intervention for up to 1 additional dose while waiting for complete disease assessment findings, if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms, including worsening of laboratory values, indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease

Based on urine cytology, cystoscopy, and pathology assessment results, treatment with study intervention may be discontinued before CTU/MRU evaluation. In such cases, CTU/MRU should be performed at the earliest possible time unless CTU/MRU was obtained in the last 4 weeks.

Figure 3 Disease Assessment Decision Tree



*If study treatment discontinued prior to CTU/MRU evaluation, then CTU/MRU should be performed at the earliest possible time unless CTU/MRU was obtained within the last 4 weeks.
NOTE: A surveillance CTU/MRU is required at Week 48 as per Section 8.2.5

CTU = computed tomography urography; MRU = magnetic resonance urography

Legend:

CTU/MRU results by local review:

- CTU/MRU + (positive): positive result for extravesical disease, showing upper urinary tract urothelial carcinoma (UC), locally advanced or metastatic UC
- CTU/MRU – (negative): negative result for extravesical disease, showing no upper urinary tract UC, locally advanced or metastatic UC

Cytology results by local laboratory review:

- Cytology + (positive): positive or suspicious for malignant cells (suspicious for high-grade urothelial carcinoma or high-grade urothelial carcinoma)
- Cytology – (negative): not indicative or suspicious of malignant cells (includes negative for high-grade urothelial carcinoma, atypical urothelial cells, or low-grade urothelial neoplasm)

Cystoscopy results by local evaluation:

- Cystoscopy + (positive): indicative or suspicious of malignancy
- Cystoscopy – (negative): without malignant or suspicious lesions

Biopsy results by local pathology review:

- Biopsy + (positive): presence of high-grade Ta (HG Ta), CIS, or T1 disease of the bladder, urethra, prostatic urethra, ureter, or renal pelvis; or presence of muscle-invasive bladder cancer (≥T2)
- Biopsy – (negative): low-grade Ta or no urothelial carcinoma diagnosis

8.2.1 Urine Cytology

Specimens for urine cytology evaluation will be collected as outlined in the SoA (Section 1.3).

Voided urine samples should be collected before cystoscopy; alternatively, bladder washings can be collected at the time of cystoscopy. Voided first morning urine samples are not suitable for this analysis. Urine cytology must be considered evaluable; if not, another sample must be collected as soon as possible.

Urine cytology will be evaluated locally and results will be reported using Paris System classification criteria (Appendix 8) and documented appropriately in the eCRF. Cytology results will be considered:

- Positive when diagnosis is reported as "Suspicious for high-grade UC" or "High-grade UC"
- Negative when diagnosis is reported as "Negative for high-grade UC," "Atypical urothelial cells," or "Low-grade urothelial neoplasm"
- Inconclusive when diagnosis is reported as "Nondiagnostic" or "Unsatisfactory." In such instances, another sample must be collected for review.

Participants with a positive urine cytology will undergo biopsies as detailed in Section 8.2.3 and evaluation of extravesical disease with CTU/MRU as detailed in Section 8.2.5.

8.2.2 Cystoscopy

Cystoscopy will be performed as outlined in the SoA (Section 1.3) to inspect the whole urothelial lining in the bladder for tumors. Either white light, narrow band, or fluorescence-guided cystoscopy (photodynamic diagnosis or blue light cystoscopy) may be used, if available. The treating urologist/surgeon will determine which cystoscopy technique participants should undergo at baseline, and the same technique should be used for each participant for the duration of the study when clinically feasible.

Cystoscopy results will be considered:

- Positive if abnormal and indicative of, or suspicious for, malignancy (eg, presence of papillary lesions)
- Negative if normal, or abnormal and not suspicious for malignancy (eg, without suspicious lesions)

The cystoscopy technique selected for each participant and cystoscopy results should be documented appropriately in the eCRF.

Participants with a positive cystoscopy will undergo biopsies as detailed in Section 8.2.3.

8.2.3 TURBT and Biopsies

Participants with abnormal cystoscopy suspicious for malignancy will undergo directed biopsy of the target suspicious lesion(s). Additionally, participants without suspicious lesions on cystoscopy, but whose urine cytology is confirmed as HG UC or suspicious for HG UC will undergo serial biopsies of the normal-looking mucosa (random biopsies or R-biopsies). R-biopsies should be obtained of the trigone, bladder dome, and right, left, anterior, and posterior bladder walls, as well as the prostatic urethra in participants assigned male sex at birth.

Tissue will be assessed locally for pathologic stage and grade using the AJCC TNM staging system for bladder cancer (8th edition) and the 2022 WHO Classification of Tumours of the Urinary System and Male Genital Organs [Moch, H., et al 2022]. If pathology results as determined by local assessment reveal:

- **No UC disease (T0)**, this does not constitute disease relapse/persistence/progression. The participant will be permitted to continue treatment with study intervention and/or disease assessment.
- **Low-grade Ta**, this does not constitute disease relapse/persistence/progression. The participant may undergo TURBT to fully resect the papillary lesion(s) and will be permitted to continue treatment with study intervention and/or disease assessment. If all the LG Ta is removed at initial biopsy, a repeat TURBT is not required.
- **HG Ta, CIS, ≥T1 disease of the bladder, urethra, prostatic urethra, or upper tract (ureters, renal pelvis)**, this will constitute disease relapse/persistence/progression necessitating discontinuation of study intervention and/or disease assessment.
- **Inconclusive**, a repeat biopsy should be performed.

These procedures should be performed in keeping with local clinical practice and documented appropriately in the eCRF.

8.2.4 Cystectomy

Participants who undergo radical cystectomy without having had disease relapse, persistence, or progression as defined in Section 8.2 should continue extravesical disease assessments (ie, CTU/MRU) as outlined in the SoA (Section 1.3). Participants who undergo partial cystectomy without having had disease relapse, persistence, or progression as defined in Section 8.2 should continue disease assessments (ie, cytology, cystoscopy, biopsy, and CTU/MRU, as applicable) as outlined in the SoA (Section 1.3).

Tissue from cystectomy will be assessed locally using the same criteria as tissue from biopsy/TURBT detailed in Section 8.2.3. These procedures will be documented appropriately in the eCRF.

8.2.5 Evaluation of Extravesical Disease

CTU/MRU of the abdomen and pelvis for assessment of extravesical disease (ie, upper tract UC or metastatic UC) is required for all participants. CTU is the preferred imaging modality. MRU is acceptable when CTU is medically contraindicated per the investigator's judgment.

CTU/MRU will be performed as outlined in the SoA (Section 1.3). At screening, CTU/MRU performed as part of routine clinical management is acceptable if it is of acceptable diagnostic quality and performed within 6 months before the first dose of study intervention. In addition, CTU/MRU will be performed when a participant has a positive urine cytology (HG UC or suspicious for HG UC) or a positive biopsy (Section 8.2.3) if one was not performed within the last 4 weeks. Results of any unscheduled imaging, including via other

modalities, may also be collected if it captures extravesical disease based on investigator assessment.

A surveillance CTU/MRU is mandatory during the Week 48 disease assessment period (irrespective of disease assessment results). A surveillance CTU/MRU should be performed at Week 48 if a CTU/MRU was not performed within 36 weeks of the disease assessment.

Imaging will be evaluated locally per the following criteria:

- **Positive for extravesical disease** if it shows upper urinary tract UC or metastatic UC. This will constitute disease progression necessitating discontinuation of study intervention and/or disease assessments.
- **Negative for extravesical disease** if it does not show upper urinary tract UC or metastatic UC. Management of study participation will be guided by results of biopsy findings, as outlined in Section 8.2.3.

All CTUs/MRUs should be reviewed by the local radiologist and documented appropriately in the eCRF.

8.3 Safety Assessments

Details regarding specific safety procedures/assessments to be performed in this study are provided below.

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

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard. Height and weight will also be measured and recorded.

A brief directed physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard, and will include an oral examination.

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

8.3.1.1 Full Physical Examination

The investigator or qualified designee will perform a complete physical examination during the Screening period. Clinically significant abnormal findings should be recorded as medical history. The time points for full physical exams are described in Section 1.3. After the first dose of study intervention, new clinically significant abnormal findings should be recorded as AEs.

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

8.3.1.2 Directed Physical Examination

For weeks 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 oral examination) as clinically indicated. On dosing days, the directed physical examination will be performed prior to study intervention administration.

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

8.3.2 Vital Signs

The investigator or qualified designee will take vital signs as directed in the SoA (Section 1.3) with the following considerations:

- Vital signs will be assessed in a semirecumbent, supine, or sitting position after 5 minutes of rest and will include systolic and diastolic blood pressure, pulse/heart rate, respiratory rate, and temperature.
- BP and pulse/heart rate measurements should be obtained with a completely automated device. Manual techniques will be used only if an automated device is not available.

8.3.3 Electrocardiograms

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

Clinically significant abnormal findings of the Screening ECG should be recorded as medical history, and clinically significant abnormal findings of any subsequent ECGs should be recorded as AEs.

Refer to Appendix 10.3.2 for evaluation and potentially significant findings.

8.3.4 Echocardiogram or Multiple Gated Acquisition Scan

MUGA scan (using technetium-based tracer) or an echocardiogram will be performed to assess LVEF as specified in the SoA (Section 1.3). MUGA or echocardiogram scans should be performed locally in accordance with the institution’s standard practice. However, whichever modality is used for an individual participant at baseline should be repeated for all subsequent LVEF assessments for that participant as clinically feasible. Investigator assessment will be based on institutional reports.

8.3.5 Clinical Safety Laboratory Assessments

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

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual 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.
- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.3.5.1 Laboratory Safety Evaluations (Hematology, Chemistry, and Urinalysis)

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

8.3.6 Pregnancy Testing

- Pregnancy testing:
  - Pregnancy testing requirements for study inclusion are described in Section 5.1.
  - Pregnancy testing (urine or serum) should be conducted, as per the SoA.
  - Pregnancy testing (urine or serum) should be conducted for the time required to eliminate systemic exposure after the last dose of each study intervention and should correspond with the time frame for the participant's contraception, as noted in Section 5.1. The length of time required to continue pregnancy testing for each study intervention is:
    - MK-3120: 210 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.

See Appendix 7 for country-specific requirements.

8.3.7 Performance Assessments

8.3.7.1 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) as specified in the SoA (Section 1.3).

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.

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

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

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

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

All AEs, SAEs, and other reportable safety events that occur after the participant provides documented informed consent, but before intervention allocation, must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes 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 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 through 30 days after cessation of study intervention must be reported by the investigator

- All pregnancies and exposure during breastfeeding, from the time of intervention allocation through the time required to eliminate systemic exposure after cessation of study intervention as described in Sections 5.1 and 8.3.6, 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 10.

Table 10 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 AE Collection Period**	**Reporting Period: After the Protocol-specified AE Collection 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	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-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 AE Collection Period	**Reporting Period:** After the Protocol-specified AE Collection 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
Potential DILI events meeting biochemical criteria of Hy's Law (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report - regardless of suspected etiology - to be reported as an ECI and SAE with OME criteria in the absence of other serious criteria	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (requires regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – requires regulatory reporting	Previously reported – Follow to completion/ termination; report outcome	Within 24 hours of learning of event
ECI (does not require regulatory reporting)	Report if: – due to intervention – causes exclusion	Report – those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event (unless an SAE)
New Cancer (that is not the cancer under study)	Report if: – due to intervention – causes exclusion	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)
Overdose	Report if: – receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event (unless an SAE)

AE=adverse event; DILI=drug-induced liver injury; ECI=event of clinical interest; NSAE=nonserious adverse event; OME=other important medical 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. SAEs and other reportable safety events, including potential DILI events meeting biochemical criteria of Hy's Law, 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). The investigator will also make every attempt to follow nonserious AEs that occur in allocated 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), or a pregnancy that occurs during the study in a nonparticipant whose sexual partner is a participant capable of producing ejaculate is 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.

ECIs for this study include:

All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as both an ECI and SAE, with OME criteria in the absence of other SAE criteria, within 24 hours of learning of the event. Potential DILI events are defined as:

- An elevated AST or ALT laboratory value that is greater than or equal to 3× the ULN and,
- An elevated total bilirubin laboratory value that is greater than or equal to 2× the ULN and,
- At the same time, an alkaline phosphatase laboratory value that is less than 2× the ULN,

determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based on available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an

additional evaluation for an underlying etiology. The study-site guidance for assessment and follow up of these criteria can be found in the Investigator Study File Binder (or equivalent).

8.5 Treatment of Overdose

For purposes of this study, an overdose will be defined as any dose exceeding the prescribed dose for MK-3120 by ≥20% of the indicated dose. No specific information is available on the treatment of overdose of MK-3120. In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

8.6 Pharmacokinetics

To further evaluate MK-3120 immunogenicity and exposure in this indication, and to evaluate exposure of the proposed dosing regimen, sample collections for analysis of PK and ADA are currently planned as shown in Section 1.3 (Table 3). Blood samples will be obtained to measure PK of serum TAb and ADC.

PK assessment includes measurements of free payload, TAb, and ADC in serum or plasma. For free payload, plasma will be collected. For ADC and TAb, serum will be collected. C_{max} and C_{min} at planned visits and times will be summarized.

Blood samples collected may be stored and further analysis may be performed, if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued, and sites will be notified accordingly.

8.6.1 Blood Collection for MK-3120 PK

Sample collection, storage, and shipment instructions for serum or plasma samples will be provided in the Central Laboratory Manual. PK samples should be drawn according to the PK collection schedule for all participants.

8.6.2 Blood Collection for Antidrug Antibodies

Sample collection, storage, and shipment instructions for serum samples will be provided in the Central Laboratory Manual. Anti-MK-3120 antibody samples should be drawn according to the ADA collection schedule for all participants (Section 1.3). Simultaneous PK sampling is required for interpretation of ADA analysis.

8.6.3 Urine Collection for Urinary MK-3120 PK

Sample collection, storage, and shipment instructions for urine samples will be provided in the Central Laboratory Manual.

8.7 Pharmacodynamics

Exploratory pharmacodynamic assays may be performed on samples described in Section 8.8.

8.8 Biomarkers

To identify novel predictive/pharmacodynamic 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
- Plasma for ctDNA
- Urine for Biomarkers
- Urine for utDNA
- Tissue for Biomarkers

Exploratory biomarker specimens may also be used to improve and develop study-related tests (eg, assay development). Sample collection, storage, and shipment instructions for the exploratory biomarker specimens will be provided in the Central Laboratory Manual.

See Appendix 6 for additional information on exploratory biomarkers.

8.8.1 Planned Genetic Analysis Sample Collection

The genetic analysis specimen should be collected for the analysis of the association between genetic variants in DNA and drug response. This specimen will not be collected as mandatory at the site if the IRB/IEC does not approve the collection based on a local law or regulation. If the genetic analysis specimen is not approved as mandatory, this specimen can be collected under a separate optional informed consent. If the specimen is collected, leftover extracted DNA will be stored for Additional Research if the participant provides documented informed consent for this research.

The genetic analysis specimen should be obtained on Day 1 but may be collected at a future visit, if needed. Specimen collection, storage, and shipment instructions for genetic analysis specimens will be in the Central Laboratory Manual.

8.9 Additional Research

All specimen collections for study-specific assessments shown in the SoA are described within the full Informed Consent.

If the participant has provided documented informed consent for Additional Research, the following leftover specimens will be included for Additional Research:

- Leftover specimens listed in Section 8.8.

8.10 Medical Resource Utilization and Health Economics

Not applicable.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3 (Table 1 and Table 2). Specific procedure-related details are provided in Section 8.

Any visits that do not require participants to be on site (eg, concomitant medication review, AE review, etc) can be done via a telephone contact, or a telehealth visit, at the discretion of the investigator.

8.11.1 Screening

Approximately 28 days before intervention allocation, potential participants will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures are to be completed within 28 days before the first dose of study intervention.

A test performed, as part of routine clinical management prior to the participant signing consent, is not to be repeated if performed within the specified time frame and the results are acceptable.

Screening procedures may be repeated after consultation with the Sponsor. If a study assessment needs to be repeated, the investigator may perform a retest of screening procedures to assess the eligibility of a participant as noted in Sections 5.1 and 5.2. Participants who are retested will retain their original screening number.

If a participant fails to meet eligibility criteria during the initial screening period, the investigator may initiate a rescreening period per Section 1.3 and Section 5.4 after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

8.11.2 Treatment Period

Visit requirements are outlined in the SoA (Section 1.3). Specific procedure-related details are provided in Section 8.

8.11.3 Participants Discontinued From Study Intervention but Continuing to be Monitored in the Study

When a participant discontinues study intervention during the treatment period, procedures for discontinuation will be performed.

The EOT/Discontinuation Visit should occur at the time study intervention is discontinued for any reason. If EOT/Discontinuation Visit occurs 7 or more days after the last dose of study intervention, the EOT/Discontinuation Visit and any additional safety follow-up procedures should be performed and combined into 1 visit. Visit requirements are outlined in the SoA (Section 1.3). Additional details regarding participant withdrawal and discontinuation are described in Section 7.

8.11.4 Posttreatment Visit

Posttreatment visit requirements are outlined in the SoA (Section 1.3.2, Table 2). A separate EOT/Discontinuation Visit is not performed when study treatment administration is completed.

8.11.4.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 14 days after the last dose of study intervention or before initiation of a new anticancer treatment, whichever comes first.

8.11.4.2 Efficacy Follow-up Visits

Participants who complete the protocol-required doses of study intervention or who discontinue study intervention for a reason other than disease progression, persistence, or relapse; death, or the initiation of a new anticancer therapy will begin Efficacy Follow-up and should be assessed as outlined in the SoA and Section 8.2 to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anticancer therapy, disease progression, persistence, or relapse; completion of the Week 108 disease assessment, death, or end of study. Information regarding poststudy anticancer treatment will be collected if new treatment is initiated. Participants who discontinue efficacy assessments prior to completion of the Week 108 disease assessment must enter Survival Follow-up.

8.11.4.3 Survival Follow-up Contacts

Participant survival follow-up status will be assessed approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or completion of the survival follow-up period (ie, after total of approximately 2 years on 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 discontinue 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.

Where allowed, participants who discontinue efficacy follow-up before meeting a criterion for discontinuation (see Section 8.11.4.2) will be encouraged to allow the results of disease assessments performed during Survival Follow-up (including urine cytology, cystoscopy, and/or biopsy/CTU/MRU) as SOC to be submitted to the eCRF. Urine cytology, cystoscopy, and TURBT/biopsy results will only be collected if performed at the investigator's site or performed by an investigator/designee. Imaging results may be submitted regardless of where the imaging was performed.

8.11.4.3.1 Bladder Follow-up Contacts

Participant bladder status will be assessed approximately every 12 weeks in the same manner described for survival status in Section 8.11.4.3. Any new anticancer therapies, along with bladder status (ie, intact vs. removed), stage at removal, or rationale for not removing the bladder will be assessed with survival follow-up.

8.11.5 Vital Status

To ensure current and complete survival information (vital status) is available at the time of database locks, updated vital status may be requested during the study by the Sponsor. For example, updated vital status may be requested before but not limited to, a DMC 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, vital status (survival information) may be obtained by review of public records, in accordance with local regulations. If a participant 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.

8.11.5.1 Bladder Status

Bladder status may also be requested during the course of the study by the Sponsor in the same manner described for vital status in Section 8.11.5. New anticancer treatments will be assessed, as appropriate, during this contact including bladder status (ie, intact vs. removed/cystectomy performed), stage at cystectomy/removal, or the rationale for not removing the bladder.

9 KEY STATISTICAL CONSIDERATIONS

This section details the principal statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to the statistical analysis plan stated below, then these deviations to the plan will be listed, along with an explanation as to why they occurred, in the Clinical Study Report.

9.1 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, i.e., participants, investigators, and Sponsor personnel will be aware of participant treatment assignments after each participant is enrolled and treatment is assigned.

9.2 Hypotheses/Estimation

There is no formal hypothesis testing in the study. Objectives of the study are stated in Section 3.

9.3 Analysis Endpoints

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

9.3.1 Efficacy/Pharmacokinetics Endpoints

There is no primary efficacy endpoint. The secondary efficacy endpoints include complete response (CR) at 3 months.

CR at 3 months is evaluated by the complete response rate (CRR) at 3 months, defined as the proportion of participants who are absent of all the following as determined by local assessment using urine cytology, cystoscopy, biopsy and radiology assessments as applicable: high-risk non-muscle invasive UC (defined as HG Ta, CIS, or any T1 disease of the bladder, urethra, or upper tract [ureters, renal pelvis]), any T2 or greater in the bladder, including transurethral prostate stromal invasion of UC, or in the upper trace (ureters, renal pelvis), and metastatic UC, defined as regional lymph node metastasis of UC (N1 or greater) and distant lymph node or visceral metastasis of UC (M1).

Exploratory efficacy endpoints include overall CR, duration of CR, and OS.

PK endpoints include blood levels of MK-3120 ADC, TAb, and payload. If feasible, pharmacokinetic parameters such as C_{max}, C_{trough} and AUC for ADC, TAb and payload will be estimated. Additional PK endpoints include assessment of urine levels of payload. Immunogenicity endpoints include ADA formation to I-VESIC MK-3120.

9.3.2 Safety Endpoints

The primary safety endpoints are the incidence of DLTs, AEs, and discontinuation of study intervention due to AEs. In addition, safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, laboratory tests, and vital signs.

9.4 Analysis Populations

9.4.1 Efficacy/Pharmacokinetic Analysis Populations

The FAS population will be used for the analyses of efficacy data in this study. It consists of all participants with a baseline evaluation consisting of pre-enrollment cystoscopy, TURBT/biopsy, urine cytology, and baseline CTU imaging, and who were administered at least 1 dose of study intervention.

The per protocol population will be used for the analysis of PK in this study. The per protocol population consists of the subset of participants who complied with the protocol sufficiently and have available data from at least 1 treatment. Any participants or data values excluded from the analyses will be identified, along with the reasons for exclusion, in the CSR.

9.4.2 Safety Analysis Populations

The APaT population will be used for the analysis of safety data in this study. The APaT population consists of all participants who received at least 1 dose of study intervention.

The DLT-evaluable population includes APaT participants that meet the criteria for DLT evaluability (i.e., finished DLT evaluation period without a DLT or experienced a DLT in the DLT evaluation period). See Section 5.5 and Section 6.6 for details.

At least 1 laboratory or vital sign measurement obtained after 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 Statistical Methods

9.5.1 Statistical Methods for Efficacy/Pharmacokinetic Analyses

The point estimate of CRR at 3 months and overall CRR will be provided by dose levels, together with 95% CI using exact binomial method proposed by Clopper and Pearson [Clopper, C. J. and Pearson, E. S. 1934]. Participants with missing data are considered non-responders and included in the total number of participants.

If sample size permits, duration of CR will be summarized descriptively using Kaplan-Meier medians and quartiles. Otherwise, only descriptive summary statistics will be provided. Censoring rules for duration of CR are summarized in Table 11.

Table 11 Censoring Rules for Duration of CR

Situation	Date of Progression or Censoring	Outcome
No progression or death, no new anticancer therapy initiated	Last adequate disease assessment	Censor (nonevent)
No progression or death, new anticancer therapy initiated	Last adequate disease assessment before new anticancer therapy initiated	Censor (nonevent)
Death or progression immediately after ≥2 consecutive NE disease assessments or after new anticancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 consecutive NE disease assessments and new anticancer therapy, if any	Censor (nonevent)
Death or progression after ≤1 NE disease assessment and before new anticancer therapy, if any	PD or death	End of response (event)
PD=progressive disease; NE=non-evaluable (missing any of the required disease assessments at a protocol-specified efficacy time point).		

PK parameters of study interventions will be reported separately.

9.5.2 Statistical Methods for Safety Analyses

AEs will be summarized by counts and frequencies for each dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

The overall safety evaluation will include a summary of the number and percentage of participants in each dose level with at least one AE, drug-related AE, serious AE, serious drug-related AE, Grade 3-5 AE, drug related Grade 3-5 AE, discontinuation from study intervention due to an AE, interruption of study intervention due to an AE, an AE resulting in dose reduction, and an AE resulting in death. The number and percentage of participants with specific AEs will also be provided by dose levels.

The number and percentage of participants with laboratory toxicity grade increased from baseline will be summarized by the post-baseline maximum toxicity grade per CTCAE V5.0 for each gradable laboratory test in each dose level.

For continuous safety measures, such as change from baseline in laboratory values, vital signs, and ECG parameters, summary statistics for baseline, on-treatment, and change from baseline values will be provided by dose levels.

DLTs will be listed and summarized by dose levels. The pool-adjacent-violators algorithm [Liu, S. and Yuan, Y. 2015] may be used to assist with the estimation of the DLT rates across doses in each treatment arm as appropriate. The estimate of the DLT rate among participants treated at the preliminary RP2D and the 90% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

9.6 Interim Analyses

There are no planned IAs for this study.

9.7 Multiplicity

No multiplicity adjustment is planned as there are no statistical hypotheses in this study.

9.8 Sample Size and Power Calculations

Approximately 3 to 6 participants will be enrolled at each dose level during the initial dose escalation. The dose levels may be expanded (including backfilling during dose escalation and extended backfilling) to approximately 15 participants per dose level. The sample size for Part 1 of this study is expected to be approximately 45 for the three planned dose levels. The actual sample size will depend on the safety profiles. For example, suppose the study enrolls N=3 for DL1-2 and N=10 for DL3, backfills N=7 for DL1-2 during the dose escalation, and adds another N=5 for DL1, DL2, and DL3 during extended backfilling. The total sample size will then be 45.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Code of Conduct for Interventional 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 conducting these trials in compliance with the highest ethical and scientific standards. Trial conduct includes processes from design to reporting, including planning, initiating, performing, recording, oversight, evaluation, analysis and reporting activities as appropriate. 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, randomization, and blinding) 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. The use of innovative digital health technologies will be considered. Factors critical to the quality of the trial should also be identified. These factors are attributes of a trial that are fundamental to the protection of participants, the reliability and interpretability of the trial results and the decisions made based on those trial results. Risks to critical to quality factors should be managed prospectively and adjusted when new or unanticipated issues arise once the trial has begun. 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 records 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. Informed consents include relevant aspects of the trial, such as trial design, anticipated benefits and risks of medical intervention(s), trial setting, and the potential use of technology. 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.

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 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.

10.1.5 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. For studies conducted under the EMA Clinical Trials Regulation 536/2014, a summary of the study results will be submitted in compliance with the regulation**.** 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.

10.1.6 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.

10.1.7 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.

10.1.8 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.

10.1.9 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 12 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 12 Protocol-required Clinical Laboratory Assessments

Assessments Conducted at Screening Only	
Coagulation	PT or INR aPTT
Other	If applicable: HIV antibody, HbsAg, HBV DNA, HBV viral load, HCV viral load
Assessments Conducted at Screening and During the Study	
Hematology	Hematocrit Hemoglobin Platelet count WBC (total and differential)[a] RBC (count and indices)
Chemistry	Albumin Alkaline phosphatase ALT/SGPT AST/SGOT Bicarbonate (CO2)[b] BUN[c] Calcium Chloride Creatinine Glucose (fasting or nonfasting) Potassium Sodium Total bilirubin Total protein If total bilirubin >ULN: Direct bilirubin

Assessments Conducted at Screening and During the Study	
Routine Urinalysis	Specific gravity pH Glucose Protein Blood Ketones By dipstick: Bilirubin Urobilinogen Nitrite Leukocyte esterase Microscopic examination if clinically indicated by protein, blood, nitrite, or leukocyte esterase values
Other	Urine creatinine (random) WOCBP: serum hCG or highly sensitive urine pregnancy test

ALT=alanine aminotransferase; aPTT=activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; CO2=carbon dioxide; DNA=deoxyribonucleic acid; hCG=human chorionic gonadotropin; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; PT/INR=prothrombin time/international normalized ratio; RBC=red blood cell; SGOT=serum glutamic-oxaloacetic transaminase; SGPT=serum glutamic-pyruvic transaminase; ULN=upper limit of normal; WBC=white blood cell; WOCBP=woman/women of childbearing potential.

[a] Percent or absolute (as per institutional standards).
[b] Performed only if considered local standard of care.
[c] BUN is preferred, but if not available, then urea may be tested.

- Report the results in the same manner throughout the study. Refer to the Laboratory Manual
- Pregnancy tests must be conducted as described in Sections 1.3, 5.1, and 8.3.6 or as required by local regulations

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

10.3.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

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

Misuse

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

Abuse

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

10.3.2 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.
- Note: For purposes of AE definition, study intervention includes any pharmaceutical product, biological product, vaccine, diagnostic agent, medical device, combination product, or protocol-specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

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

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

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Surgical procedure(s) planned prior to informed consent to treat a preexisting condition that has not worsened.
- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.3 Definition of SAE

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

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

a. Results in death
b. Is life-threatening
   - The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization
   - Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a preexisting condition that has not worsened is not an SAE.) A preexisting condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. Results in persistent or significant disability/incapacity
   - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
   - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

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

f. Other important medical events
   - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
   - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
   - All potential DILI events meeting biochemical criteria of Hy's Law will be reported to the Sponsor, regardless of suspected etiology, as an ECI and SAE with OME criteria in the absence of other SAE criteria within 24 hours of learning of the event.

10.3.4 Definition of a Suspected Unexpected Serious Adverse Reaction (SUSAR)

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is an adverse event that occurs during a clinical trial and meets the following criteria:

- unexpected, meaning the nature or severity of the event doesn't match the reference safety information (RSI)
- serious adverse event as defined in Section 10.3.3
- reasonable possibility the event was caused by the study drug

10.3.5 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 8.4.6.
- Is associated with an overdose.

10.3.6 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.
  - Note: A semi-colon indicates 'or' within the description of the grade.

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 reexposed 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; (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 REEXPOSURE 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 case report forms/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.

10.3.7 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: Drug–Device Combination Products/Combination Medicinal Products: Complaints, Product Quality Complaints/Malfunctions: Definitions, Recording, and Follow-up

Not applicable.

10.5 Appendix 5: Contraceptive Guidance

10.5.1 Definitions

10.5.1.1 Definition of Childbearing Potential

Individuals assigned female sex at birth are considered fertile and capable of becoming pregnant unless at least one of the following criteria is met:

- Premenarchal
- Premenopausal with documented hysterectomy and/or bilateral salpingectomy
- Postmenopausal
- Medical cause of permanent infertility (eg, Müllerian agenesis, androgen insensitivity)

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

10.5.1.2 Definition of Menopausal Status

Postmenopausal (meets at least one of the following criteria):

- Age ≥ 60 years
- Documented bilateral oophorectomy
- ≥ 12 months since LMP in participant without prior uterine surgery expected to cause amenorrhea, pregnancy, HRT, hormonal contraception, estrogen receptor antagonist, chemotherapy, ovarian suppression, and/or any other medical cause for amenorrhea since LMP
- FSH (+/− estradiol) levels consistent with postmenopausal status as per local/institutional guidelines and determined to be postmenopausal by the investigator in participants with any of the following:
  - Unknown LMP
  - ≥ 12 months since LMP in participant with prior uterine surgery expected to cause amenorrhea, pregnancy, HRT, hormonal contraception, estrogen receptor antagonist, chemotherapy, ovarian suppression and/or any other medical cause for amenorrhea since LMP
  - < 12 months since LMP (Note: Measurement of FSH at a single time point is insufficient if < 12 months since LMP)

Note: FSH and estradiol cannot reliably be used to determine menopausal status in participants currently receiving HRT, hormonal contraception, estrogen receptor antagonist or ovarian suppression. If a participant who did not meet criteria for postmenopausal status prior to initiation of any of these therapies cannot stop these therapies in order to assess menopausal status, then the participant cannot be considered postmenopausal.

Premenopausal:

- Are not postmenopausal

10.5.2 Contraceptive Requirements

10.5.2.1 Contraceptive Requirements for Study Participants Who Are of Childbearing Potential

Contraceptives allowed during the study include:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• IUS [a, b] • Progestogen-only subdermal contraceptive implant [b] • Nonhormonal IUD • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) – All sexual partner(s) of the WOCBP must be azoospermic. The participant must provide verbal confirmation of partner azoospermia during Medical History. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from penile-vaginal intercourse with partner(s) capable of producing sperm 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] IUS is a progestin-releasing IUD. [b] As some baseline ART regimens may decrease efficacy of hormonal contraception by potential drug-drug interactions (eg, CYP3A4 inducers), the investigator must assess the need for backup contraception to supplement hormonal contraceptives (preferably penile/external condoms) in accordance with the participant's specific baseline ART regimen and local product labeling. In situations where the WOCBP's baseline ART regimen could reduce their concomitant hormonal contraception efficacy, then penile/external condoms must be used in addition to hormonal contraception. Note: • Tubal occlusion includes tubal ligation

10.5.3 Participants With Partners Able to Become Pregnant

If participants capable of producing sperm engage in sexual activity with partners who can become pregnant (NPOCBP), the following contraceptive methods are acceptable:

- Progestogen-only contraceptive implant
- IUS
- Nonhormonal IUD
- Bilateral tubal occlusion (Tubal occlusion includes tubal ligation)
- Combined (estrogen- and progestogen-containing) hormonal contraception

a. Oral
b. Intravaginal
c. Transdermal

d. Injectable

- Progestogen-only hormonal contraception

a. Oral
b. Injectable

- Progesterone-only hormonal contraception where inhibition of ovulation is not the primary mode of action
- Cervical cap, diaphragm, or sponge with spermicide

10.6 Appendix 6: Exploratory Biomarkers

Information obtained from studying and testing clinical biomarker specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease, and ultimately improve public health through development of novel treatments targeted to populations with the greatest need.

Confidential Participant Information for Biomarker Research [1]

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

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

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

Biomarker Specimen Usage

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

Retention of Specimens

Biomarker and other specimens will be stored in the biorepository for potential analysis for up to 15 years from the end of the study. If there are regulatory or governmental authority questions that are being answered, specimens may be stored for longer. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

The specimens will be stored in a limited access facility that operates to assure the integrity of the specimens and under strict supervision. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

Data Security

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

Reporting of Exploratory Research Data to Participants

Results obtained from genetic and biomarker research will not be given to study participants or the trial doctor.

If important research findings are discovered, the Sponsor may share this information by:

- publishing the results in peer-reviewed journals
- presenting the results at national meetings
- providing the results on a publicly accessible website that would be available to doctors and participants

Participants will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

Questions

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

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10.7 Appendix 7: Country-specific Requirements

10.7.1 Austria-specific Requirements

Section 1.3 Schedule of Activities

Monthly pregnancy testing must be performed prior to study intervention administration at each month during the treatment period, as well as before the last dose of study intervention, and monthly for up to 210 days after the last dose at the end of study intervention.

10.7.2 France-specific Requirements

Section 1.3 Schedule of Activities

Pregnancy testing must be performed prior to study intervention administration at each month during the treatment period as well as before the last dose of study intervention, and 210 days after the last dose at the end of study intervention.

Section 4.1 Overall Design

Since this is a Phase 1/2 study, an external or internal DMC is not being used for this study.

Section 5.2 Exclusion Criteria

In addition to all exclusion criteria listed in Section 5.2, the general principles relating to research involving human beings (Art. L. 1121-6, Art. L. 1121-8, Art. L. 1121-8-1) are to be followed.

Adults protected by laws, persons deprived of their liberty by a judicial or administrative decision, those hospitalized without consent in accordance with local law as further defined in the informed consent form, persons admitted to a health or social institution for purposes other than research and adults who are subject to a legal protection measure or who are unable to express their consent are not eligible to participate.

10.7.3 Italy-specific Requirements

Section 1.3 Schedule of Activities

Monthly pregnancy testing is required during study intervention as well as at the end of study intervention treatment and monthly for up to 7 months.

Section 8.3.6 Pregnancy Testing

Monthly pregnancy testing is required during treatment and for the length of time required to eliminate systemic exposure.

10.7.4 EEA-specific Requirements

In the EEA, individuals who have reached the age of majority and require a legally designated representative for consenting purposes, as defined by Regulation (EU) 536/2014, are not eligible to participate.

10.8 Appendix 8: Paris System for Urine Cytology

Classification criteria from Paris System for Reporting Urinary Cytology [Rosenthal, D. L., et al 2016]:

- Nondiagnostic or unsatisfactory
- Negative for high-grade urothelial carcinoma
- Atypical urothelial cells
- Suspicious for high-grade urothelial carcinoma
- Low-grade urothelial neoplasia
- High-grade urothelial carcinoma
- Other malignancies, primary and metastatic[a]

[a] When applicable, this criterion will be reported as a secondary diagnosis.

10.9 Appendix 9: Abbreviations

Abbreviation	Expanded Term
ADA	antidrug antibodies
ADC	antibody-drug conjugate
ADL	activities of daily living
AE	adverse event
AIDS	Acquired Immunodeficiency Syndrome
AJCC	American Joint Committee on Cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APaT	All-Participants-as-Treated
ART	antiretroviral therapy
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the time/concentration curve
BCG	Bacillus Calmette-Guérin
BOIN	Bayesian Optimal Interval
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
CIS	carcinoma in situ
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CR	complete response
CRF	Case Report Form
CRR	complete response rate
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTU	computed tomography urography

Abbreviation	Expanded Term
CYP	cytochrome P450
DDI	drug-drug interaction
DILI	drug-induced liver injury
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
DU	unacceptably toxic (dose)
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data collection
EEA	European Economic Area
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOT	end of treatment
ePRO	electronic patient-reported outcome
EU	European Union
EU CTR	EU Clinical Trials Regulation 536/2014
EV	enfortumab vedotin
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FSR	first site ready
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus

Abbreviation	Expanded Term
HCV	hepatitis C virus
HG	high-grade
HIV	human immunodeficiency virus
HR	high-risk
HRT	hormone replacement therapy
I-VESIC	intravesical
IA(s)	interim analysis(ses)
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
ICSR	individual case safety report
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1
IHC	immunohistochemical
ILD	interstitial lung disease
IM	intramuscular
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
JRCT	Japan Registry of Clinical Trials
LG	low-grade
LLOQ	lower limit of quantitation
LMP	last menstrual period
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAD	maximum administered dose

Abbreviation	Expanded Term
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	muscle-invasive bladder cancer
MMAE	monomethyl auristatin E
MRI	magnetic resonance imaging
mRNA	messenger RNA
MRU	magnetic resonance urography
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NMIBC	non-muscle invasive bladder cancer
NPOCBP	nonparticipant of childbearing potential
NSCLC	nonsmall cell lung cancer
OME	other important medical event
ORR	objective response rate
OS	overall survival
OTC	over the counter
PD-1	programmed cell death 1 protein
PD-L1	programmed cell death ligand 1
PFS	progression free survival
PK	pharmacokinetic
po	orally
PRO	patient-reported outcome
PSA	prostate-specific antigen
QTcF	corrected QT interval by Fridericia
qw	once weekly
qXd	every X days
qXw	every X week(s)
RDE	recommended dose for expansion
RECIST	Response Evaluation Criteria In Solid Tumors
RNA	ribonucleic acid

Abbreviation	Expanded Term
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
SIM	Site Imaging Manual
SNP	single nucleotide polmorphism
SoA	schedule of activities
SOC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TAb	total antibody
TNBC	triple-negative breast cancer
TNM	Tumor, Node, and Metastasis
TURBT	transurethral resection of bladder tumor
UC	urothelial cancer
ULN	upper limit of normal
US(A)	United States (of America)
UTI	urinary tract infection
UTN	Universal Trial Number
VC	valine-citrulline
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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