Clinical Study Protocol

Drug Substance	Durvalumab
Study Code	D933RC00001
Version	7.0
Date	29 Jan 2024

A Phase III, Randomized, Open-Label, Multi-Center, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination with Gemcitabine+Cisplatin for Neoadjuvant Treatment Followed by Durvalumab Alone for Adjuvant Treatment in Patients with Muscle-Invasive Bladder Cancer (NIAGARA)

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

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Study Intervention: Durvalumab
Study Phase: 3

Short Title: A Phase III Study of the Efficacy and Safety of Neoadjuvant Durvalumab + Gemcitabine + Cisplatin Followed by Adjuvant Durvalumab in Patients with MIBC

Acronym: NIAGARA

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 6 (Version 7)	*29-Jan-2024*
Amendment 5 (Version 6)	*22-Jun-2023*
Amendment 4 (Version 5)	*01-Jun-2021*
Amendment 3 (Version 4)	*20-Jul-2020*
Amendment 2 (Version 3)	*09-Dec-2019*
Amendment 1 (Version 2)	*23-Apr-2019*
Original Protocol (Version 1)	*02-Aug-2018*

Amendment 6 (29-Jan-2024)

Overall Rationale for the Amendment: The primary reason for this amendment is to remove the censoring rule for two consecutive missed visits from the primary analysis of the primary endpoint EFS to minimize loss of clinically relevant events. Instead, a supportive sensitivity analysis applying this rule will be conducted. This is in line with European Medicines Agency guideline on methodological considerations for the evaluation of anticancer products (European Medicines Agency Guideline, 2013). Per FDA guidance (U.S. Department of Health and Human Services et al, 2018), a sensitivity analysis applying this censoring rule can be done if not used for the primary analysis.

This and other changes incorporated in this amendment are described in the following table. In addition, minor text clarifications, administrative changes, have been made; as these changes were minor, they are not listed in detail in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Title Page – EU CTR Number	Updated EU CTR Number	New EU CTR Number issued	Non-substantial
Section 9.3.1.2 (Dual primary endpoint for event-free survival [EFS]), Section 9.4 (Methods for statistical analyses, Table 18)	Removal of "However, if the patient progresses or experiences recurrent disease or dies after 2 or more missed visits, the patient will be censored at the time of the latest evaluable disease assessment."	Removing two missed visit rule from primary endpoint EFS to minimize loss of clinically relevant events.	Substantial

	Addition of sensitivity analyses "Analysis where subjects who take subsequent anti-cancer therapy prior to the EFS event will be censored at their last evaluable assessment prior to taking the subsequent therapy – attrition bias (ITT)" “Analysis using the 2 missed visit censoring rule – attrition bias (ITT)” In Table 18 of section 9.4		
Section 9.3.3 Calculation or derivation of patient-reported outcome variables	Removal of “Also, if global health status/QoL, function, or symptom deteriorates or the patient dies after 2 or more missed PRO assessment visits, the patient will be censored at the time of the last PRO assessment where global health status/QoL, function, or symptom could be evaluated prior to the 2 missed visits”	To be consistent with the EFS change	Substantial

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered, and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. PROTOCOL SUMMARY

1.1 Schedules of activities (SoAs)

The procedures for the screening and treatment periods in this study are presented in Table 1, Table 2, and Table 3, and the procedures for the follow-up period are presented in Table 4.

Whenever vital signs and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: vital signs and then blood draws. The timing of the vital signs assessments should be such that it allows the blood draw (eg, pharmacokinetic [PK] blood sample) to occur at the timepoints indicated in the schedules of activities (SoAs). Whenever electrocardiograms (ECGs), vital signs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: ECG, vital signs, and then blood draws. The timing of the first 2 assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the timepoints indicated in the SoAs.

For durvalumab treatment

- Patients may delay dosing under certain circumstances.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1), due to either an immune or a non-immune-related adverse event (AE).
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - If there is a dosing delay while on the every 3 weeks (q3w) schedule (neoadjuvant portion), it is advised to skip the durvalumab dose and resume dosing on Day 1 of the subsequent cycle. If there is a dosing delay during the adjuvant portion of therapy, dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy and patient-reported outcome (PRO) assessments. Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-life of durvalumab (see current Investigator Brochure [IB] for durvalumab).
  - In the event that durvalumab is discontinued or delayed as part of the toxicity management guidance, gemcitabine and cisplatin (G+C) may still be administered as scheduled.

For gemcitabine and cisplatin neoadjuvant treatment

- Patients may delay and subsequently resume dosing per local standard clinical practice. Patients will also be permitted to skip Day 8 chemotherapy per local toxicity management standards for chemotherapy.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible. In the event that Cycle 1 of the chemotherapy schedule is delayed, durvalumab should follow the chemotherapy schedule and should be administered on Day 1 of each cycle.
  - In the event that G+C chemotherapy is discontinued due to treatment-related toxicity, patients should proceed to radical cystectomy when clinically feasible, and the remaining durvalumab monotherapy neoadjuvant doses should be skipped. Adjuvant therapy with durvalumab may continue following radical cystectomy. Note: If the Investigator feels that a patient would benefit from administering the remaining neoadjuvant durvalumab cycles without chemotherapy, AstraZeneca should be consulted for an exception to this rule.
- In the event that creatinine clearance drops below 60 mL/min, the cisplatin dose may be divided into 2 administrations, as per local practice, for management of renal toxicity.

The study treatment phase of this study includes neoadjuvant, adjuvant, and surgical phases:

- Neoadjuvant therapy: patients receive G+C chemotherapy ± durvalumab
- Surgery: radical cystectomy
- Adjuvant therapy: patients receive durvalumab or no treatment (patients required to attend scheduled study visits)

Table 1 Schedule of assessments for screening and neoadjuvant treatment (all treatment arms)

	Screening	C1 1 cycle = 3 weeks (21 days)		C2 1 cycle = 3 weeks (21 days)		C3 1 cycle = 3 weeks (21 days)		C4 1 cycle = 3 weeks (21 days)		Pre-radical cystectomy	Radical cystectomy (≥14 days to 56 days after last dose of neo-adjuvant therapy)	For details, see Section
Week	**-4 to -1**	**1**	**2**	**4**	**5**	**7**	**8**	**10**	**11**			
Day	**-28 to -1**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**			
Window (days)	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**			
Informed consent												
Informed consent[a]	X											5.1
Randomization		X[b]										6.2.1
Study procedures												
Physical examination (full)	X											8.2.2
Targeted physical examination (based on symptoms)		X	X	X	X	X	X	X	X			8.2.2
Vital signs[c]	X	X	X	X	X	X	X	X	X			8.2.3
ECG (resting 12-lead)[d]	X	As clinically indicated										8.2.4
Concomitant medications	<----------										---------->	6.4
Demography, including baseline characteristics and tobacco use	X											5.1, 5.2
Eligibility criteria	X	X										5.1, 5.2
Medical/surgical history	X											5.1
Laboratory assessments												
Clinical chemistry[e,f]	X	X[g]	X	X	X	X	X	X	X			Table 12
Hematology[e, f]	X	X[g]	X	X	X	X	X	X	X			Table 13
Coagulation parameters		X[g]										Table 13
TSH (reflex free T_3 or free T_4[h])	X	X[i]		X		X		X				Table 12
Hepatitis B and C and HIV	X											8.2.1

	Screening	C1 1 cycle = 3 weeks (21 days)		C2 1 cycle = 3 weeks (21 days)		C3 1 cycle = 3 weeks (21 days)		C4 1 cycle = 3 weeks (21 days)		Pre-radical cystectomy	Radical cystectomy (≥14 days to 56 days after last dose of neo-adjuvant therapy)	For details, see Section
Week	**-4 to -1**	**1**	**2**	**4**	**5**	**7**	**8**	**10**	**11**			
Day	**-28 to -1**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**			
Window (days)	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**			
Urinalysis	X	As clinically indicated										8.2.1
Pregnancy test[j]	X	X		X		X		X				8.2.1
Pharmacokinetics												
Durvalumab PK sample (serum) (Arm 1 only)		X[k]		X[l]				X[l]				8.5
Monitoring												
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X			8.2.5
AE/SAE assessment[m]	<----------											8.3
IP administration												
Durvalumab (Arm 1 only) [f,n]		X		X		X		X				6.1.2.1
Gemcitabine[n]		X	X	X	X	X	X	X	X			6.1.1.3
Cisplatin[n]		X	X[o]	X	X[o]	X	X[o]	X	X[o]			6.1.1.3
Other assessments and assays												
Durvalumab immunogenicity assessment (ADA and neutralizing antibodies) (Arm 1 only)		X[l]		X[l]				X[l]				8.5.1.1
Tumor biopsy (newly acquired or archival ≤3 months old)[p]	X[a]											8.8.1
Radical cystectomy											X	6.1.5
Tumor assessments: pathology testing											X[q]	8.8.1

	Screening	C1 1 cycle = 3 weeks (21 days)		C2 1 cycle = 3 weeks (21 days)		C3 1 cycle = 3 weeks (21 days)		C4 1 cycle = 3 weeks (21 days)		Pre-radical cystectomy	Radical cystectomy (≥14 days to 56 days after last dose of neo-adjuvant therapy)	For details, see Section
Week	**-4 to -1**	**1**	**2**	**4**	**5**	**7**	**8**	**10**	**11**			
Day	**-28 to -1**	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**			
Window (days)	**NA**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**	**+3**	**±2**			
Optional additional tumor biopsies		The collection of additional tumor biopsies upon progression of patients in Arm 1 and Arm 2 is strongly encouraged.										8.8.1
Urine sample for biomarker[r]		X (pre-dose)								X[s]		8.8.2
Urine sample for cytology[t]		X (pre-dose)								X[s]		8.8.2
Blood sample for PaxGene-RNA analysis[u]		X										8.8.2
Serum sample for biomarkers		X										8.8.2
Plasma for ctDNA/circulating soluble factors[u]	X	X (pre-dose)				X				X[s]		8.8.2
Blood sample for genetic analysis (Gx) (optional)[v]		X										8.7
Distribute ePRO device		X										8.1.3
ePRO device training		X										8.1.3
EORTC QLQ-C30, PGIS, and EQ-5D-5L		To be completed at C1D1 and every 4 weeks thereafter										8.1.3.1, 8.1.3.2, 8.1.3.4
PRO-CTCAE[w]		To be completed at C1D1 and every 2 weeks thereafter										8.1.3.4
PGIC		To be completed at 4 weeks post-C1D1 and every 4 weeks thereafter										8.1.3.3
Efficacy evaluations												
Neoadjuvant tumor assessments: RECIST 1.1	X[x]									X[y]		8.1, Appendix F[z]

[a] Informed consent includes consent for study procedures and biopsy of baseline tumor tissue for PD-L1 status and pathology testing; genetic testing of tissue obtained at baseline and from radical cystectomy tumor tissue is an optional part of the informed consent. Informed consent of study procedures may be obtained prior to the 28-day

screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization, with the exception of the patient's tumoral PD-L1 status (must be obtained within ≤3 months before screening).

[b] Every effort should be made to minimize the time between randomization and starting treatment; the maximum interval is 3 working days.

[c] Vital signs will be evaluated per Section 8.2.3.

[d] Any clinically significant abnormalities detected require triplicate ECG results obtained over a brief period (eg, 30 minutes).

[e] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.

[f] Results for LFTs, electrolytes, full blood count, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing; a creatinine clearance determination is required prior to each Day 1and Day 8 dose of cisplatin (if applicable).

[g] If screening clinical chemistry and hematology assessments are performed within 3 days prior to Day 1 (first infusion day), they do not need to be repeated at Day 1. For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline on Day 1 (unless performed within 3 days prior to Day 1).

[h] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.

[i] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.

[j] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 3 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.

[k] Pre-dose (within 60 minutes before start of infusion) and post-dose (within 10 minutes after the end of infusion).

[l] Pre-dose (within 60 minutes before start of infusion) only.

[m] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed.

[n] In Arm 1 only, durvalumab will be administered first; G+C infusion will start approximately 1 hour after the end of the durvalumab infusion. If there are no clinically significant concerns after the first cycle, reduction of the observation period may be at the Investigator's discretion (suggested 30 minutes).

[o] This is required for patients with borderline renal function only. In the event that creatinine clearance drops below 60 mL/min, the cisplatin dose may be divided into 2 administrations, as per local practice, for management of renal toxicity.

[p] Archival tissue must be from a tumor sample when the patient has confirmed MIBC (ie, non-MIBC samples will not be acceptable). This tumor specimen should be of sufficient quantity to allow for prospective PD-L1 IHC evaluation, retrospective evaluation of muscle invasive disease, and other exploratory biomarker analyses.

[q] A specimen from radical cystectomy must be provided for local and central pathological review; additional samples should also be collected for exploratory analyses for all surgical procedures (including a partial cystectomy).

[r] Urine biomarker sample will be done by central laboratory.

[s] Collect in the morning prior to radical cystectomy or within 7 days immediately prior to radical cystectomy. Also, to be done upon progression or end of treatment if patient terminates the study prior to radical cystectomy.

[t] Cytology will be done by local laboratory.

[u] Also to be collected at recurrence or progression. If a patient is discontinued from treatment prematurely during the neoadjuvant phase (prior to cystectomy) due to either progression or recurrence, PaxGene and ctDNA/circulating soluble factors samples should also be collected.

[v] The sample for genetic research will be obtained at Day 1 pre-dose. If, for any reason, the sample is not drawn at Day 1, it may be taken at any visit until the last study visit. Only 1 sample should be collected per patient for genetics during the study.

[w] PRO-CTCAE will only be administered in those countries where a linguistically validated version is available.

[x] A CT (preferred) or MRI of the chest, abdomen, and pelvis must be performed within 28 days prior to and as close as possible to randomization, and this scan is designated as the "Neoadjuvant Baseline" scan (ie, lesions are classified as neoadjuvant baseline Target Lesions or Non-Target Lesions). Lesions in the wall of distensible organs are not reproducibly measurable and should be classified NTLs.

[y] A neoadjuvant follow up scan must be performed upon completion of neoadjuvant chemotherapy prior to surgery; consideration should be given to scheduling this scan as part of the pre-surgical workup, to confirm patient is still eligible for a radical cystectomy.

[=z] For patients who are medically precluded from, refuse, or withdraw from a radical cystectomy, refer to Section 8.1.1 for tumor assessment schedule

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

ADA Antidrug antibody; AE Adverse event; BP Blood pressure; C Cycle; CT Computed tomography; ctDNA Circulating tumor DNA; D Day; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; ePRO Electronic patient reported outcome; EQ-5D-5L EuroQol 5-dimension, 5-level health state utility index; G+C gemcitabine and cisplatin; HIV Human immunodeficiency virus; IP Investigational product; LFT Liver function test; MIBC Muscle-invasive bladder cancer; MRI Magnetic resonance imaging; NA Not applicable; PD-L1 Programmed cell death-ligand 1; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; PK Pharmacokinetic(s); PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 2 Schedule of assessments for the adjuvant treatment phase (Arm 1)

		C1 1 cycle = 4 weeks (28 days)	C2 1 cycle = 4 weeks (28 days)	C3 1 cycle = 4 weeks (28 days)	C4 1 cycle = 4 weeks (28 days)	C5 1 cycle = 4 weeks (28 days)	C6 1 cycle = 4 weeks (28 days)	C7 1 cycle = 4 weeks (28 days)	C8 1 cycle = 4 weeks (28 days)	For details, see Section
Week	**NA**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	
Day	**42 days after radical cystectomy**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Window (days)	**(±14 days)**	**(±3 days, tumor assessment ±7 days)**								
Study procedures										
Targeted physical examination (based on symptoms)		X	X	X	X	X	X	X	X	8.2.2
Vital signs[a]		X	X	X	X	X	X	X	X	8.2.3
ECG (resting 12-lead)[b]	As clinically indicated									8.2.4
Concomitant medications	<----------								---------->	6.4
Laboratory assessments										
Clinical chemistry[c]		X	X	X	X	X	X	X	X	Table 12
Hematology[c]		X	X	X	X	X	X	X	X	Table 13
Coagulation parameters (Arm 1 only)		X								Table 13
TSH (reflex free T_3 or free T_4)[d]		X	X	X	X	X	X	X	X	Table 12
Urinalysis	As clinically indicated									8.2.1
Pregnancy test[e]		X[e]	X[e]	X[e]	X	X	X	X	X	8.2.1
Pharmacokinetics										
Durvalumab PK sample (serum) (Arm 1 only)			X[f]			X[f]				8.5
Monitoring										
WHO/ECOG performance status		X	X	X	X	X	X	X	X	8.2.5
AE/SAE assessment[g]	<----------								---------->	8.3

		C1 1 cycle = 4 weeks (28 days)	C2 1 cycle = 4 weeks (28 days)	C3 1 cycle = 4 weeks (28 days)	C4 1 cycle = 4 weeks (28 days)	C5 1 cycle = 4 weeks (28 days)	C6 1 cycle = 4 weeks (28 days)	C7 1 cycle = 4 weeks (28 days)	C8 1 cycle = 4 weeks (28 days)	For details, see Section
Week	**NA**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	
Day	**42 days after radical cystectomy**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Window (days)	**(±14 days)**	**(±3 days, tumor assessment ±7 days)**								
IP administration										
Durvalumab (Arm 1 only)		X	X	X	X	X	X	X	X	6.1.2.1
Other assessments and assays										
Durvalumab immunogenicity assessment (ADA and neutralizing antibodies) (Arm 1 only)			X			X				8.5.1.1
Optional additional tumor biopsies		The collection of additional tumor biopsies upon recurrence in patients in Arm 1 and Arm 2 is strongly encouraged.								8.8.1
Clavien-Dindo assessment		90 days post-cystectomy (including a partial cystectomy, if performed)								8.2.7
Blood sample for PaxGene-RNA analysis[h]		X		X						8.8.2
Serum sample for biomarkers		X		X						8.8.2
Plasma for ctDNA/circulating soluble factors[h]		X		X						8.8.2
EORTC QLQ-C30, PGIS, PGIC, and EQ-5D-5L	To be completed at C1D1 and every 4 weeks thereafter									8.1.3.1-8.1.3.4
PRO-CTCAE[i]	To be completed at C1D1 and every 2 weeks up to Week 13, then every 4 weeks thereafter									8.1.3.5

		C1 1 cycle = 4 weeks (28 days)	C2 1 cycle = 4 weeks (28 days)	C3 1 cycle = 4 weeks (28 days)	C4 1 cycle = 4 weeks (28 days)	C5 1 cycle = 4 weeks (28 days)	C6 1 cycle = 4 weeks (28 days)	C7 1 cycle = 4 weeks (28 days)	C8 1 cycle = 4 weeks (28 days)	For details, see Section
Week	**NA**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	
Day	**42 days after radical cystectomy**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Window (days)	**(±14 days)**	**(±3 days, tumor assessment ±7 days)**								
Efficacy evaluations										
Adjuvant assessments (RECIST 1.1)	X[j]	Adjuvant tumor assessments occur every 12 weeks ±7 days after the date of radical cystectomy for the first 24 months, then every 24 weeks ±7 days for 36 months, and then every 52 weeks (annually) thereafter until progression, the end of study, death, study discontinuation, or Sponsor decision, whichever comes first.[k] During adjuvant treatment, the imaging schedule MUST be followed regardless of any delays in dosing. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments according to the original imaging schedule. For patients who are medically precluded from, refuse, or withdraw from a radical cystectomy, refer to Section 8.1.1 for tumor assessment schedule.								6.1.3, 8.1, Appendix F

[a] Vital signs will be evaluated per Section 8.2.3.
[b] Any clinically significant abnormalities detected require triplicate ECG results obtained over a brief period (eg, 30 minutes).
[c] Serum or plasma clinical chemistry (including LFT monitoring) and hematology are to be collected q4w prior to the start of infusion for Arm 1 and as clinically indicated (may be performed more frequently if clinically indicated). Results for LFTs, electrolytes, full blood count, and creatinine must be available before commencing an infusion (within 3 days) and reviewed by the treating physician or Investigator prior to dosing.
[d] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[e] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then q4w. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion.
[f] Arm 1: Pre-dose (within 60 minutes before start of infusion) only.
[g] For AEs/SAEs reported resulting from the radical cystectomy, additional information such as concomitant medications must be reported.
[h] Also to be collected at recurrence or progression. If a patient is discontinued from treatment prematurely during the adjuvant phase due to either progression or recurrence, PaxGene and ctDNA/circulating soluble factors samples should also be collected.
[i] PRO-CTCAE will only be administered in those countries where a linguistically validated version is available.
[j] A CT (preferred) or MRI of the chest, abdomen, and pelvis must be performed 42 days (±2 weeks) after radical cystectomy and must be prior to the start of adjuvant therapy, and this scan is designated as the “Adjuvant Baseline” scan. In most instances, no lesions will be observed on the Adjuvant Baseline scans and ‘No Evidence of Disease’ will be recorded for the Adjuvant Baseline RECIST assessment; however, if any radiologically observable tumors exist, a fresh selection of Target and Non-Target lesions should be applied.
[k] Where possible or feasible, radiological progression should be biopsy proven. Other imaging modalities (eg, bone scan, MRI scan) may be required to define progression in equivocal cases.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.
ADA Antidrug antibody; AE Adverse event; BP Blood pressure; C Cycle; CT Computed tomography; ctDNA Circulating tumor DNA; D Day; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EQ-5D-5L EuroQol 5-dimension, 5-level health state utility index; IP Investigational product; LFT Liver function test; MRI Magnetic resonance imaging; NA Not applicable; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; PK Pharmacokinetic(s); PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; q4w every 4 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 3 Schedule of assessments for the adjuvant phase visits (Arm 2)

		C1 1 cycle = 4 weeks (28 days)	C2 1 cycle = 4 weeks (28 days)	C3 1 cycle = 4 weeks (28 days)	C4 1 cycle = 4 weeks (28 days)	C5 1 cycle = 4 weeks (28 days)	C6 1 cycle = 4 weeks (28 days)	C7 1 cycle = 4 weeks (28 days)	C8 1 cycle = 4 weeks (28 days)	For details, see Section
Week	**NA**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	
Day	**42 days after radical cystectomy**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Window (days)	**(±14 days)**	**(±3 days, tumor assessment ±7 days)**								
Study procedures										
Targeted physical examination (based on symptoms)		X		X		X		X		8.2.2
Vital signs[a]		X		X		X		X		8.2.3
ECG (resting 12-lead)[b]	As clinically indicated									8.2.4
Concomitant medications	<----------								---------->	6.4
Laboratory assessments										
Clinical chemistry[c]		X		X		X		X		Table 12
Hematology[c]		X		X		X		X		Table 13
TSH (reflex free T_3 or free T_4)[d]		X		X		X		X		Table 12
Urinalysis	As clinically indicated									8.2.1
Pregnancy test[e]		X[e]		X[e]						8.2.1
Monitoring										
WHO/ECOG performance status		X		X		X		X		8.2.5
AE/SAE assessment[f]	<----------								---------->	8.3
Patient follow-up contact/patient review for safety			X		X		X		X	8.2.6
Optional additional tumor biopsies	The collection of additional tumor biopsies upon recurrence in patients is strongly encouraged.									8.8.1
Clavien-Dindo assessment	90 days post-cystectomy (including a partial cystectomy, if performed)									8.2.7
Blood sample for PaxGene-RNA analysis[g]		X		X						8.8.2

		C1 1 cycle = 4 weeks (28 days)	C2 1 cycle = 4 weeks (28 days)	C3 1 cycle = 4 weeks (28 days)	C4 1 cycle = 4 weeks (28 days)	C5 1 cycle = 4 weeks (28 days)	C6 1 cycle = 4 weeks (28 days)	C7 1 cycle = 4 weeks (28 days)	C8 1 cycle = 4 weeks (28 days)	For details, see Section
Week	**NA**	**1**	**5**	**9**	**13**	**17**	**21**	**25**	**29**	
Day	**42 days after radical cystectomy**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Window (days)	**(±14 days)**	**(±3 days, tumor assessment ±7 days)**								
Serum sample for biomarkers		X		X						8.8.2
Plasma for ctDNA/circulating soluble factors[g]		X		X						8.8.2
EORTC QLQ-C30, PGIS, PGIC, and EQ-5D-5L	To be completed at C1D1 and every 4 weeks thereafter									8.1.3.1-8.1.3.4
PRO-CTCAE[h]	To be completed at C1D1 and every 2 weeks up to Week 13, then every 4 weeks thereafter									8.1.3.5
Efficacy evaluations										
Adjuvant assessments (RECIST 1.1)	X[i]	Adjuvant tumor assessments occur every 12 weeks ±7 days after the date of radical cystectomy for the first 24 months, then every 24 weeks ±7 days for 36 months, and then every 52 weeks (annually) thereafter until progression, the end of study, death, study discontinuation, or Sponsor decision, whichever comes first.[j] During adjuvant treatment, the imaging schedule MUST be followed regardless of any delays in dosing. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments according to the original imaging schedule. For patients who are medically precluded from, refuse, or withdraw from a radical cystectomy, refer to Section 8.1.1 for tumor assessment schedule.								6.1.3, 8.1, Appendix F

[a] Vital signs will be evaluated per Section 8.2.3.
[b] Any clinically significant abnormalities detected require triplicate ECG results obtained over a brief period (eg, 30 minutes).
[c] Serum or plasma clinical chemistry (including LFT monitoring) and hematology are to be collected at any time during the visit for Arm 2, and as clinically indicated (may be performed more frequently if clinically indicated).
[d] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[e] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then q4w. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion. For patients in Arm 2, pregnancy test will only be required for Cycle 1 and Cycle 3.
[f] For AEs/SAEs reported resulting from the radical cystectomy, additional information such as concomitant medications must be reported.
[g] Also to be collected at recurrence or progression. If a patient is discontinued from treatment prematurely during the adjuvant phase due to either progression or recurrence, PaxGene and ctDNA/circulating soluble factors samples should also be collected.

[h] PRO-CTCAE will only be administered in those countries where a linguistically validated version is available.

[i] A CT (preferred) or MRI of the chest, abdomen, and pelvis must be performed 42 days (±2 weeks) after radical cystectomy and must be prior to the start of adjuvant therapy, and this scan is designated as the "Adjuvant Baseline" scan. In most instances, no lesions will be observed on the Adjuvant Baseline scans and "No Evidence of Disease" will be recorded for the Adjuvant Baseline RECIST assessment; however, if any radiologically observable tumors exist, a fresh selection of target and non-target lesions should be applied.

[j] Where possible or feasible, radiological progression should be biopsy proven. Other imaging modalities (eg, bone scan, MRI scan) may be required to define progression in equivocal cases.

Note: All assessments on treatment days are to be performed prior to infusion, unless otherwise indicated.

AE Adverse event; C Cycle; CT Computed tomography; ctDNA Circulating tumor DNA; D Day; ECG Electrocardiogram; ECOG Eastern Cooperative Oncology Group; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EQ-5D-5L EuroQol 5-dimension, 5-level health state utility index; LFT Liver function test; MRI Magnetic resonance imaging; NA Not applicable; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; q4w every 4 weeks; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

Table 4 Schedule of assessments for patients who have discontinued treatment or completed study visits/treatment

NOTE: If a patient is discontinued from study treatment either during or at the completion of the neoadjuvant phase and has not undergone a cystectomy or does not enter adjuvant phase, follow-up visits will be calculated from "time since last dose of treatment", BUT it is anticipated that 30 and/or 60 days would have passed since last dose of treatment; therefore in those cases, study activities may be waived for the Day 30 and/or Month 2 visits (with the exception of AE/SAE follow-up as per section 8.3.2). However, the Month 3 (90-day) visit must be performed and documented, even if delayed beyond the actual 90-days since last dose of treatment. In addition, a pregnancy test must be performed at this Month 3 visit if Day 30 visit (in which a pregnancy test is required) is not done.

	Time since last dose of treatment (Arm 1) or adjuvant phase study visits (Arm 2)							
	Day (±3)	**Months (±1 week)**				**Month 12 (±2 weeks)**	**Every 6 months thereafter (±2 weeks)**	**For details, see Section**
Evaluation	**30**	**2[a]**	**3**	**6**	**9**			
Physical examination (full)	X							8.2.2
Vital signs (temperature, respiratory rate, blood pressure, and pulse)	X							8.2.3
Weight	X	X[a]	X					8.2.3
Urinalysis	As clinically indicated							8.2.1
Pregnancy test[b]	X	As clinically indicated						8.2.1
AE/SAE assessment	X	X	X					8.3
Concomitant medications	X	X	X					6.4
WHO/ECOG performance status	At timepoints consistent with tumor assessments; at 30, 60, and 90 days; and then at initiation of subsequent anticancer therapy[c]							8.2.5
Subsequent anticancer therapy[d]	<----------						---------->	
Survival status[e]			X	X	X	X	X	8.1.2
Hematology	X	X[a]	X					Table 13
Clinical chemistry	X	X[a]	X					Table 12
TSH (reflex free T3 or free T4[f])	X	X[a]	X					Table 12
Durvalumab PK assessment[g] (Arm 1 only)			X					8.5

	Time since last dose of treatment (Arm 1) or adjuvant phase study visits (Arm 2)							
	Day (±3)	**Months (±1 week)**				**Month 12 (±2 weeks)**	**Every 6 months thereafter (±2 weeks)**	**For details, see Section**
Evaluation	**30**	**2[a]**	**3**	**6**	**9**			
Durvalumab immunogenicity assessment (ADA sampling) to identify ADA responses[g] (Arm 1 only)			X					8.5
Blood sample for PaxGene-RNA analysis[k] Plasma for ctDNA/circulating soluble factors[k]	As indicated							
EORTC QLQ-C30, EQ-5D-5L, PGIC, and PGIS	X	X	X	Every 8 weeks until recurrence of disease, subsequent therapy, or study discontinuation (whichever occurs first).[h]				8.1.3.1, 8.1.3.2, 8.1.3.3, 8.1.3.4
PRO-CTCAE[i]	X	X	X					8.1.3.4
Tumor assessment	Tumor assessments occur every 12 weeks ±7 days after the date of radical cystectomy for the first 24 months, then every 24 weeks ±7 days for 36 months, and then every 52 weeks (annually) thereafter until progression, the end of study, death, study discontinuation, or Sponsor decision, whichever comes first.[j] During adjuvant treatment, the imaging schedule MUST be followed regardless of any delays in dosing. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments according to the original imaging schedule. For patients who are medically precluded from, refuse, or withdraw from a radical cystectomy, refer to Section 8.1.1 for tumor assessment schedule.							6.1.3, 8.1, Appendix F

[a] Patients in Arm 2 will be required to have a follow-up call to collect AEs and concomitant medications. Weight, ECOG at 60 days, clinical chemistry, hematology, and TSH will not be required for this visit.
[b] For women of childbearing potential only. A urine or serum pregnancy test is acceptable.
[c] WHO/ECOG performance status should also be collected at other site visits that the patient attends, if appropriate site staff are available to collect such information. In addition, WHO/ECOG performance status should be provided when information on subsequent anticancer therapy is provided, where possible.
[d] Details of any treatment for bladder cancer (including surgery and radiation) post the last dose of IP must be recorded in the eCRF. At a minimum, the start date and description of the subsequent anticancer therapy should be collected.
[e] Patients may be contacted in the week following data cutoffs to confirm survival status. Details of any treatment for MIBC (including surgery) post the last dose of IP must be recorded in the eCRF.
[f] Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[g] PK and immunogenicity samples are collected 90 days (3 months) (±7 days) after treatment with IP ends.
[h] Study sites will send reminders to patients to complete questionnaires during follow-up
[i] PRO-CTCAE will only be administered in those countries where a linguistically validated version is available.

[j] Where possible or feasible, radiological progression should be biopsy proven. Other imaging modalities (eg, bone scan, MRI scan) may be required to define progression in equivocal cases.

[k] Also to be collected at recurrence or progression. If a patient discontinues from follow-up visits due to either progression or recurrence, PaxGene and ctDNA/circulating soluble factors samples should also be collected ***unless*** the patient previously collected these samples due to earlier progression or recurrence.

ADA Antidrug antibody; AE Adverse event; CT Computed tomography; ECOG Eastern Cooperative Oncology Group; eCRF Electronic case report form; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EQ-5D-5L EuroQol 5-dimension, 5-level health state utility index; IP Investigational product; MIBC Muscle-invasive bladder cancer; MRI Magnetic resonance imaging; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; PK Pharmacokinetic(s); PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events; RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1; SAE Serious adverse event; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone; WHO World Health Organization.

1.2 Synopsis

Protocol title:

A Phase III, Randomized, Open-Label, Multi-Center, Global Study to Determine the Efficacy and Safety of Durvalumab in Combination with Gemcitabine+Cisplatin (G+C) for Neoadjuvant Treatment Followed by Durvalumab Alone for Adjuvant Treatment in Patients with Muscle-Invasive Bladder Cancer (NIAGARA)

Rationale:

The standard management for patients with muscle-invasive bladder cancer (MIBC) involves radical cystectomy and pelvic lymph node dissection. Several studies have demonstrated improved pathologic complete response (pCR), event-free survival (EFS), and overall survival (OS) with the integration of neoadjuvant, cisplatin-based combination chemotherapy when compared with radical cystectomy alone.

Despite improvements of pCR and survival rates with neoadjuvant chemotherapy, many patients will still develop recurrence and will ultimately die of metastatic bladder cancer. Recently, multiple programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) inhibitors have demonstrated activity in metastatic bladder cancer patients and have been granted approval in the platinum refractory setting, as well as pembrolizumab and atezolizumab accelerated approval in the first-line metastatic setting for patients unable to tolerate cisplatin chemotherapy (KEYTRUDA [package insert] 2018, TECENTRIQ [package insert] 2018).

The benefits of adjuvant chemotherapy after radical cystectomy in patients with MIBC without clinically detectable metastases are unclear. There is limited evidence from adequately conducted, randomized, Phase III trials to support the use of adjuvant chemotherapy in patients immediately following surgery. However, in 2 separate meta-analyses conducted in 2013 (Leow et al 2014) and 2016 (Kim et al 2017), with 9 and 11 randomized controlled studies in MIBC, respectively, suggested an OS benefit in patients receiving adjuvant cisplatin-based chemotherapy. Multiple Phase III trials evaluating adjuvant PD-1 or PD-L1 inhibitors and Phase II trials reveal promising activity and safety for single-agent neoadjuvant pembrolizumab or atezolizumab are ongoing (Necchi et al 2018, Powles et al 2018).

Durvalumab is a human monoclonal antibody of the immunoglobulin G1 kappa (subclass that inhibits binding of PD-L1 (B7 homolog 1, cluster of differentiation [CD]274) to PD-1 (CD279) and CD80 (B7-1). Nonclinical and clinical studies have indicated that blockade of the immune checkpoints PD-1/PD-L1 can have a positive effect on antitumor activity. Clinical benefit has been observed in a wide range of tumor types, including metastatic melanoma, squamous and nonsquamous non-small-cell lung cancer, head and neck squamous cell carcinoma, and urothelial carcinoma (UC).

The benefit of this class of compound and specifically durvalumab in bladder cancer has been demonstrated in a cohort of 182 patients with locally advanced or metastatic UC who progressed despite platinum-based chemotherapy (IMFINZI [package insert] 2017, Massard et al 2016). Durvalumab has been approved to treat locally advanced or metastatic urothelial carcinoma, unresectable stage III non-small cell lung cancer, and extensive-stage small cell lung cancer

(administered in combination with chemotherapy). Refer to the package insert (or label) for your specific country, as applicable.

The addition of immunotherapy to chemotherapeutic agents has been shown to result in improved response rates relative to chemotherapy alone. Cytotoxic chemotherapy has been shown to modulate the immune response via several mechanisms, such as stimulating T cell activation by increasing the expression of MHC-1 molecules, stimulating dendritic cell maturation, inducing immunogenic cell death (a form of cell death that induces dendrites to stimulate tumor antigen presentation to T cells), and reducing the immunosuppressive function of regulatory T cells and myeloid-derived suppressor cells (Kodumudi et al 2010, Kroemer et al 2013, Liu et al 2010, Zhang et al 2008). Combining a PD-L1 antagonist with cytotoxic agents may provide complementary benefit in mounting an effective antitumor immunity by promoting the antigen presentation, increasing the production of protective T cells, and overcoming immunosuppression in the tumor bed (Mellman et al 2011). In addition, a variety of approaches for combining PD-1 pathway blockers with other agents has been explored over the past few years in an effort to both improve the efficacy of treatment and/or position the treatment regimen for testing in patients who are treatment-naive with a variety of cancers (Langer et al 2016). The rationale for the present study is that PD-L1 inhibition through exposure to durvalumab, in combination with chemotherapeutics such as G+C, may increase both the long-term response rate and the frequency of response by preventing the MIBC tumor cells (TCs) from evading immune-mediated antitumor response. Administering durvalumab may provide a benefit to this subgroup of patients by averting intrinsic resistance. Adjuvant durvalumab monotherapy may further improve time to disease relapse in these patients.

Objectives and endpoints:

Primary objectives:	**Endpoints/variables:**
To assess the efficacy of durvalumab + G+C combination therapy (neoadjuvant)/durvalumab alone (adjuvant) (Arm 1) compared to G+C combination therapy (neoadjuvant)/no adjuvant treatment (Arm 2) in terms of pCR and EFS in MIBC patients	pCR using assessments per central pathology review EFS using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion
Secondary objectives:	**Endpoints/variables:**
To assess the efficacy of Arm 1 versus Arm 2 in terms of EFS at 24 months in MIBC patients	EFS24 using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion

To assess the efficacy of Arm 1 compared to Arm 2 in terms of pathologic response at radical cystectomy and EFS in MIBC patients	pCR using assessments per local pathology review Proportion of patients who achieve <P2 per local pathology review EFS using assessments per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion EFS24 using assessments per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion
To assess the efficacy of Arm 1 versus Arm 2 in MIBC patients	Metastasis-free survival and disease-specific survival per Investigator assessments or local biopsy review if a biopsy is required for a suspected new lesion Overall survival (OS) OS at 5 years Disease-free survival in patients who undergo radical cystectomy Proportion of patients who undergo radical cystectomy PFS2 as defined by local standard clinical practice
To assess the efficacy of Arm 1 versus Arm 2 in terms of pCR and EFS in MIBC patients in the PD-L1-high subgroup	pCR using assessments per central pathology review EFS using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion
To assess disease-related symptoms, physical function, and other HRQoL in Arm 1 versus Arm 2 using the EORTC QLQ-C30 questionnaire	Adjusted mean change from baseline and time to definitive clinically meaningful deterioration in EORTC QLQ-C30 scale/item scores (prioritized domains: fatigue and pain, physical functioning, global health status/quality of life)
To assess the PK of durvalumab when used in combination with G+C	Serum concentration of durvalumab and non-compartmental PK parameters (such as peak and trough concentrations, as data allow; sparse sampling)
To investigate the immunogenicity of durvalumab when used in combination with G+C	Presence of ADAs for durvalumab (confirmatory results: positive or negative)

Safety objective:	Endpoints/variables:
To assess the safety and tolerability profile of Arm 1 versus Arm 2 in MIBC patients	AEs, laboratory findings, vital signs, and ECGs
Exploratory objectives:	**Endpoints/variables:**
To assess patient-reported treatment-related symptoms or tolerability of Arm 1 versus Arm 2 using PRO-CTCAE	PRO-CTCAE (items pre-selected based on systemic treatment arms) – descriptive summary of responses
To assess overall health status and overall severity of disease-related symptoms in patients in Arm 1 versus Arm 2 using the PGIC and PGIS questionnaires, respectively	PGIC and PGIS – descriptive summary of responses
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data
To evaluate tumor-based biomarkers and associations with efficacy parameters, potentially including, but not limited to, microsatellite stability, tumor mutational burden, and other immune-related biomarkers	Association of tumor-based assessments with efficacy and clinical parameters
To evaluate circulatory-based and urine-based biomarkers and associations with efficacy parameters, including, but not limited to, ctDNA	Association of ctDNA, whole blood gene expression, and urine biomarkers with efficacy and clinical parameters

ADA Antidrug antibody; AE Adverse event; BICR Blinded Independent Central Review; ctDNA Circulating tumor DNA; ECG Electrocardiogram; EFS Event-free survival; EFS24 Proportion of patients alive and event free at 24 months using local pathology or BICR; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EQ-5D-5L EuroQol 5-dimension, 5-level health state utility index; G+C gemcitabine plus cisplatin; HRQoL Health-related quality of life; MIBC Muscle-invasive bladder cancer; OS Overall survival; pCR Pathologic complete response; PD-L1 Programmed cell death-ligand 1; PFS2 Time from the date of randomization to the earliest date of progression which occurs on subsequent therapy following an EFS event or death; PGIC Patient Global Impression of Change; PGIS Patient Global Impression of Severity; PK Pharmacokinetics; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events.

Overall design:

This is a Phase III, randomized, open-label, multi-center, global study to evaluate durvalumab (MEDI4736) in combination with G+C chemotherapy (neoadjuvant) followed by durvalumab alone (adjuvant) versus G+C (neoadjuvant) followed by no adjuvant treatment in patients with MIBC.

Study period:

- Estimated date of first patient enrolled Q4 2018
- Estimated date of last patient completed Q2 2026

Number of patients:

Approximately 1050 patients globally will be randomized in a 1:1 ratio to receive durvalumab + G+C combination therapy q3w (Arm 1) or G+C combination therapy q3w (Arm 2) for 4 cycles of neoadjuvant chemotherapy prior to radical cystectomy. Following radical cystectomy and during adjuvant therapy, patients in Arm 1 will receive durvalumab monotherapy every 4 weeks (q4w) for 8 additional cycles, and patients in Arm 2 will receive no adjuvant treatment.

Recruitment for patients with borderline renal function will be limited to up to 20% of the targeted global population. Recruitment for patients with T2N0 disease will be limited to approximately 40% of the targeted global population (for both treatment arms); once the 40% cap has been reached, only clinical stage T2-T4aN1M0 or T3-T4aN0M0 patients will be allowed to be enrolled onto the study.

Randomization will be stratified by clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively; renal function (adequate renal function versus borderline renal function), and PD-L1 status (high versus low/negative, based on Ventana assay; see Table 6). Patients will provide a tumor tissue sample at screening to determine PD-L1 status for stratification.

Treatments and treatment duration:

Neoadjuvant therapy

Patients randomized to the 2 treatment arms, Arm 1 or Arm 2, will be treated according to their renal function.

Patients with adequate renal function (creatinine clearance [CrCl] ≥60 mL/min)

- Arm 1: Day 1: durvalumab 1500 mg intravenous (IV), cisplatin 70 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2; every 21 days for 4 cycles.
- Arm 2: Day 1: cisplatin 70 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2; every 21 days for 4 cycles.

Patients with borderline renal function (CrCl ≥40 mL/min to <60 mL/min)

- Arm 1: Day 1: durvalumab 1500 mg IV, cisplatin 35 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2, cisplatin 35 mg/m^2; every 21 days for 4 cycles.
- Arm 2: Day 1: cisplatin 35 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2, cisplatin 35 mg/m^2; every 21 days for 4 cycles.

***In scenarios when patients are unable to complete the intended 4 cycles of chemotherapy prior to radical cystectomy, patients will be permitted to receive less than 4 cycles of chemotherapy, at the discretion of the Investigator and upon discussion with AstraZeneca.**

Adjuvant therapy (regardless of renal status)

- Arm 1: Day 1: durvalumab 1500 mg IV; every 28 days for 8 cycles.
- Arm 2: No adjuvant treatment.

Durvalumab (Arm 1 only): Patients will receive durvalumab 1500 mg via IV infusion q3w for 4 cycles as neoadjuvant treatment prior to radical cystectomy. Following radical cystectomy, patients will receive durvalumab 1500 mg q4w for 8 cycles as adjuvant treatment, unless specific study discontinuation criterion are met. Please note, if a patient's weight falls to 30 kg or below (≤30 kg), the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q3w (neoadjuvant treatment) or q4w (adjuvant treatment) after consultation between the Investigator and the Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q3w (neoadjuvant treatment) or q4w (adjuvant treatment).

Gemcitabine + cisplatin: Patients will receive neoadjuvant gemcitabine + cisplatin (1000 mg/m^2, Days 1 and 8, q3w + 70 mg/m^2, Day 1, q3w via IV infusion) for patients with adequate renal function (CrCl ≥60 mL/min) or split-dose gemcitabine + cisplatin (1000 mg/m^2, Days 1 and 8, q3w + 35 mg/m^2, Days 1 and 8, q3w via IV infusion) for patients with borderline renal function (CrCl ≥40 mL/min to <60 mL/min), starting on Week 1, for a maximum of 4 cycles, followed by radical cystectomy.

Duration of treatment:

Unless specific treatment discontinuation criteria are met, adjuvant treatment in Arm 1 will continue for a maximum of 8 cycles (durvalumab 1500 mg administered q4w) following radical cystectomy. Patients in Arm 2 will receive no adjuvant treatment.

Progression during treatment:

During the neoadjuvant treatment phase, patients who have Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)-defined radiological progression may continue to the adjuvant portion of treatment if the progression event did not preclude the patient from having a radical cystectomy (ie, progression is local and/or limited to regional lymph nodes that will be removed at radical cystectomy). In the event progression precludes the patient from undergoing radical cystectomy (ie, distant metastases), the patient will proceed to follow-up.

During the adjuvant treatment phase, patients with proven recurrence (see Sections 8.1.1.1 and 8.1.1.2) will proceed to follow-up.

Progression during follow-up:

Patients who do not have an event of progression during study visits and who develop PD/recurrence in the follow-up period are not eligible for retreatment.

Follow-up of patients post-discontinuation of study drug:

Patients who have discontinued study treatment due to toxicity or symptomatic deterioration, clinical progression/recurrence, or who have commenced subsequent anticancer therapy will be followed up until RECIST 1.1-defined PD, biopsy-proven recurrence, if clinically feasible and safe, or death (whichever comes first) and for survival.

Survival:

All patients randomized in the study should be followed up for survival.

Independent data monitoring committee:

An independent data monitoring committee (IDMC) comprising independent experts will be convened and will meet approximately 6 months after the study has started or after the first 90 patients have been randomized, whichever occurs first, to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. The committee will meet approximately every 6 months thereafter. The IDMC will separately assess the safety of durvalumab + gemcitabine/cisplatin in Japanese patients for the initial data review meetings and make recommendation if additional separate safety reviews are required. For the interim analysis, the IDMC will review interim data and inform the Sponsor whether the interim boundaries specified in Section 9.4.3 are crossed.

Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

Statistical methods:

The dual primary objectives of this study are to assess the efficacy of Arm 1 versus Arm 2 in terms of EFS as assessed by Blinded Independent Central Review (BICR) or by central pathology review if a biopsy is required for a suspected new lesion and pCR rate per central pathology review in MIBC patients.

pCR rate is defined as the proportion of patients whose pathological staging was T0N0M0 as assessed per central pathology review using specimens obtained via radical cystectomy following the neoadjuvant treatment.

EFS, as assessed by BICR or by central pathology review if a biopsy is required for a suspected new lesion, is defined as the time from randomization to the first recurrence of disease post-radical cystectomy, time of first documented progression in patients who were precluded from radical cystectomy, or time of expected surgery in patients who refuse to undergo a radical cystectomy or failure to undergo a radical cystectomy in participants with residual disease , or death due to any cause, whichever occurs first. A recurrence of disease includes local (pelvic) recurrence of UC, urinary tract recurrence of UC, or distant metastasis of UC.

To control Type I error, the 5% 2-sided alpha used will be split into significance levels of 0.1% and 4.9% for pCR and EFS in MIBC patients respectively.

The secondary objectives include: pCR using assessment per local pathology, EFS using assessments per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion, disease-specific survival (DSS) in MIBC patients , OS, proportion of patients alive at 5 years (OS5) in MIBC patients , disease-free survival (DFS) in MIBC patients who undergo radical cystectomy, proportion of patients who achieve <P2 per local pathology review in MIBC patients, DFS in MIBC patients who undergo radical cystectomy, etc.

Unless otherwise specified, efficacy data will be summarized and analyzed on an ITT basis, and the treatment arms will be compared on the basis of randomized treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the ITT population.

Approximately 1050 patients will be randomized in a 1:1 ratio to Arm 1 or Arm 2.

The randomization will be stratified according to the following 3 factors:

- Clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively
- Renal function (adequate renal function versus borderline renal function)
- PD-L1 status (high versus low/negative, based on Ventana assay; see Table 6)

The final analysis of the dual-primary endpoint of pCR will be performed approximately 6 months after the last patient is randomized to the study.

The final analysis of the dual-primary endpoint of EFS will be performed when approximately 451 EFS events in ITT have occurred across the 2 arms (43% maturity) or June 2025 (approximately 45 months after the last subject is randomized), whichever occurs first. For the primary EFS endpoint in MIBC patients (Arm 1 versus Arm 2), two superiority interim analyses for EFS will be conducted: the first when the pCR analysis is conducted and the second when approximately 410 EFS events have occurred (39% maturity) across the 2 arms in ITT, or in April 2024, whichever occurs first. The latter interim is expected approximately 31 months after the last patient is randomized. The interim analyses will be assessed by an IDMC. Details of the plan and communication process will be provided in the statistical analysis plan (SAP) and in the IDMC charter.

Arm 1 versus Arm 2 (pCR in ITT)

It is assumed that the pCR for patients in Arm 2 is 35% (Grossman et al 2003). Under the alternative hypothesis, pCR is assumed to be 50% for Arm 1. With 525 patients in each arm, the study will have at least 95% power to demonstrate a statistically significant difference at a 2-sided alpha level of 0.1%. Assuming a pCR rate of 35% in Arm 2, the smallest pCR rate that could be observed as being statistically significant at the time of pCR analysis is a 10-percentage point increase to 45% in Arm 1.

Arm 1 versus Arm 2 (EFS in ITT)

The assumed EFS treatment effect under the alternative hypothesis is an average HR of 0.733 for Arm 1 versus Arm 2. This is based on the following assumptions:

An exponential model was assumed for EFS such that in patients who are assigned to the Arm 1, the overall median EFS is 38.0 months and the EFS rate at 24 months is 64.5%.

For Arm 2, an exponential model was assumed for EFS such that patients who are assigned to Arm 2, the overall median EFS is 27.8 months and the EFS rate at 24 months is 55%.

Based on a blinded event prediction, an estimated 451 EFS events (43% maturity) are expected to be observed at 45 months after the date of the last patient randomized. With 451 EFS events, the study will have at least 90% power to demonstrate a statistically significant difference at a 2-sided overall alpha level of 4.90%, allowing two interim analyses to be conducted at approximately 67% and 91% of the target events. The smallest treatment difference that could be statistically significant will be an average HR of 0.82.

Arm 1 versus Arm 2 (OS in ITT)

The assumed OS treatment effect under the alternative hypothesis is an average HR of 0.76 for Arm 1 versus Arm 2. This is based on the following assumptions:

- An exponential model was assumed for OS such that in all patients who are assigned to Arm 1, the overall median OS is 8.6 years (103 months), and the OS rate at 5 years is 66.8%.

- For Arm 2, an exponential model was assumed for OS such that in all patients who are assigned to Arm 2, the overall median OS is 6.5 years (78 months), and the OS rate at 5 years is 58.7%.

The final analysis of OS based on approximately 428 OS events for the comparison of Arm 1 versus Arm 2 (41% maturity, 428/1050), from ITT, is expected to occur 5 years (60 months) after the last patient is randomized to the study and will provide at least 80% power to demonstrate a statistically significant difference in OS at a 2-sided alpha level of 4.9%, allowing two interim analysis to be conducted at approximately 67% and 74% of the target events. The smallest treatment difference that could be statistically significant will be an HR of 0.82.

Arm 1 versus Arm 2 (OS5 in ITT)

The statistical model assumptions for OS5 in the ITT of each arm are stated above.

The analysis of OS5 that is performed at the time of final analysis of OS will provide at least 77% power to demonstrate a statistically significant difference in OS5 at a 2-sided alpha level of 4.9%.

pCR will be analyzed using a stratified logistic regression model adjusting for stratification factors: clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively; renal function (adequate renal function versus borderline renal status); and PD-L1 status (high versus low/negative, based on Ventana assay; see Table 6). The result of the analysis will be presented in terms of an odds ratio together with a 99.9% confidence interval (CI) and p-value.

EFS will be analyzed using a stratified log-rank test, stratified for clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively; renal function (adequate renal function versus borderline renal status); and PD-L1 status (high versus low/negative, based on Ventana assay; see Table 6). The effect of treatment will be estimated by the HR together with the corresponding ([1-adjusted alpha] × 100%) CIs and p-values for EFS.

EFS24 will be analyzed using the Kaplan-Meier estimator of EFS at 24 months for each treatment to obtain the HR.

OS will be analyzed using a stratified log-rank test, stratified for clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively; renal function (adequate renal function versus borderline renal status); and PD-L1 status (high versus low/negative, based on Ventana assay; see Table 6.

OS5 will be analyzed using the Kaplan-Meier estimator of OS at 5 years for each treatment to obtain the HR.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm.

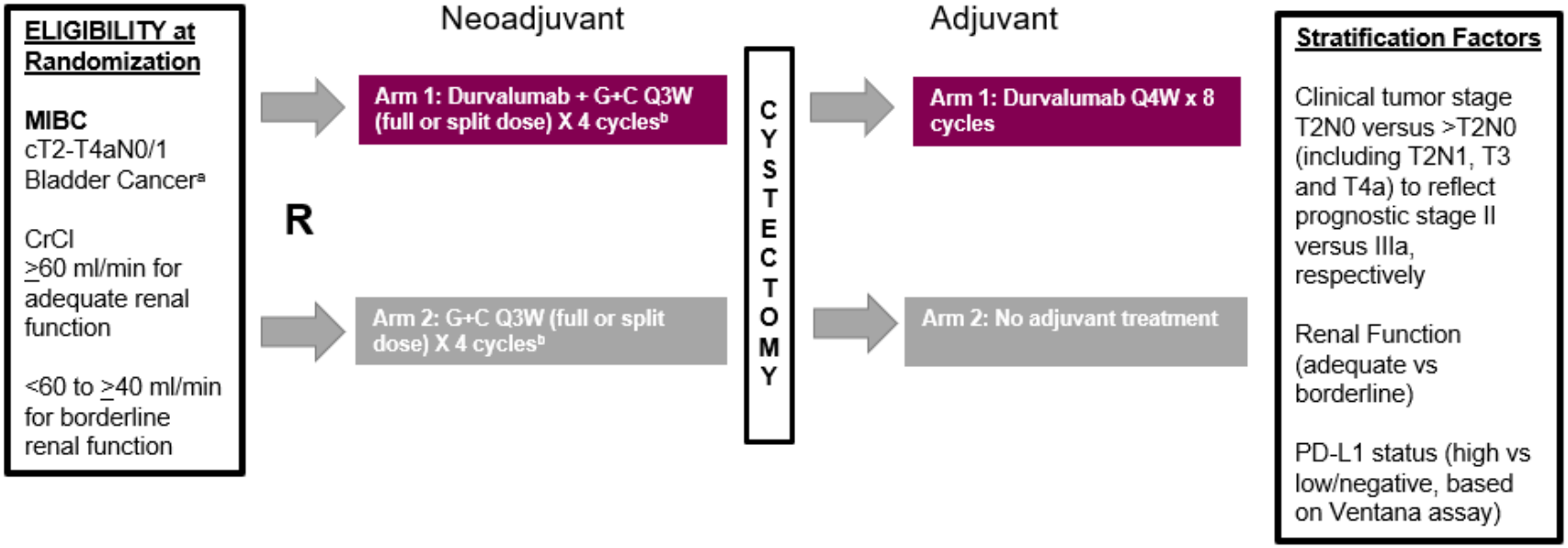
Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of investigational product (IP), except for efficacy variables. For efficacy variables except DFS (including pCR rate, EFS, EFS24, proportion of patients who achieve <P2, metastasis-free survival (MFS), disease-specific survival (DSS), OS, OS5, the time from the date of randomization to the earliest date of progression which occurs on subsequent therapy following an EFS event or death (PFS2), proportion of patients who undergo radical cystectomy, PRO, demography, and PK data), baseline is defined as the last visit prior to randomization. A second (“adjuvant”) baseline scan will be performed 42 days (±2 weeks) following the date of radical cystectomy and prior to the start of adjuvant therapy for radiological assessments. Efficacy assessments of pCR and proportion of patients who achieve <P2 will be derived (by AstraZeneca) using local pathology review of the radical cystectomy sample.

Safety data from all cycles of treatment will be presented for neoadjuvant treatment and neoadjuvant followed by adjuvant treatment separately as appropriate. Adverse events (AEs; in terms of both Medical Dictionary for Regulatory Activities preferred terms and Common Terminology Criteria for Adverse Events [CTCAE] grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Other safety data will be assessed in terms of physical examinations, laboratory assessments, vital signs, and ECGs. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

1.3 Schema

The general study design is summarized in Figure 1.

Figure 1 Study design



[a] Enrolment of patients with T2N0 disease is limited to approximately 40% of the targeted global population (for both treatment arms).
[b] Patients with borderline renal function will receive split-dose G+C and will be limited to up to 20% of the targeted global population.
CrCl Creatinine clearance; Durva Durvalumab; G+C Gemcitabine and cisplatin; q3w Every 3 weeks; q4w Every 4 weeks; MIBC Muscle-invasive bladder cancer; PD-L1 Programmed cell death-ligand 1; R Randomization.

2. INTRODUCTION

Bladder cancer (BC) is the 9th most common cancer diagnosed worldwide, with an estimated 429800 new cases each year and 165100 cancer-related deaths reported globally in 2012 (Ferlay et al 2015, Torre et al 2015). Bladder cancer is generally divided into muscle-invasive and non-muscle-invasive disease based on invasion of the muscularis propria. At the initial diagnosis of BC, 70% to 75% of cases are diagnosed as non-MIBC (NMIBC), and approximately 25% to 30% are diagnosed as MIBC (Babjuk et al 2014, Boccardo and Palmeri 2006, Burger et al 2013).

Cisplatin-based neoadjuvant chemotherapy is the standard first-line (1L) treatment in patients with MIBC fit enough to receive this. The combination of neoadjuvant therapy and radical cystectomy has shown potential for an increase in pathologic complete response (pCR), event-free survival (EFS), and overall survival (OS) in patients with MIBC (Grossman et al 2003, Sonpavde et al 2009). Grossman et al showed an increase in pCR rate of 38% in patients who had neoadjuvant therapy followed by cystectomy versus 15% in the cystectomy alone group and an increase of OS5 (Grossman et al 2003). Despite these measures, patients with MIBC still have high rates of disease recurrence and possible development of advanced cancer, with most recurrences occurring within the first 2 to 3 years after cystectomy (Chang et al 2017, Witjes et al 2016). Because of the significant rate of recurrence (approximately 56% in patients with pathological stage T3), the use of perioperative chemotherapy has been explored in an effort to eliminate distant micrometastatic disease and improve the outcomes achieved with radical cystectomy alone (Grossman et al 2003). However, there is still a significant unmet medical need for additional treatment options to improve survival in this patient population.

2.1 Study rationale

The standard management for patients with MIBC involves radical cystectomy and pelvic lymph node dissection. Several studies have demonstrated improved pCR, EFS, and OS with the integration of neoadjuvant, cisplatin-based combination chemotherapy when compared with radical cystectomy alone. The treatment recommendation since the NCCN 2018 guideline is cisplatin-based neoadjuvant chemotherapy with radical cystectomy surgery for patients with stage II and stage IIIa, according to AJCC 8th edition criteria.

The current AJCC 8th criteria reflect a modification to the previously defined stage III and IV patient populations. In this updated version, T1-T4 patients with node-positive disease (regional lymph nodes) are now classified as IIIa (cN1 disease) and IIIb (N2/N3 disease); prior to this revision, all patients with node-positive disease were classified as stage IV. Also in 2018, the NCCN guidelines were revised to reflect the treatment approach of neoadjuvant chemotherapy followed by radical cystectomy plus lymphadenectomy, be offered to all stage IIIa patients, when feasible; previously patients with node-positive disease were not considered cystectomy candidates (Flaig, 2018). The rationale provided for this change reflects clinical data demonstrating a better prognosis for patients with cN1 disease compared with similar patients with N2 and N3 disease; it was also suggested that this patient population would benefit from a more aggressive approach. It is acknowledged therefore, that in addition to stage II patients, that all IIIa patients (T3-T4N0 and T1-T4N1) should now be offered treatment with potential curative intent; therefore, patients with T2-4N1 are being included in the study. Despite improvements of

pCR and survival rates with neoadjuvant chemotherapy, many patients will still develop recurrence and will ultimately die of metastatic bladder cancer. Recently, multiple programmed cell death-1 (PD-1) and programmed cell death-ligand 1 (PD-L1) have demonstrated activity in patients with metastatic BC and have been granted approval in the platinum refractory setting as well as pembrolizumab and atezolizumab accelerated approval in the 1L metastatic setting for patients unable to tolerate cisplatin chemotherapy (KEYTRUDA [package insert] 2018, TECENTRIQ [package insert] 2018).

The benefits of adjuvant chemotherapy after radical cystectomy in patients with MIBC without clinically detectable metastases are unclear. There is limited evidence from adequately conducted, randomized, Phase III trials to support the use of adjuvant chemotherapy in patients immediately following surgery. However, in 2 separate meta-analyses conducted in 2013 (Leow et al 2014) and 2016 (Kim et al 2017), with 9 and 11 randomized controlled studies in MIBC, respectively, suggested an OS benefit in patients receiving adjuvant cisplatin-based chemotherapy. Multiple Phase III trials evaluating adjuvant PD-1 or PD-L1 inhibitors and Phase II trials reveal promising activity and safety for single-agent neoadjuvant pembrolizumab or atezolizumab are ongoing (Necchi et al 2018, Powles et al 2018).

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin (Ig) G1 kappa (IgG1κ) subclass that inhibits binding of PD-L1 (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to PD-1 (CD279) and CD80 (B7-1). Nonclinical and clinical studies have indicated that blockade of the immune checkpoints PD-1/PD-L1 can have a positive effect on antitumor activity. Clinical benefit has been observed in a wide range of tumor types, including metastatic melanoma, squamous and nonsquamous non-small-cell lung cancer (NSCLC), head and neck squamous cell carcinoma, and urothelial carcinoma (UC).

The benefit of this class of compound and specifically durvalumab in BC has been demonstrated in a cohort of 182 patients with locally advanced or metastatic UC who progressed despite platinum-based chemotherapy (IMFINZI [package insert] 2017, Massard et al 2016). Durvalumab has been approved to treat locally advanced or metastatic urothelial carcinoma, unresectable stage III non-small cell lung cancer, and extensive-stage small cell lung cancer (administered in combination with chemotherapy). Refer to the package insert (or label) for your specific country, as applicable.

The addition of immunotherapy to chemotherapeutic agents has been shown to result in improved response rates relative to chemotherapy alone. Cytotoxic chemotherapy has been shown to modulate the immune response via several mechanisms, such as stimulating T cell activation by increasing the expression of MHC-1 molecules, stimulating dendritic cell maturation, inducing immunogenic cell death (a form of cell death that induces dendrites to stimulate tumor antigen presentation to T cells), and reducing the immunosuppressive function of regulatory T cells and myeloid-derived suppressor cells (Kodumudi et al 2010, Kroemer et al 2013, Liu et al 2010, Zhang et al 2008). Combining a PD-L1 antagonist with cytotoxic agents may provide complementary benefit in mounting an effective antitumor immunity by promoting the antigen presentation, increasing the production protective T cells, and overcoming immunosuppression in the tumor bed (Mellman et al 2011). In addition, a variety of approaches for combining PD-1 pathway blockers with other agents has been explored over the past few

years in an effort to both improve the efficacy of treatment and/or to position the treatment regimen for testing in patients who are treatment-naive with a variety of cancers (Langer et al 2016). The rationale for the present study is that PD-L1 inhibition through exposure to durvalumab, in combination with chemotherapeutics such as gemcitabine plus cisplatin (G+C), may increase both the long-term response rate and frequency of response by preventing the MIBC tumor cells (TCs) from evading immune-mediated antitumor response. Administering durvalumab- may provide a benefit to this subgroup of patients by averting intrinsic resistance.

2.1.1 Rationale for durvalumab as a potential therapy for MIBC

Efficacy of immuno-oncology agents pembrolizumab, atezolizumab, nivolumab, and avelumab has been demonstrated in a number of recent studies (reviewed in Gill et al 2017).

The following immuno-oncology agents are currently approved in the US for treatment of UC:

- Pembrolizumab (KEYTRUDA [package insert] 2018):
  - For the treatment of patients with locally advanced or metastatic UC who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (combined positive score ≥10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status
  - For the treatment of patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- Avelumab (BAVENCIO [package insert] 2017), a PD-L1 inhibitor, for patients with locally advanced or metastatic UC who:
  - Have disease progression during or following platinum-containing chemotherapy
  - Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- Atezolizumab (TECENTRIQ [package insert] 2018), a PD-L1 blocking antibody indicated for the treatment of patients with locally advanced or metastatic UC who:
  - Are not eligible for cisplatin-containing chemotherapy, and whose tumors express PD-L1 (PD-L1 stained tumor-infiltrating immune cells [ICs] covering ≥5% of the tumor area), or are not eligible for any platinum-containing chemotherapy regardless of level of tumor PD-L1 expression
  - Have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant chemotherapy

Approval of atezolizumab was based on a multinational Phase II study with 315 patients who experienced significant increases in objective response rate (ORR) and durability of responses

(Rosenberg et al 2016). In a recent Phase III study (KEYNOTE-045), pembrolizumab, a human anti-PD-L1 antibody, demonstrated a significant 3-month improvement in OS over chemotherapy as second-line treatment for platinum-refractory advanced UC (Bellmunt et al 2017). Presumably, the success of PD-L1 pathway blockade in UC is due to the high rate of PD-L1 expression in UC tumors. PD-L1 expression is also high in the tumors of patients with NMIBC who have had prior Bacillus Calmette Guerin (BCG) treatment (Lerner et al 2016).

Collectively, existing efficacy data and PD-L1 expression data support the potential therapeutic effect of durvalumab in bladder cancer, including MIBC.

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the Investigator Brochure (IB).

2.2.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors (Dunn et al 2004).

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. The programmed cell death 1 (PD-1) receptor (CD279) is expressed on the surface of activated T cells (Keir et al 2008). It has 2 known ligands: PD-L1 (B7-H1; CD274) and PD-L2 (B7-DC; CD273) (Okazaki and Honjo 2007). PD-1 and PD-L1/PD-L2 belong to the family of immune checkpoint proteins that act as co-inhibitory factors, which can halt or limit the development of T-cell response. When PD-L1 binds to PD1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. TCs exploit this immune checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PDL1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al 2016). Importantly, PD-L1 is commonly overexpressed on TCs or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PDL1 expressed on the TCs binds to PD-1 receptors on the activated T cells, leading to the inhibition of cytotoxic T cells. These deactivated T cells remain inhibited in the tumor microenvironment. The PD-1/PDL1 pathway represents an adaptive immune resistance mechanism that is exerted by TCs in response to endogenous antitumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on ICs. This activity overcomes PD-L1-mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of pre-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the

PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al 2012, Hirano et al 2005, Iwai et al 2002, Okudaira et al 2009, Topalian et al 2012, Zhang et al 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al 2014, Rizvi et al 2015, Segal et al 2015). In addition, high mutational burden (eg, in bladder carcinoma; Alexandrov et al 2013) may contribute to the responses seen with immune therapy.

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T cells such as with PD-L1 has promising clinical activity. Nivolumab and pembrolizumab, 2 anti-PD-1 agents, and atezolizumab, an anti-PD-L1 agent, have been granted approvals by agencies such as the US Food and Drug Administration (FDA) and the European Medicines Agency for the treatment of a number of malignancies, including metastatic melanoma, squamous and NSCLC, squamous cell carcinoma of the head and neck, and UC. In addition there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

Immunotherapy with PD-1 (ie, PDCD1) or PD-L1 (ie, CD274) inhibitors has shown significant activity in advanced UC. Atezolizumab, a PD-L1 inhibitor, showed an ORR of 23% and median OS of 15.9 months (95% confidence interval [CI] 10.4 to not estimable). Treatment was generally well tolerated with only 8% of patients discontinuing therapy due to an adverse event (AE) (Balar et al 2017). Durvalumab monotherapy studies in patients with UC are ongoing.

Immunotherapy with PD-1 or PD-L1 has proven to be an important advance for patients with metastatic BC; however, initiating immunotherapy earlier in the treatment of BC may provide potential long-term benefit and improved outcomes for patients with MIBC.

Comprehensive genomic analysis of urothelial bladder cancers have provided an understanding of the molecular mutations underlying the disease. The most frequent recurrent mutations occur in genes controlling cell cycle and chromatin or receptor kinase signaling (Cancer Genome Atlas Research Network 2014). For UC patients treated with radical cystectomy, PIK3CA mutations correlate with a better prognosis than TP53 and CDKN2A alterations (Kim et al 2015). Deleterious mutations in DNA damage response and repair (DDR) genes, such as NBN and ERCC2, have also been implicated in the progression and/or prognosis of bladder cancer (Bellmunt et al 2007, Mullane et al 2016).

Genomic predictors have also been used retrospectively to analyze patient outcome data. An extensive panel of DDR genes (MSK-IMPACT) has been interrogated in UC patients to determine whether DDR pathway alterations are predictive of response to standard of care (SoC) (Teo et al 2017). The presence of DDR alterations is associated with increased response to neoadjuvant chemotherapy, improved outcome following platinum-based chemotherapy, and trends toward improved outcome after chemoradiation (Desai et al 2016, Iyer et al 2016, Teo et al 2017). Of note, analysis of the DDR gene panels in bladder tumors has been used to impute the overall tumor mutational burden (TMB) and has demonstrated an association between the prevalence of DDR aberrations and TMB (Teo et al 2017). The estimates for TMB have also been generated using the FoundationOne Assay and are reported to align with the distribution of TMB in TCGA bladder tumors and the MSK-IMPACT panel (Rosenberg et al 2016).

2.2.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin G 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand 2 [PD-L2]) with PD-1 on T cells and CD80 (B7.1) on ICs. It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer. (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon-gamma (IFN-γ) (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date, durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anticancer agents. Details on the safety profile of durvalumab monotherapy are summarized in Section 4.3.1 and Section 8.3.12. Refer to the current durvalumab IB for a complete summary of nonclinical and clinical information including safety, efficacy, and pharmacokinetics (PK).

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of durvalumab may be found in the IB.

See Section 9.6 for information regarding the independent data monitoring committee (IDMC).

2.3.1 Potential benefits

2.3.1.1 Durvalumab

A total of 23 sponsored clinical studies have been or are being conducted with durvalumab as a single agent or in combination with other agents. As of 12 July 2017, an estimated 4067 patients had received at least 1 dose of durvalumab across a number of tumor types (refer to the current durvalumab IB).

The potential benefit of durvalumab in bladder cancer was demonstrated in a cohort of 182 patients with locally advanced or metastatic UC who had progressed while on or after a platinum-based chemotherapy. The overall ORR based on Blinded Independent Central Review (BICR) was 17%. In patients who had received only 1 neoadjuvant or adjuvant prior therapy, the ORR was 24%. With a median follow-up time of 5.6 months, among the responding patients, 45% had ongoing responses of 6 months or longer, and 16% had ongoing responses of 12 months or longer (median DoR: not reached [range: 0.9+ months to 19.9+ months]).

2.3.1.2 Durvalumab in combination with chemotherapy

As a human mAb directed against PD-L1 (a ligand that is expressed in most types of cancer), durvalumab is expected to enhance the antitumor immune responses in patients with a number of cancers, including BC. PD-L1 is commonly expressed in UC specimens (Inman et al 2007), and 95% of lymphocytes that invade bladder tumors express the PD-1 receptor. Urothelial expression of PD-L1 is also predictive of mortality following cystectomy in patients with organ-limited disease. PD-L1 expression is significantly associated with a higher grade and stage in UC patients (Inman et al 2007). High mutational burden in bladder carcinoma (Alexandrov et al 2013) may contribute to the responses seen with immune therapy. In addition, the utilization of chemotherapy may potentially upregulate the expression of PD-L1. Based on these findings, an anti-PD-L1 antibody is being used therapeutically to enhance antitumor immune responses in patients with cancer. PD-L1 inhibition through exposure to durvalumab, in combination with chemotherapeutics such as G+C, may increase both the long-term response rate and frequency of response by preventing the MIBC TCs from evading immune-mediated antitumor response. Administering durvalumab may provide a benefit to this subgroup of patients by averting intrinsic resistance.

Studies evaluating PD-L1 inhibitors and other immunotherapy agents in combination with chemotherapy have yielded encouraging results (Langer et al 2016, Rizvi et al 2016, Horn et al 2018). The PD-1 inhibitor pembrolizumab received FDA approval under accelerated assessment for the treatment of first line metastatic, nonsquamous NSCLC patients in combination with pemetrexed and carboplatin. Approval was based on impressive ORR (55% versus 29%) and progression-free survival (PFS) (13.0 versus 6 months) data and a compelling hazard ratio (HR) of 0.53 (95% CI 0.31, 10.3) for pembrolizumab plus carboplatin versus carboplatin alone (KEYTRUDA [package insert] 2018). Although these results relate to first-line treatment of patients with metastatic disease, these data are supportive of the theory that combining chemotherapy with immunotherapeutic agents has the potential to significantly improve clinical outcomes.

2.3.2 Overall risks

mAbs directed against immune checkpoint proteins, such as PD-L1, as well as those directed against PD-1, aim to boost endogenous immune responses directed against tumor cells. By stimulating the immune system, however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or hormone therapy. These immune-mediated effects can occur in nearly any organ system and are most commonly seen as gastrointestinal (GI) AEs such as colitis and diarrhea; pneumonitis/interstitial lung disease (ILD); myocarditis; hepatic AEs such as hepatitis and transaminase increases; skin events such as pruritus, rash, and dermatitis; and endocrinopathies such as hypothyroidism and hyperthyroidism.

2.3.2.1 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis, pneumonitis/ILD, hepatitis/transaminase increases, endocrinopathies (ie, events of hypophysitis/ hypopituitarism, adrenal insufficiency, hypothyroidism and hyperthyroidism, type I diabetes mellitus and diabetes insipidus), rash/dermatitis (including pemphigoid), nephritis/blood creatinine increases, myocarditis, myositis/polymyositis, immune thrombocytopenia, infusion-related reactions, hypersensitivity reactions, pancreatitis, serious infections, and other inflammatory responses that are rare/less frequent, including neuromuscular toxicities (eg, Guillain-Barré syndrome and myasthenia gravis) (see Section 8.3.12).

For information on all identified and potential risks with durvalumab, please always refer to the current version of the durvalumab IB.

In monotherapy clinical studies, AEs at an incidence of >20% include fatigue, nausea, decreased appetite, dyspnea, and cough. Approximately 10% of patients experienced an AE that resulted in permanent discontinuation of durvalumab, and approximately 6% of patients experienced a serious adverse event (SAE) that was considered to be related to durvalumab by the Study Investigator.

The majority of treatment-related AEs were manageable with dosing delays, symptomatic treatment, and, in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity (see Section 8.4.5).

A detailed summary of durvalumab monotherapy AE data can be found in the current version of the durvalumab IB.

2.3.2.2 Durvalumab in combination with chemotherapy

Safety and tolerability data for durvalumab and tremelimumab, a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) mAb of the IgG2 kappa isotype, in combination with standard first-line platinum-based chemotherapy in advanced solid tumors are being generated from 2 ongoing Phase I studies: an AstraZeneca internal study (D419SC00001) and a Canadian Cancer Trials Group study (NCT02537418).

As of 12 July 2018, a total of 22 patients with advanced solid tumors have been treated with durvalumab and tremelimumab in combination with platinum-based chemotherapy in Study D419SC00001. All patients had at least 1 AE (regardless of causality). AEs (all grades) reported in >20% of patients were nausea (68.2%); neutrophil count decreased (63.6%); decreased appetite (50.0%); cough, diarrhea, and rash (36.4% each); anemia and pyrexia (31.8% each); constipation, dizziness, insomnia, myalgia, platelet count decreased, and pruritus (27.3% each); ALT increased, alopecia, dyspepsia, peripheral sensory neuropathy, vomiting, and white blood cell count decreased (22.7% each). All patients had AEs considered by the Investigator to be related to study treatment. SAEs were reported in a total of 10 patients (45.5%). With the exception of pneumonia and pyrexia (3 patients each) and diarrhea and neutrophil count decreased (2 patients each), all other SAEs were reported in 1 patient each. One patient had a fatal AE of lung infection, which was considered treatment related. A total of 13.6% of patients had AEs that led to permanent discontinuation of treatment.

In the CCTG study (NCT02537418), a total of 488 cycles have been administered up to the data cutoff of October 2016, with 103 patients evaluable for non-hematologic AEs. Overall, all patients experienced at least 1 AE; 96% were considered by the Investigator as causally related to chemotherapy, 75% were considered as causally related to durvalumab, and 55% were considered as causally related to tremelimumab. A total of 69 events (26% of all events) were Grade ≥3, regardless of causality. Of these, 20 events were considered by the Investigator as causally related to durvalumab treatment, and 15 events were considered as causally related to tremelimumab treatment. SAEs were reported in 38% of patients (39/103) regardless of causality; 19% were considered by the Investigator as related to chemotherapy, 15% were considered as related to durvalumab, and 11% were considered as related to tremelimumab treatment. Note that some events considered related to durvalumab and tremelimumab treatment may be reported in the same patient(s).

Overall, the common AEs reported were of Grade 1 to 2 with the most commonly reported being fatigue (93%), nausea (72%), dyspnea (63%), constipation (59%), and cough (52%), regardless of causality. The most common chemotherapy-related AEs were fatigue (62%), nausea (58%), vomiting (32%), anorexia (28%), alopecia (27%), and peripheral sensory neuropathy (24%). The most common durvalumab-related AEs were fatigue (42%), rash maculo-papular (17%), nausea (16%), and diarrhea (12%). The most common tremelimumab‑related AEs were fatigue (26%), rash maculo-papular (13%), and diarrhea (11%). The most common Grade >3 events were fatigue (11 events), thrombotic events (9 events), dyspnea (7 events), lung infection (7 events), and diarrhea (7 events). Transient elevations in amylase and lipase were seen, but no patient had clinical or radiological evidence of pancreatitis. Thyroid-stimulating hormone (TSH) elevations of ≥5× the upper limit of normal (ULN) were documented in 10 patients (10%), and 6 patients required initiation of thyroid replacement therapy on study. Three of these patients with elevated TSH had a previous history of hypothyroidism. In all dose levels, dose delays of durvalumab were mostly for administrative reasons/patient request and neutropenia related to chemotherapy, while those for durvalumab ± tremelimumab were interrupted in 4 patients because of pneumonitis, colitis, or rash.

Seven patients (6.7%) discontinued durvalumab ± tremelimumab due to the following AEs: pneumonitis (3 patients) and hepatitis, myocarditis, hyperthyroidism, and limbic encephalitis (1 patient each).

There were 7 deaths within 30 days of the last dose of protocol therapy. Two of these were considered to be at least possibly related to durvalumab or tremelimumab; 1 patient had diarrhea, hyperthyroidism, and myocarditis, which was steroid responsive, but later declined active therapy. The cause of death has not yet been determined. The final post-mortem examination has not been reported. One patient had confusion and possible encephalitis.

Overall in these 2 studies, toxicities related to the platinum-based chemotherapy core regimen and to durvalumab and tremelimumab were as expected for these agents. In general, the combination of immunotherapy agent durvalumab + tremelimumab with chemotherapy appears tolerable and manageable.

External published data evaluating the use of an immune checkpoint inhibitor administered in combination with a conventional lung cancer chemotherapy have reported acceptable toxicity profiles. Toxicity data from the Impower133 study that combined atezolizumab (PD-L1) with carboplatin + etoposide as first-line therapy for extensive small-cell lung cancer demonstrated equivalent hematologic side effects in both groups and a similar incidence and types of immune-mediated AEs to those seen with atezolizumab alone (Horn et al 2018). Pembrolizumab (PD-1) has been administered in NSCLC trials in combination with various platinum-based doublets (ie, with carboplatin). Toxicity data specifically from the KEYNOTE-021 study revealed a higher incidence of non-hematologic chemotherapy AEs reported with combination therapy; however, the incidence of potential immune-mediated toxicity for the combination group was comparable to that observed with pembrolizumab monotherapy (Langer et al 2016). Additional data from another first-line NSCLC study (Rizvi et al 2016) evaluating nivolumab (PD-L1) in combination with 4 cycles of a platinum doublet (including gemcitabine and cisplatin) reported toxicities commonly described with platinum-based therapy and a rate of non-hematologic toxicities consistent with chemotherapy alone; in this study, there was, however, an increased frequency of immune-related AEs reported with the combination compared with nivolumab alone.

Overall, the above data demonstrate that anti-PD-L1 immunotherapy (including durvalumab) in combination with chemotherapy is reasonably well tolerated and has an acceptable safety profile.

2.3.3 Overall benefit/risk

The treatment options currently available for these patients remain limited, current standard therapy is likely to result in modest improvements in long-term survival, and additional and alternative therapies are required for patients with MIBC. Therefore, there remains an unmet medical need for this patient population. In this study, gemcitabine and cisplatin will be combined with the PD-L1 inhibitor durvalumab to broaden the therapeutic effect of durvalumab monotherapy for the treatment of patients with MIBC.

3. OBJECTIVES AND ENDPOINTS

Table 5 Study objectives and endpoints

Primary objective:	Endpoints/variables:
To assess the efficacy of durvalumab + G+C combination therapy (neoadjuvant)/durvalumab alone (adjuvant) (Arm 1) compared to G+C combination therapy (neoadjuvant)/no adjuvant (Arm 2) in terms of pCR and EFS in MIBC patients	pCR using assessments per central pathology review EFS using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion

Table 5 Study objectives and endpoints

Secondary objectives:	Endpoints/variables:
To assess the efficacy of Arm 1 versus Arm 2 in terms of EFS at 24 months in MIBC patients	EFS24 using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion
To assess the efficacy of Arm 1 compared to Arm 2 in terms of pathologic response at radical cystectomy and EFS in MIBC patients	pCR using assessments per local pathology review Proportion of patients who achieve <P2 per local pathology review EFS using assessments per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion EFS24 using assessments per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion
To assess the efficacy of Arm 1 versus Arm 2 in MIBC patients	Metastasis-free survival and disease-specific survival per Investigator assessments or Investigator biopsy review if a biopsy is required for a suspected new lesion Overall survival (OS) OS at 5 years Disease-free survival in patients who undergo radical cystectomy Proportion of patients who undergo radical cystectomy PFS2 as defined by local standard clinical practice
To assess the efficacy of Arm 1 versus Arm 2 in terms of pCR and EFS in MIBC patients in the PD-L1-high subgroup	pCR using assessments per central pathology review EFS using assessments per BICR or by central pathology review if a biopsy is required for a suspected new lesion
To assess disease-related symptoms, physical function, and other HRQoL in Arm 1 versus Arm 2 using the EORTC QLQ-C30 questionnaire	Adjusted mean change from baseline and time to definitive clinically meaningful deterioration in EORTC QLQ-C30 scale/item scores (prioritized domains: fatigue and pain, physical functioning, and global health status/quality of life)

Table 5 Study objectives and endpoints

To assess the PK of durvalumab when used in combination with G+C	Serum concentration of durvalumab and non-compartmental PK parameters (such as peak and trough concentrations, as data allow; sparse sampling)
To investigate the immunogenicity of durvalumab when used in combination with G+C	Presence of ADAs for durvalumab (confirmatory results: positive or negative)
Safety objective:	**Endpoints/variables:**
To assess the safety and tolerability profile of Arm 1 versus Arm 2 in MIBC patients	AEs, laboratory findings, vital signs, and ECGs
Exploratory objectives:	**Endpoints/variables:**
To assess patient-reported treatment-related symptoms or tolerability of Arm 1 versus Arm 2 using PRO-CTCAE	PRO-CTCAE (items pre-selected based on systemic treatment arms) – descriptive summary of responses
To assess overall health status and overall severity of disease-related symptoms in patients in Arm 1 versus Arm 2 using the PGIC and PGIS questionnaires, respectively	PGIC and PGIS – descriptive summary of responses
To explore the impact of treatment and disease state on health state utility using the EQ-5D-5L	The EQ-5D-5L health state utility index will be used to derive health state utility based on patient-reported data
To evaluate tumor-based biomarkers and associations with efficacy parameters, potentially including, but not limited to, microsatellite stability, tumor mutational burden, and other immune-related biomarkers	Association of tumor-based assessments with efficacy and clinical parameters
To evaluate circulatory-based and urine-based biomarkers and associations with efficacy parameters, including, but not limited to, ctDNA	Association of ctDNA, whole blood gene expression, and urine biomarkers with efficacy and clinical parameters

ADA Antidrug antibody; AE Adverse event; BICR Blinded Independent Central Review; ctDNA Circulating tumor DNA; ECG electrocardiogram; EFS event-free survival; EFS24 proportion of patients alive and event free at 24 months using local pathology or BICR; EORTC QLQ-C30 European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire; EQ-5D-5L EuroQol 5-dimension, 5-level health state utility index; G+C gemcitabine plus cisplatin; HRQoL health-related quality of life; MIBC muscle-invasive bladder cancer; OS Overall survival; pCR pathologic complete response; PD-L1 Programmed cell death-ligand 1; PFS2 Time from the date of randomization to the earliest date of progression which occurs on subsequent therapy following an EFS event or death; PGIC Patient Global

Impression of Change; PGIS Patient Global Impression of Severity; PK Pharmacokinetics; PRO-CTCAE Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events.

4. STUDY DESIGN

4.1 Overall design

This is a Phase III, randomized, open-label, multi-center, global study to determine the efficacy and safety of durvalumab + G+C combination therapy versus G+C for the neoadjuvant and adjuvant treatment of patients with histologically or cytologically documented, resectable MIBC (ie, T2N0/1M0-T4aN0/1M0) and transitional cell carcinoma (TCC; transitional cell and mixed transitional/nontransitional cell histologies) of the urothelium (excluding renal pelvis and ureters) who are candidates for radical cystectomy and have not received prior systemic chemotherapy or immunotherapy for treatment of MIBC.

Approximately 1050 patients globally will be randomized in 1:1 ratio to receive durvalumab + G+C combination therapy every 3 weeks (q3w) (Arm 1) or G+C combination therapy q3w (Arm 2) for 4 cycles of neoadjuvant chemotherapy prior to radical cystectomy. Following the radical cystectomy and during adjuvant therapy, patients in Arm 1 will receive durvalumab monotherapy q4w for 8 additional cycles and patients in Arm 2 will receive no adjuvant treatment. Crossover from Arm 1 to Arm 2 will not be permitted.

Patients randomized to the 2 treatment arms, Arm 1 or Arm 2, will be treated according to their renal function. Recruitment for borderline renal function patients will be limited to up to 20% of the targeted global population.

Recruitment for patients with T2N0 disease will be limited to approximately 40% of the targeted global population (for both treatment arms); once the 40% cap has been reached, only T2-4N1M0 and T3-4N0M0 patients will be allowed to be enrolled onto the study

Neoadjuvant therapy

Patients with adequate renal function (CrCl ≥60 mL/min)

- Arm 1: Day 1: durvalumab 1500 mg intravenously (IV), cisplatin 70 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2; every 21 days for 4 cycles.
- Arm 2: Day 1: cisplatin 70 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2; every 21 days for 4 cycles.

Patients with borderline renal function (CrCl ≥40 mL/min to <60 mL/min)

- Arm 1: Day 1: durvalumab 1500 mg IV, cisplatin 35 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2, cisplatin 35 mg/m^2; every 21 days for 4 cycles.
- Arm 2: Day 1: cisplatin 35 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2, cisplatin 35 mg/m^2; every 21 days for 4 cycles.

***In scenarios when patients are unable to complete the intended 4 cycles of chemotherapy prior to radical cystectomy, patients will be permitted to receive less than 4 cycles of chemotherapy, at the discretion of the Investigator and upon discussion with AstraZeneca.**

Adjuvant therapy (regardless of renal status)

- Arm 1: Day 1: durvalumab 1500 mg IV; every 28 days for 8 cycles.
- Arm 2: No adjuvant treatment.

Patients will receive 4 cycles of study treatment in the neoadjuvant setting prior to radical cystectomy. After radical cystectomy and adequate recovery, patients will continue to receive up to a maximum of 8 cycles of durvalumab monotherapy or no adjuvant treatment based on the original randomized treatment assignment prior to neoadjuvant treatment.

Randomization will be stratified by clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively; renal function (adequate renal function versus borderline renal function; see Inclusion Criteria 7); and PD-L1 status (high versus low/negative, based on Ventana assay; see Table 6). Patients will provide a tumor tissue sample at screening (Table 6) to determine PD-L1 status for stratification.

Table 6 PD-L1 status defined by scoring of Ventana PD-L1 (SP263) Assay

PD-L1 Interpretation	Staining description
PD-L1 status is determined by the percentage of tumor cells with any membrane staining above background by the percentage of tumor-associated ICs with staining (IC+) at any intensity above background. The percent of tumor area occupied by any tumor-associated ICs (Immune Cells Present, ICP) is used to determine IC+, which is the percent area of ICP exhibiting PD-L1 positive IC staining is also evaluated.	
High	PD-L1 status is considered high if any of the following are met: • ≥25% of tumor cells exhibit membrane staining • ICP >1% and IC+ ≥25% • ICP = 1% and IC+ = 100%
Low/Negative	PD-L1 status is considered low/negative if: • None of the criteria for PD-L1 high status are met

PD-L1 Programmed cell death-ligand 1.
Source: VENTANA PD-L1 (SP263) Assay Package Insert.

For an overview of the study design, see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and endpoints.

4.1.1 Study Conduct Mitigation During Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

The guidance given below supersedes instructions provided elsewhere in this CSP and should be implemented only during cases of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions, and considerations if site personnel or study patients become infected with SARSCoV-2 or similar pandemic infection) which would prevent the conduct of study-related activities at study sites, thereby compromising the study site staff or the patient's ability to conduct the study. The investigator or designee should contact the study Sponsor to discuss whether the mitigation plans below should be implemented.

To ensure continuity of the clinical study during a civil crisis, natural disaster, or public health crisis, changes may be implemented to ensure the safety of study patients, maintain compliance with Good Clinical Practice, and minimize risks to study integrity.

Where allowable by local health authorities, ethics committees, healthcare provider guidelines (eg, hospital policies) or local government, these changes may include the following options:

- Obtaining consent/reconsent for the mitigation procedures (note, in the case of verbal consent/reconsent, the Informed Consent Form (ICF) should be signed at the patient's next contact with the study site).
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened patients. The investigator should confirm this with the designated study physician.
- Telemedicine visit: Remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

For further details on study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix K (Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis).

4.2 Scientific rationale for study design

4.2.1 Rationale for study design

Durvalumab, along with other PD-1/PD-L1 inhibitors, has already been established as treatment regimens for patients with locally advanced or metastatic UC, and there exists strong rationale that durvalumab could also be effective in earlier stages of BC such as localized MIBC. Furthermore, there is growing evidence that the addition of immunotherapy to 1L chemotherapeutic agents can improve clinical benefit when compared to the standard chemotherapy options alone (Langer et al 2016). In May 2017, the PD-1 inhibitor pembrolizumab received FDA approval under accelerated assessment for the treatment of 1L metastatic, nonsquamous NSCLC patients in combination with pemetrexed and carboplatin. Approval was based on impressive ORR (55% versus 29%) and PFS (13.0 months versus

6 months) data and a compelling HR of 0.53 (95% CI: 0.31, 10.3) for pembrolizumab plus carboplatin versus carboplatin alone (KEYTRUDA [package insert] 2018). Although these results relate to 1L treatment of patients with metastatic disease, these data are supportive of the theory that combining chemotherapy with immunotherapeutic agents has the potential to significantly improve clinical outcomes. AstraZeneca has therefore designed the proposed Phase III study to evaluate the clinical utility of adding durvalumab to the established chemotherapy regimen in patients with MIBC.

4.2.2 Rationale for efficacy study endpoints

The primary aims of this study are to assess the efficacy of Arm 1 versus Arm 2 (neoadjuvant/adjuvant) in MIBC patients in terms of EFS and to assess the efficacy of Arm 1 versus Arm 2 (neoadjuvant) MIBC patients in terms of pCR rate.

EFS is defined as the time from randomization to the first recurrence of disease after radical cystectomy, the time of first documented progression in patients who are precluded from radical cystectomy, time of documented residual disease in patients who refuse to undergo a radical cystectomy, or the time of death due to any cause, whichever occurs first. A recurrence of disease includes local (pelvic) recurrence of UC, urinary tract recurrence of UC, or distant metastases of UC. EFS will be assessed using computed tomography (CT)/magnetic resonance imaging (MRI) and pathology testing performed according to local standards and as clinically indicated.

pCR rate is defined as the proportion of patients whose pathological staging was T0N0M0 as assessed per central pathology review using specimens obtained via radical cystectomy following the neoadjuvant treatment and will be calculated among patients within the ITT population

This Phase III study will be sized to detect evidence of improved efficacy. Based on available datasets regarding response characteristics, pCR and EFS, will be improved by the addition of G+C to durvalumab.

Other secondary and exploratory endpoints will be examined to further evaluate the antitumor effect of Arm 1 versus Arm 2, including EFS rate at 24 months (EFS24), metastasis-free survival (MFS), DSS as per Investigator assessments, proportion of patients who achieve <P2 as per local pathology review, OS, and OS5.

Efficacy (pCR and EFS) is also being evaluated in the subset of patients characterized as PD-L1-high. This subset analysis is being performed based on available evidence from other clinical trials in MIBC, which have reported a survival benefit in objective response rate for the PD-L1-high population compared with the ITT population. Antitumor activity will be based on Investigator assessment according to disease assessment guidelines.

4.2.3 Rationale for other study endpoints

Biological samples will be used to explore potential biomarkers in tumor, plasma, urine, and/or serum, which may influence the progression of cancer (and associated clinical characteristics) and/or response.

Blood samples will be taken to allow for research into PK of durvalumab and G+C, immunogenicity of durvalumab, and the relationship between durvalumab PK exposure and clinical outcomes, efficacy, AEs, and/or safety parameters.

In addition to assessing EFS and other clinical endpoints in the trial, it is important to examine the impact of neoadjuvant and adjuvant therapy on disease-related symptoms, physical function, and other health-related quality of life (HRQoL) of the patient to aid understanding of how clinical benefit relates to patient wellbeing and for considering in making risk-benefit evaluations. Moreover, patient reported outcomes assist in the documentation of symptoms and specifically what symptoms and impacts are most important to patients and how these relate to clinical outcomes. Disease-related symptoms, physical function, and other HRQoL will be assessed using the EORTC QLQ-C30 questionnaire. The rationale for selecting the EORTC QLQ-C30 is primarily because it has good coverage of the conceptual model of general cancer symptoms and impact concepts. The impact of treatment on the overall health status and overall severity of cancer symptoms will be assessed using the Patient Global Impression of Change (PGIC) and Patient Global Impression of Severity (PGIS) single-item questionnaires, respectively. PGIC and PGIS are useful for determining the responder threshold of other PRO measures such as the EORTC QLQ-C30. Finally, pre-selected questions from the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) items bank will be evaluated to characterize treatment-related adverse events or tolerability directly from patients' perspective.

4.2.4 Safety monitoring rationale

The study design aims to minimize potential safety risks by intensive monitoring and ongoing safety monitoring at each office visit, during the conduct of the trial. In addition, an IDMC will assess the safety profile of G+C with or without durvalumab at regular intervals. See Section 9.6 for details on the IDMC.

Risk associated with durvalumab, G+C, and the combination of durvalumab and G+C are discussed in Section 2.3.2.

4.2.5 Rationale for gemcitabine and cisplatin as comparator

The standard management for patients with MIBC involves radical cystectomy and pelvic lymph node dissection. Several studies have demonstrated improved pCR, EFS, and OS with the integration of neoadjuvant, cisplatin-based combination chemotherapy when compared with radical cystectomy alone. Specifically, 2 large randomized studies have demonstrated improvement in survival with the integration of neoadjuvant, cisplatin-based combination chemotherapy, leading to the utilization of neoadjuvant chemotherapy in the perioperative setting for patients with MIBC (Grossman et al 2003, International Collaboration of Trialists 2011).

Despite the improvement in survival demonstrated in the randomized studies with the use of neoadjuvant MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) or CMV (cisplatin, methotrexate, and vinblastine), concerns regarding the balance between the toxicity and the efficacy of these regimens have contributed, at least in part, to the reduced acceptance of neoadjuvant chemotherapy. In 2000, the results from a randomized Phase III study comparing G+C with standard MVAC in patients with metastatic BC were published. G+C was associated

with similar efficacy compared with MVAC, albeit with overall less toxicity, leading to the adoption of the regimen among the most commonly used systemic treatments for patients with metastatic disease. Pragmatically, yet in somewhat of a departure from the evidence-based oncology paradigm, the results from that study have also been used to justify the routine use and integration into standard practice guidelines of neoadjuvant G+C, despite lack of prospective randomized data in this setting (National Comprehensive Cancer Network 2019). Although there are no studies reporting level 1 data comparing MVAC to G+C in the neoadjuvant setting, retrospective analyses have reported no significant difference in pCR and OS between the 2 treatment arms (Dash et al 2008, Galsky et al 2015).

4.3 Justification for dose

This study will utilize a fixed dose for durvalumab treatment (1500 mg q3w IV as neoadjuvant treatment and 1500 mg q4w IV as adjuvant treatment). Based on an average body weight of 75 kg, a fixed dose of 1500 mg of durvalumab q4w is equivalent to 20 mg/kg q4w.

G+C will be dosed at 1000 mg/m^2 IV on Days 1 and 8 q3w (gemcitabine) + 70 mg/m^2 IV on Day 1 q3w (cisplatin) for patients with adequate renal function (creatinine clearance [CrCl] ≥60 mL/min) and at 1000 mg/m^2 IV on Days 1 and 8 q3w (gemcitabine) + 35 mg/m^2 IV on Days 1 and 8 q3w (cisplatin) for patients with borderline renal function (CrCl ≥40 mL/min to <60 mL/min).

4.3.1 Durvalumab monotherapy dose rationale

4.3.1.1 Durvalumab q4w dose rationale

A durvalumab dose of 20 mg/kg q4w is supported by in vitro data, nonclinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg q2w or 15 mg/kg q3w, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg q2w, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg q2w is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab. (For further information on immunogenicity, please see the current durvalumab IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg q2w or 15 mg/kg q3w; European Medicines Agency 2013

Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man; Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials. 2012. Available at URL: https://www.ema.europa.eu/en/appendix-1-guideline-evaluation-anticancer-medicinal-products-man-methodological-consideration-using-progression-free-survival-pfs-or-disease-free-survival-dfs-confirmatory-trials-scientific-guideline.

EuroQol Group 1990
EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

Fairman et al 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg q2w and 20 mg/kg q4w regimens, as represented by AUC_{ss} (4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg q4w (~1.5 fold), and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg q2w (~1.25 fold). Clinical activity with the 20 mg/kg q4w dosing regimen is anticipated to be consistent with 10 mg/kg q2w with the proposed similar dose of 20 mg/kg q4w expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of antidrug antibody (ADA) impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the serum drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg q4w and 10 mg/kg q2w regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg q4w.

Clinical data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK at the 20 mg/kg q4w regimen.

Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from Study 1108. Population PK analysis indicated only minor impact of body weight on PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg q2w or 20 mg/kg q4w) and fixed dosing (750 mg q2w or 1500 mg q4w) of durvalumab was evaluated by comparing predicted steady-state PK exposures ($AUC_{ss,0-28}$, $C_{max,ss}$, and $C_{min,ss}$) using the population PK model. A fixed dose of 750 mg q2w was selected to approximate 10 mg/kg q2w and a fixed dose of 1500 mg q4w was selected to approximate 20 mg/kg q4w (based on median body weight of approximately 75 kg). A total of 1000 patients were simulated using body weight distribution of 40 to 110 kg. Simulation results demonstrate that body weight-based (10 mg/kg q2w) and fixed dosing (750 mg q2w) regimens yield similar median steady-state exposures and associated variability, supporting the potential switch of durvalumab from weight-based to fixed dose. Similar considerations hold for the q4w dosing regimens (20 mg/kg q4w versus 1500 mg q4w).

Similar findings have been reported by others (Narwal et al 2013, Ng et al 2006, Wang et al 2009, Zhang et al 2012). Wang and colleagues investigated 12 mAbs and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamic parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, AstraZeneca considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg q4w durvalumab (equivalent to 20 mg/kg q4w) is included in the current study.

Rationale for proposed Phase III dose and schedule

The proposed dosing schedule is aligned with the standard fixed dosing of durvalumab 1500 mg q4w, which is supported by efficacy and safety as well as tolerability data across multiple studies in multiple tumor types. To conform to the chemotherapy schedule in the study, we propose to use standard fixed dose of durvalumab 1500 mg at a q3w dosing interval for the first 4 cycles rather than the standard q4w schedule. The safety of a q3w dosing schedule in combination with chemotherapy has been explored in the ongoing Study D419SC00001, where tremelimumab is administered at 75 mg in combination with durvalumab 1120 mg q3w followed by durvalumab 1120 mg q3w. The combination has been declared tolerable and manageable. The 1120-mg dose of durvalumab is the q3w equivalent of the standard 1500-mg q4w dose. The tremelimumab dose was not lowered proportionally to 56 mg because 75 mg is the lowest tested biologically effective dose. In this study, AstraZeneca proposes to use the Phase III fixed dose of durvalumab, so this study will combine durvalumab 1500 mg q3w with chemotherapy for 4 cycles. The relative increase in dose density of durvalumab (ie, 1500 mg q3w instead of q4w) is supported by the fact that toxicities attributable to durvalumab do not appear dose dependent, and PK modeling reveals no meaningful differences in drug levels between q3w and q4w dosing. After chemotherapy, the dose will be durvalumab 1500 mg q4w.

Study BR.34 is a Phase II randomized trial of durvalumab and tremelimumab ± platinum-based chemotherapy in patients with metastatic (Stage IV) squamous or non-squamous NSCLC. Both Study BR.34 and the CCTG (NCT02537418) study are assessing tremelimumab 75 mg with durvalumab 1500 mg q3w in combination with platinum-based chemotherapy.

4.3.1.2 Durvalumab q3w dose rationale

PK modeling and simulation have been conducted to evaluate the switch from q4w dosing to q3w dosing for durvalumab. For durvalumab, median C_{max} following the 5th dose of the q3w regimen and the 4th dose of the q4w regimen was 689 and 624 µg/mL, median trough concentration at Week 16 was 125 and 94.5 µg/mL, and $AUC_{0\text{-}16wk}$ was 28726 and 22772 µg*day/mL for the q3w and q4w schedule, respectively. Therefore, PK modeling suggests that a q3w schedule does not impose a significant increased safety risk based on expected durvalumab exposures.

4.3.2 Gemcitabine plus cisplatin dose rationale

A dose schedule (frequency) using a 21-day gemcitabine and cisplatin (G+C) regimen was selected based on better tolerability and similar efficacy compared with the G+C regimen administered on an every 28-day cycle.

A randomized Phase III study of G+C (administered on an every-28-day cycle) compared with MVAC in patients with locally advanced and/or metastatic bladder cancer demonstrated similar efficacy between the 2 regimens when using gemcitabine 1000 mg/m^2 on Days 1, 8, and 15 and cisplatin 70 mg/m^2 on Day 2 (Von der Maase et al 2000). However, a high incidence of hematologic toxicity was reported, compromising the gemcitabine dose intensity; consequently, gemcitabine doses were modified in 37% of the G+C cycles in this Phase III study. A retrospective study comparing a 21-day cycle versus a 28-day cycle of G+C in patients with Stage IV transitional cell carcinoma demonstrated similar efficacy (overall response rates of 59.7% and 55.6%, respectively, for the 21-day and 28-day regimen) and better tolerability (ie, reduced hematologic toxicity) with the use of a 21-day cycle; use of the 21-day regimen did not result in an increase in renal toxicity (Birgitte et al 2008). Another retrospective study evaluated the tolerability of a 21-day G+C regimen, specifically in elderly patients (≥65 years old) with urothelial cancer; 57% of patients received treatment in the neoadjuvant setting. Results demonstrated acceptable tolerability of this regimen with primary dose modifications only for the gemcitabine dose; 1 case of Grade IV renal toxicity was reported (Jan et al 2016).

Although a large randomized Phase III has not been conducted to directly compare a 21-day and a 28-day G+C regimen in the neoadjuvant setting for UC, published results demonstrating similar efficacy, acceptable tolerability, and also the incorporation of the 21-day regimen into the current National Comprehensive Cancer Network bladder cancer guidelines (National Comprehensive Cancer Network 2019) as an acceptable regimen in the neoadjuvant setting, a 21-day G+C regimen was selected for this study.

4.3.2.1 Split-dose rationale

Despite the standard, recommended treatment with cisplatin-based chemotherapy and radical cystectomy, significant limitations remain in the treatment of MIBC. Some patients with MIBC may be limited with regard to treatment options, as they are likely unable to tolerate the standard dose regimen of cisplatin due to impaired or borderline renal function (Dash et al 2006). For patients with borderline renal function or minimal dysfunction, a split-dose regimen of 1000 mg/m^2 IV q3w gemcitabine plus 35 mg/m^2 IV on Day 1 and Day 8 q3w has been considered a reasonable option for patients who would otherwise have no option for treatment with neoadjuvant chemotherapy. This modified regimen has shown potential for an improvement in tolerability compared with current treatment options for patients with borderline renal function, has shown potential to avoid dosing delays, has demonstrated reduced toxicity, and has comparable benefit to the standard G+C dose in patients with adequate renal function (Abdelhafez and Williams 2017, Hussain et al 2012).

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last patient undergoing the study.

A patient is considered to have completed the study when he/she has completed his/her last scheduled visit or last scheduled procedure shown in the schedule of activities (SoA).

In the event that a roll-over or safety extension study is available at the time of the final data cutoff (DCO) and database closure, all patients still on the study will be asked to transition to such a study for the purposes of OS, and the current study would reach its end. Any patient who would be proposed to move to such a study would be given a new informed consent.

Patients may be withdrawn from the study if the study itself is stopped. The study may be stopped if, in the judgment of AstraZeneca, study patients are placed at undue risk because of clinically significant findings.

See Section 6.6 for a description of treatment options following the final DCO as well as following study completion. See Appendix A 6 for guidelines for the dissemination of study results.

For the purpose of Clinical Trial Transparency (CTT) the definition of the end of the study differs under FDA and EU regulatory requirements:

European Union requirements define study completion as the last visit of the last subject for any protocol related activity.

Food and Drug Administration requirements defines two completion dates:

Primary Completion Date – the date that the final participant is examined or receives an intervention for the purposes of final collection of data for the primary outcome measure, whether the clinical study concluded according to the pre-specified protocol or was terminated. In the case of clinical studies with more than one primary outcome measure with different completion dates, this term refers to the date on which data collection is completed for all of the primary outcomes.

Study Completion Date – the date the final participant is examined or receives an intervention for purposes of final collection of data for the primary and secondary outcome measures and AEs (for example, last participant's last visit), whether the clinical study concludes according to the pre-specified protocol or is terminated.

A participant is considered to have completed the study if they have completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA.

5. STUDY POPULATION

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

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to be assigned/randomized to a study intervention. Under no circumstances can

there be exceptions to this rule. Patients who do not meet the entry requirements are screen failures; refer to Section 5.4.

In this protocol, "enrolled" patients are defined as those who sign the informed consent form (ICF). "Randomized" patients are defined as those who undergo randomization and receive a randomization number.

For procedures for withdrawal of incorrectly enrolled patients see Section 7.3.

5.1 Inclusion criteria

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

Informed consent

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

2. Provision of signed and dated written ICF prior to any mandatory study specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3.

Age

3. Age ≥18 years at the time of screening. For patients aged <20 years and enrolled in Japan, a written informed consent should be obtained from the patient and his or her legally acceptable representative.

Type of patient and disease characteristics

4. Patients with histologically or cytologically documented muscle-invasive TCC (also known as UC) of the bladder.
   - Patients with transitional cell and mixed transitional/non-transitional cell histologies (adenocarcinoma, squamous cell)/variant transitional (eg, micropapillary, plasmacytoid, sarcomatoid, nested variant, lymphoepitheliod, nested variant) histologies. Patients with pure non-transitional cell variant histologies and any small cell histology are not eligible.
   - Patients with clinical tumor stage T2-T4aN0/1M0 according to the American Joint Committee on Cancer Staging Manual (AJCC Cancer Staging Manual, 8th Edition) TCC of the bladder. cN1 disease is defined as the presence of a single lymph node in the true pelvis (perivesical, obturator, internal and external iliac, and sacral lymph node); lymph node must measure < 20 mm in the short axis (small volume metastasis) and be resectable, as per the planned lymphadenectomy procedure (see section 6.1.5 [surgical plan]). Lymph nodes with <10 mm short axis diameter are considered non-pathological per RECIST1.1.

A single tumor (T)-stage is determined by the Investigator and is used for documentation of baseline disease characteristics and also for registering the patient for randomization (ie, for stratification purposes). Clinical staging, specifically for the determination of the clinical tumor stage (cT), is a composite of combined results obtained from a pathological assessment of the tumor (from a TURBT sample, confirming muscle invasion), an examination under anesthesia procedure (performed after the completion of the TURBT procedure), and results from a CT/MRI image. Patients should also meet the following additional criteria:

- Must be planning and per the judgment of the Investigator medically fit for treatment with neoadjuvant therapy prior to radical cystectomy (ie, patients should not be randomized if they are not eligible or cannot receive any neoadjuvant treatment)

- Must be planning and per the judgment of the Investigator medically fit to undergo a radical cystectomy at time of enrollment and randomization.

- Have not received prior systemic chemotherapy or immunotherapy for treatment of MIBC. (Prior local intravesical chemotherapy is allowed regardless of time frame. Prior local intravesical immunotherapy (eg, BCG) is allowed if completed at least 6 weeks prior to the initiation of study treatment.)

5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 at enrollment.

6. Tumor PD-L1 status, with immunohistochemistry (IHC) assay confirmed by a reference laboratory, must be known prior to randomization. As such, all patients must give valid written consent to provide a newly acquired MIBC tumor biopsy during screening (preferred) or provide an available archival MIBC tumor sample taken ≤3 months prior to screening. Tumor lesions submitted must be when the patient was determined to have MIBC (ie, NMIBC samples will not be acceptable). Samples with limited tumor content are not acceptable. The tumor specimen submitted to evaluate PD-L1 status should be of sufficient quantity to allow for PD-L1 IHC, retrospective evaluation of muscle invasive disease, and other exploratory biomarker analyses and is preferred in formalin-fixed paraffin-embedded (FFPE) blocks. (Refer to Section 6.2.1 for information regarding obtaining tumoral PD-L1 status prior to the 28-day screening window.)

7. Adequate organ and marrow function as defined below:

   - Hemoglobin ≥9.0 g/dL

   - Absolute neutrophil count $\geq 1.5 \times 10^9$/L

   - Platelet count $\geq 100 \times 10^9$/L

- Serum bilirubin ≤1.5× ULN. This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician.

- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5×ULN

- CrCl calculated by Cockcroft-Gault equation (using actual body weight) or measured by 24-hour urine collection for determination. (In cases where both are performed, measured 24-hour urine collection will be used to determine eligibility, providing an adequate collection was performed.)*

    - CrCl for Borderline Renal Function arm: ≥40 mL/min to <60 mL/min

    - CrCl for Adequate Renal Function arm: ≥60 mL/min

Cockcroft-Gault equation

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

8. Must have a life expectancy of at least 12 weeks at randomization.

Weight

9. Body weight >30 kg at enrollment and randomization

Reproduction

10. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

    - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

*The method used to determine CrCl for study eligibility will be the same method used to determine cisplatin chemotherapy regimen used on study entry. If more than 1 evaluation of CrCl has been obtained during the screening period, the CrCl value closest to Cycle 1 Day 1 should be entered into the interactive voice response system (IVRS)/interactive web response system (IWRS) for randomization purposes. See Section 6.2.1 for detailed requirements regarding IVRS/IWRS data entry for purposes of randomization.

5.2 Exclusion criteria

Patients are not eligible to be included in the study if any of the exclusion criteria apply:

Medical conditions

1. Evidence of lymph node (N2-3) or metastatic TCC/UC (M1), extravesical TCC/UC that invades the pelvic and/or abdominal wall for bladder cancer (T4b), or primary non-bladder (ie, ureter, urethral, or renal pelvis) TCC/UC of the urothelium. Patients with cN1 and additional radiologically suspected lymph node metastasis within or outside the pelvis should be excluded if the short axis is ≥10 mm as per IV contrast-enhanced CT or MRI scan. If an enlarged lymph node ≥10 and <15 mm can be confirmed pathologically (eg, by biopsy) as a non-cancer [benign] lesion and/or by positron emission tomography-CT, the patient may be considered eligible.

2. Per the judgement of the Investigator, if a nephroureterctomy is required at the time of randomization for tumor of the mid ureter, renal pelvis, or collecting system

3. If a ureteral tumor is present proximal to common iliacs that would require ureterectomy in addition to the planned cystectomy

4. Inoperable tumor(s) with fixation to the pelvic wall on clinical exam.

5. History of allogeneic organ transplantation that requires use of immunosuppressive agents. Patients with a history of allogenic stem cell transplantation are also excluded.

6. Active or prior documented autoimmune or inflammatory disorders (including but not limited to inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], autoimmune pneumonitis, autoimmune myocarditis systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

   – Patients with vitiligo or alopecia

   – Patients with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement

   – Any chronic skin condition that does not require systemic therapy

- Patients without active disease in the last 5 years may be included but only after consultation with AstraZeneca

- Patients with celiac disease controlled by diet alone may be included but only after consultation with AstraZeneca

7. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, uncontrolled diabetes, symptomatic congestive heart failure, uncontrolled hypertension, uncontrolled angina, uncontrolled cardiac arrhythmia, active interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs, or compromise the ability of the patient to give written informed consent.

8. History of a myocardial infarction within 6 months prior to randomization due to potential cardiotoxic effects observed with gemcitabine

9. History of another primary malignancy, except for:

   - Prostate cancer (tumor/node/metastatsis) of stage ≤T2cN0M0 without biochemical recurrence or progression and who in the opinion of the Investigator are not deemed to require active intervention, or patients with incidental histologic findings of prostate cancer that has not been treated prior to the study and who do not require specific therapy for prostate cancer beyond the surgery described in the protocol and also are considered to be at low risk for recurrence per the Investigator

   - Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of investigational product (IP) and of low potential risk for recurrence

   - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease

   - Adequately treated carcinoma in situ without evidence of disease

10. History of active primary immunodeficiency

11. History of leptomeningeal carcinomatosis

12. Active infection including **tuberculosis** (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), **hepatitis B** (known positive hepatitis B virus [HBV] surface antigen [HBsAg] result), **hepatitis C**, or **human immunodeficiency virus** (positive HIV 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible.

Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid (RNA).

13. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria

    – Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with AstraZeneca.

14. New York Heart Association Class III or IV heart failure (Criteria Committee NYHA 1964).

15. (Exclusion Criterion 15 was removed in Protocol Amendment 2.)

16. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients

17. Any medical contraindication to platinum (cisplatin)-based doublet chemotherapy, including:

    – CTCAE Grade ≥2 audiometric hearing loss

    – CTCAE Grade ≥2 peripheral neuropathy

Prior/concomitant therapy

18. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (eg, hormone replacement therapy) is acceptable.

19. Prior exposure to immune-mediated therapy (with exclusion of Bacillus-Calmette Guerin [BCG]), including but not limited to other anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-PD-L2 antibodies.

20. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP.

21. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP.

22. Prior pelvic radiotherapy treatment within 2 years of randomization to study.

23. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

    – Intranasal, inhaled, topical steroids, or local steroid injections (eg, intra-articular injection)

- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent

- Steroids as premedication for hypersensitivity reactions (eg, CT scan premedication).

Prior/concurrent clinical study experience

24. Prior randomization or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of the treatment arm (until the primary endpoint of that study has read out)

25. Previous IP assignment in the present study

26. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study

27. Participation in another clinical study with an IP administered during the last 28 days

Other exclusions

28. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab.

29. Judgment by the Investigator that the patient should not participate in the study if the patient is unlikely to comply with study procedures, restrictions, and requirements.

For procedures for withdrawal of incorrectly enrolled patients, see Section 6.2.2.

5.3 Lifestyle restrictions

The following restrictions apply while the patient is receiving IP and for the specified times before and after:

1. Female patient of childbearing potential

   - Female patients of childbearing potential who are not abstinent and intend to be sexually active with a nonsterilized male partner must use at least 1 **highly** effective method of contraception (Table 7) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilized male partners of a female patient of childbearing potential must use a male condom plus spermicide (except in countries where spermicide is not approved) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female patients should refrain from breastfeeding throughout this period.

2. Male patients with a female partner of childbearing potential

   – Non-sterilized male patients who are not abstinent and intend to be sexually active with a female partner of childbearing potential must use a male condom plus spermicide (except in countries where spermicide is not approved) from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

   – Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 7).

Please note, females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
- Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, or had chemotherapy-induced menopause with last menses >1 year ago.
- Women who are surgically sterile (ie, bilateral salpingectomy, bilateral oophorectomy, or complete hysterectomy) are eligible.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 7. Note that some contraception methods are not considered highly effective (eg, male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel, which is considered highly effective]; and triphasic combined oral contraceptive pills).

All patients: Follow the local prescribing information related to contraception, the time limits for such precautions, and any additional restrictions for the chemotherapy agents (G+C).

Table 7 Highly effective methods of contraception (<1% failure rate)

Barrier/intrauterine methods	Hormonal methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[a]	• Implants: Etonogestrel-releasing implants (eg, Implanon® or Norplant®) • Intravaginal Devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Injection: Medroxyprogesterone injection (eg, Depo-Provera®) • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Ortho Evra®) • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method.

3. All patients: Patients should not donate blood or blood components while participating in this study and through 90 days after receipt of the final dose of durvalumab or until alternate anticancer therapy is started.

4. Restrictions relating to concomitant medications are described in Section 6.4.

5.4 Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study and therefore must not be randomized. These patients should have the reason for study withdrawal recorded as "eligibility criteria not fulfilled" (ie, patient does not meet the required inclusion/exclusion criteria). This reason for study withdrawal is only valid for screen failures (ie, not randomized patients). Patients may be rescreened a single time, but they may not be re-randomized.

If a patient who has failed screening is rescreened, a new E-code must not be assigned. Patients will reconfirm their consent to participate in the study by resigning and dating their original consent form(s), next to their original signature and date. All assessments except the tumor biopsy for PD-L1 testing must be repeated for rescreening, unless they are within 28 days of randomization.

A minimal set of screen failure information is required in the CRF to ensure transparent reporting of screen failure patients; this includes demography, screen failure details, eligibility criteria, any SAEs, and PD-L1 biopsy/tumor sample (if the sample was sent to the central laboratory during screening).

6. STUDY TREATMENTS

Study treatment is defined as any IP(s) (including marketed product comparator) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to durvalumab, gemcitabine, and cisplatin.

6.1 Treatments administered

6.1.1 Investigational products

AstraZeneca will supply durvalumab (MEDI4736). Neoadjuvant agents gemcitabine and cisplatin will be supplied locally. Under certain circumstances when local sourcing is not feasible, gemcitabine and cisplatin may be supplied centrally through AstraZeneca

Table 8 Study treatments

	Treatment 1	Treatment 2
Study treatment name:	Durvalumab (MEDI4736)	Gemcitabine and cisplatin[a]
Dosage formulation:	500-mg vial solution for infusion after dilution, 50 mg/mL	As sourced locally
Route of administration:	IV	IV
Dosing instructions:	1500 mg IV q3w (neoadjuvant)[b] 1500 mg IV q4w (adjuvant, post-radical cystectomy)	Day 1 and Day 8 (gemcitabine 1000 mg/m^2 IV) of each 21-day cycle (neoadjuvant) Day 1 and Day 8 (cisplatin 35mg/m^2 IV) or Day 1 (cisplatin 70 mg/m^2 IV) each 21-day cycle (neoadjuvant)
Packaging and labelling:	Study treatment will be provided in 500-mg vials. Each vial will be labeled in accordance with GMP Annex 13 and per country regulatory requirements.[c]	Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local language.
Provider:	AstraZeneca	Sourced locally by site[a]

[a] Under certain circumstances when local sourcing is not feasible, G+C treatment may be supplied centrally through AstraZeneca.
[b] Dosing of durvalumab will occur prior to the dosing of G+C chemotherapy
[c] Label text prepared for durvalumab (MEDI4736) will show the product name as "MEDI4736" or "durvalumab (MEDI4736)" depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.

G+C Gemcitabine and cisplatin; GMP Good Manufacturing Practice; IV Intravenous(ly); q3w Every 3 weeks; q4w Every 4 weeks.

6.1.1.1 Order of administration

Immunotherapy administration will be followed by G+C chemotherapy via IV infusion as indicated in Section 6.1.1.3.

If corticosteroid anti-emetics are required, medications should be administered 30 minutes prior to chemotherapy, not prior to durvalumab.

Patients in Arm 1 will receive durvalumab via IV infusion over 60 minutes. It is recommended that a 60-minute observation period take place after durvalumab is administered, at least for Cycle 1.

If no issues are observed following durvalumab administration during the first cycle, reduction of the observation period may be at the Investigator's discretion (suggested 30 minutes).

G+C chemotherapy is administered per local practice.

6.1.1.2 Durvalumab (MEDI4736)

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL. IP vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure.

Preparation of durvalumab (MEDI4736) doses for administration with an IV bag

The dose of durvalumab (MEDI4736) for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab (MEDI4736) vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

A dose of 1500 mg (for patients >30 kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing. Add 30.0 mL of durvalumab (MEDI4736) (ie, 1500 mg of durvalumab [MEDI4736]) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤30 kg, weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with

a 0.2- or 0.22-µm filter; acceptable configurations include an IV set containing an in-line filter or the attachment of a separate filter to the distal end of the IV tubing.

Standard infusion time is 1 hour; however, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours at room temperature.

Do not co-administer other drugs through the same infusion line.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used, after the contents of the IV bag are fully administered, or the infusion is completed, according to institutional policy to ensure the full dose is administered.

If either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. Durvalumab (MEDI4736) does not contain preservatives, and any unused portion must be discarded.

6.1.1.3 Gemcitabine and cisplatin

Gemcitabine and cisplatin will be locally sourced by AstraZeneca marketing companies and/or sites and will be infused according to prescribing information or treatment guidance in general use by the Investigating site. Under certain circumstances when local sourcing is not feasible, AstraZeneca will centrally supply the drugs, which will be labeled with local language translated text in accordance with regulatory guidelines.

6.1.2 Dose and treatment regimens

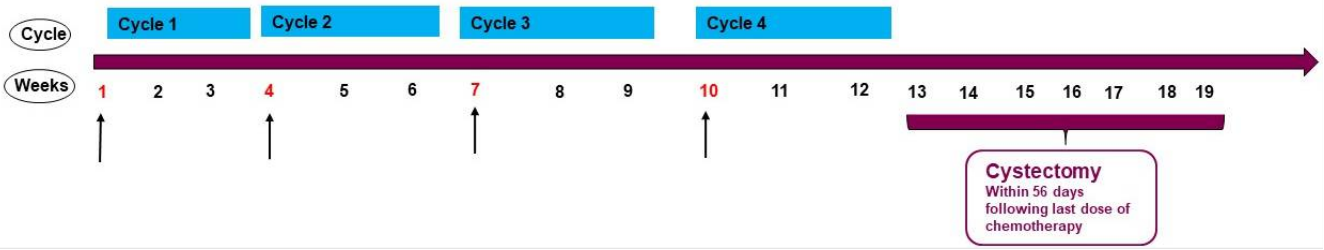
Patients will be randomized to the 2 treatment arms, Arm 1 or Arm 2, and will be treated according to their renal function based on randomization. Recruitment for patients with borderline renal function will be limited to up to 20% of the targeted global population.

Table 9 Treatment scheme

Treatment arm	**Neoadjuvant therapy 1 cycle = 3 weeks (21 days)**				**Radical cystectomy** 56 days (8 weeks)	**Adjuvant therapy 1 cycle = 4 weeks (28 days)**
	Cycle 1 Week 1	**Cycle 2 Week 4**	**Cycle 3 Week 7**	**Cycle 4 Week 10**		**Treatment will start 42-120 days following radical cystectomy**
Durva + G+C (Arm 1)	Durva + G+C	Durva + G+C	Durva + G+C	Durva + G+C		Durva x 8 cycles
G+C (Arm 2)	G+C	G+C	G+C	G+C		No adjuvant treatment

Durva Durvalumab; G+C Gemcitabine and cisplatin.
Note: If there is a dosing delay for neoadjuvant chemotherapy, durvalumab doses should be held to ensure that dosing is administered on Day 1 of each cycle.

Figure 2 Neoadjuvant dosing schedule



Note: Vertical arrows represent Day 1 of dosing for each cycle.

Neoadjuvant therapy

Patients with adequate renal function (CrCl ≥60 mL/min)

- Arm 1: Day 1: durvalumab 1500 mg IV, cisplatin 70 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2; every 21 days for 4 cycles.
- Arm 2: Day 1: cisplatin 70 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2; every 21 days for 4 cycles.

Patients with borderline renal function (CrCl ≥40 mL/min to <60 mL/min)

- Arm 1: Day 1: durvalumab 1500 mg IV, cisplatin 35 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2, cisplatin 35 mg/m^2; every 21 days for 4 cycles.
- Arm 2: Day 1: cisplatin 35 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2, cisplatin 35 mg/m^2; every 21 days for 4 cycles.

Results of serum creatinine and a determination of creatinine clearance must be available and reviewed by the treating physician or Investigator prior to dosing of cisplatin on Day 1 and Day 8 (if applicable, for patients on the cisplatin split dose regimen).

***In scenarios when patients are unable to complete the intended 4 cycles of chemotherapy prior to radical cystectomy, patients will be permitted to receive less than 4 cycles of chemotherapy, at the discretion of the Investigator and upon discussion with AstraZeneca.**

Noncystectomy extension phase:

Patients in either treatment arm who fulfil the necessary criteria (see Section 6.1.5) may enter the noncystectomy extension phase after consultation and approval by AstraZeneca. Patients enrolled into Arm 1 who enter the noncystectomy extension phase may be administered durvalumab 1500 mg (as monotherapy) every 28 days for a maximum of 8 doses (corresponding to a maximum exposure of 12 months) or until study-specific discontinuation criteria is met. For patients who enter the noncystectomy extension phase and subsequently undergo a radical cystectomy, further treatment should be discussed and agreed upon with AstraZeneca.

Adjuvant therapy (regardless of renal status)

- Arm 1: Day 1: durvalumab 1500 mg IV; every 28 days for 8 cycles.
- Arm 2: No adjuvant treatment.

Adjuvant therapy is recommended to begin as soon as the patient recovers from radical cystectomy and within 120 days after and no earlier than 42 days after radical cystectomy. Cycle 1 Day 1 of the adjuvant treatment phase for patients in Arm 2 is recommended to occur as soon as the patient recovers from the radical cystectomy (no earlier than 42 days and no later than 120 days after radical cystectomy).

6.1.2.1 Durvalumab (MEDI4736)

This is a Phase III, randomized, open-label, multi-center, global study to evaluate durvalumab (MEDI4736) in combination with G+C chemotherapy (neoadjuvant) followed by durvalumab alone (adjuvant) versus G+C (neoadjuvant) followed by no adjuvant treatment in patients with MIBC.

Approximately 1050 patients globally will be randomized in a 1:1 ratio to receive durvalumab + G+C combination therapy q3w (Arm 1) or G+C combination therapy q3w (Arm 2) for 4 cycles of neoadjuvant chemotherapy prior to radical cystectomy. Following radical cystectomy and during adjuvant therapy, patients in Arm 1 will receive durvalumab monotherapy q4w via IV infusion over 60 minutes for 8 additional cycles.

If a patient's weight falls to 30 kg or below (≤30 kg), the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab q3w (neoadjuvant treatment) or q4w (adjuvant treatment) after consultation between the Investigator and the Study Physician, until the weight improves to above 30 kg (>30 kg), at which point the patient should start receiving the fixed dosing of durvalumab 1500 mg q3w (neoadjuvant treatment) or q4w (adjuvant treatment).

Patients in Arm 2 will receive no adjuvant treatment.

The order of administration of durvalumab and G+C is presented in Section 6.1.1.1.

6.1.3 Duration of treatment and criteria for treatment through progression

For patients in Arms 1 and 2, neoadjuvant treatment will be administered beginning on Day 1 of Cycle 1 q3w for 4 cycles

Following radical cystectomy, Arm 1 patients will receive adjuvant treatment with durvalumab q4w for 8 cycles for up to a maximum of 8 cycles, unless specific study discontinuation criteria are met.

Following radical cystectomy, Arm 2 patients will receive no additional treatment but will follow the visit schedule per Table 3, unless specific study discontinuation criteria are met.

During the neoadjuvant treatment phase, patients who have Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1)-defined radiological progression may continue to the

adjuvant portion of treatment if the progression event did not preclude the patient from having a radical cystectomy (ie, progression is local and/or limited to regional lymph nodes that will be removed during the radical cystectomy/bilateral lymph node dissection procedure). In the event progression (ie, distant metastases) precludes the patient from undergoing radical cystectomy, the patient will proceed to follow-up, with no additional tumor assessments performed and the patient will be followed for OS.

Following radical cystectomy, patients with proven recurrence (see Section 8.1.1.1) will proceed to follow-up.

Crossover from Arm 1 to Arm 2 will not be permitted.

6.1.4 Storage

The Investigator, or an approved representative (eg, pharmacist), will ensure that all IP is stored in a secured area, under refrigerated temperatures (2°C to 8°C), and in accordance with applicable regulatory requirements. A temperature log will be used to record the temperature of the storage area. Temperature excursions outside the permissible range listed in the clinical supply packaging are to be reported to the monitor upon detection. A calibrated temperature monitoring device will be used to record the temperature conditions in the drug storage facility. Storage conditions stated in the IB may be superseded by the label storage.

6.1.5 Surgical plan

Radical cystectomy is performed as soon as possible after completion of and recovering from neoadjuvant therapy and is recommended to occur within 56 days after the last **dose** of neoadjuvant chemotherapy. Radical cystectomy is not recommended earlier than 14 days after the last dose of neoadjuvant therapy.

If it is anticipated that the radical cystectomy cannot be performed within the 56-day timeframe (8 weeks) from the last dose of neoadjuvant chemotherapy due to a medical reason and may be delayed up to 70 days (10 weeks), AstraZeneca should be consulted.

Male patients will undergo radical cystoprostatectomy and urinary diversion along with bilateral pelvic lymph node dissection. Female patients will undergo radical cystectomy. A hysterectomy and bilateral salpingectomy may be performed by the patient's choice if no gross evidence of oncologic involvement is noted by the surgeon. Oophorectomy may be omitted if clinically indicated. Urinary diversion creation will be via an ileal conduit, ileal neobladder, Indiana Pouch, or as per local practice. Bilateral pelvic lymph node dissection will follow a minimum of the following template to include the 1) external iliac, 2) obturator, and 3) internal iliac nodes, and 4) common iliac nodes to the level of the ureteric crossing and must include a lymph node classified as cN1 at baseline if one was present. Removal of other nodes is per the surgeon's discretion. The boundaries of the template will be the circumflex iliac vein and Cloquet's node, laterally by the genitofemoral nerve, medially by the bladder, posteriorly by the obturator fossa, and proximally to the ureter.

Radical cystectomy is a mandatory study procedure for all patients. If an alternative procedure is performed, it may result in a protocol deviation. However, if a patient is only able to undergo a

partial cystectomy based on Investigator and/or surgical assessment, these patients may proceed into the adjuvant phase to continue with the same assessments and study procedures, based on their treatment assignment at randomization.

In a setting in which a patient refuses a radical cystectomy at the study specified time, after having a complete clinical response determined locally by multimodal assessment (see below) and without any additional intervention (eg, TURBT), he/she may be permitted to continue into a noncystectomy extension phase to continue with study procedures that mirror those for the adjuvant phase (including collection of samples for PK, ADA, and research lab testing, but without a Clavien-Dindo assessment), relevant to the arm to which they are randomized (see Table 2 for Arm 1 and Table 3 for Arm 2); this allowance is only permitted after consultation and agreement with AstraZeneca. Patients in Arm 1 who enter the noncystectomy extension phase may be administered durvalumab 1500 mg (as monotherapy) for a total of 8 doses (see Section 6.1.2); patients in Arm 2 will receive no additional treatment. Multimodal assessment for determining a complete clinical response includes:

- Required: cystoscopy (with biopsies, per local practice and if feasible), examination under anesthesia, and CT/MRI
- Should be obtained if feasible and per local practice: biopsies and urinalysis for cytology, PET-CT for patients enrolled with cN1

These assessments will need to be performed within 56 days of the last dose of neoadjuvant treatment to claim a complete response.

6.2 Measures to minimize bias: randomization and blinding

6.2.1 Patient enrollment and randomization

All patients will be centrally/regional/local assigned to randomized study treatment using an IVRS/IWRS. Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site. **Note: If more than 1 evaluation of CrCl has been obtained during the screening period, the CrCl value closest to Cycle 1 Day 1 should be entered into the IVRS/IWRS for randomization purposes (see Section 5.1 for details). The method used to determine CrCl for study eligibility should be the same method used to determine cisplatin chemotherapy regimen used on study entry. CrCl values used in IVRS/IWRS will determine the chemotherapy regimen patients will initiate as neoadjuvant chemotherapy. Investigators are encouraged to determine CrCl as close to randomization as possible.**

If a patient withdraws from the study, then his/her enrollment/randomization code cannot be reused. Patients who withdraw after randomization will not be replaced.

Investigators should keep a record (ie, the patient screening log) of patients who entered screening.

At screening/baseline (Days -28 to -1), the Investigators or suitably trained delegate will:

- Obtain signed informed consent before any study specific procedures are performed. If laboratory or imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient. However, all screening laboratory and imaging results must have been obtained within 28 days of randomization, with the exception of the patient's tumoral PD-L1 status (must be obtained within ≤3 months before screening). Informed consent of study procedures may be obtained prior to the 28-day screening window, if necessary, in order to permit tumor biopsy sample acquisition and analysis prior to randomization.

- Obtain a unique 7-digit enrollment number (E-code), through the IVRS/IWRS in the following format PPD This number is the patient's unique identifier and is used to identify the patient on the electronic case report forms (eCRFs).

- Obtain tumor sample and send for PD-L1 expression analysis. **(Obtaining the tumor biopsy sample should be given the highest priority and, as such, the sample may be obtained and sent for PD-L1 status evaluation prior to the 28-day screening window, but within ≤ 3 months before screening, in order to permit analysis prior to randomization.)** PD-L1 status must be available in the IVRS/IWRS in order for the patient to be randomized, as it is a stratification factor.

- Determine patient eligibility. Only patients who meet all eligibility criteria (see Section 5.1 and Section 5.2) and have a centrally identified PD-L1 status will be considered eligible for randomization.

- Ensure PD-L1 status results are received by the IVRS/IWRS from the reference laboratory prior to randomization.

- Determine a single tumor stage; a single tumor stage is determined by the Investigator and is used for documentation of baseline disease characteristics and also for registering the patient for randomization (ie, for stratification purposes) (See Section 5.1, item #4).

At randomization, once the patient is confirmed to be eligible, the Investigator or suitably trained delegate will:

- Obtain a unique randomization number via the IVRS/IWRS. Numbers will start at PPD and will be assigned PPD by IVRS/IWRS as patients are eligible for entry into the study. The system will randomize the eligible patient to 1 of the 2 treatment arms.

  If the patient is ineligible and not randomized, the IVRS/IWRS should be contacted to terminate the patient in the system.

Patients will begin treatment on Day 1. Treatment should start no more than 3 working days after being randomized. Patients must not be randomized and treated unless all eligibility criteria have been met.

If a patient withdraws from participation in the study, then his or her enrollment/randomization code cannot be reused. Withdrawn patients will not be replaced.

6.2.2 Procedures for handling incorrectly enrolled or randomized patients

Patients who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Patients who are enrolled but are subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment and must be withdrawn from the study.

When a patient does not meet all the eligibility criteria but is randomized in error, or incorrectly started on treatment, the Investigator should inform AstraZeneca immediately and a discussion should occur between AstraZeneca and the Investigator regarding whether to continue or discontinue the patient from treatment, taking into consideration the benefit/risk of study continuation for that patient. The AstraZeneca representative must ensure all decisions are appropriately documented. In situations where an agreement between the Investigator and AstraZeneca cannot be reached regarding the treatment plan, the patient should have their study treatment stopped and be withdrawn from the study.

6.2.3 Methods for assigning treatment arms

The actual treatment given to patients will be determined by the randomization scheme in the IVRS/IWRS. The randomization scheme will be produced by a computer software program that incorporates a standard procedure for generating randomization numbers. One randomization list will be produced for each of the randomization strata. A blocked randomization will be generated, and all centers will use the same list in order to minimize any imbalance in the number of patients assigned to each treatment arm.

Patients will be identified to the IVRS/IWRS per country regulations. Randomization codes will be assigned PPD , within each stratum, as patients become eligible for randomization. The IVRS/IWRS will provide the kit identification number to be allocated to the patient at the randomization visit and subsequent treatment visits.

6.2.4 Methods for ensuring blinding

Not applicable; this is an open-label study.

6.2.5 Methods for unblinding the study

Not applicable; this is an open-label study.

6.3 Treatment compliance

Any change from the dosing schedule, dosing delays/interruptions, dose reductions, and dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the IP from receipt by the study site until the destruction or return of all unused IP. The Investigator(s) is responsible for ensuring that the patient has returned all unused IP.

6.4 Concomitant therapy

The Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical treatment phase of the study (final study visit), including the 90-day follow-up period following the last dose of durvalumab (Arm 1) or adjuvant treatment phase visit (Arm 2).

Any medication or vaccine, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, that the patient is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose, unit, and frequency

EXCEPTION: The following medications, administered for the purpose of performing the on-study radical cystectomy procedure, are exempt. Although not an inclusive list, examples of exempted therapies include bowel preparations, sedatives/anxiolytics, anesthesia, analgesics, neuromuscular blockers (and reversal agents), electrolyte solutions, anti-emetics, vasopressor support (eg, epinephrine, norepinephrine).

Concomitant medications that are administered in the peri-operative period of an on-study radical cystectomy, however, must be recorded if any of the following criteria are met:

- Medications administered in the peri-operative period that were used to treat an unexpected adverse event/complication, occurring peri-operatively
- Medications administered in the peri-operative period that contributed to an unexpected adverse event/complication, occurring post-operatively
- Medications administered as surgical prophylaxis, including antibiotics administered peri-operatively
- Medications administered during the surgery about which the Sponsor has requested specific additional information as part of documentation pertaining to a particular patient or as a program-wide requirement

Medications and fluids for chemo-immunotherapy infusions:

Any medication administered as a pre-medication for a gemcitabine, cisplatin, and durvalumab infusion is to be recorded as a concomitant medication; examples include anti-emetics (including a corticosteroid), medications used as prophylaxis for infusion/hypersensitivity reactions, and

antipyretics. Additionally, IV fluids containing electrolytes (ie, potassium chloride, magnesium sulfate) used in conjunction with the administration of cisplatin are to be recorded; plain IV solutions (ie, sodium chloride-containing solutions) are exempt from this requirement. Mannitol (as an osmotic diuretic), if administered with a cisplatin infusion, must also be recorded.

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator.

Restricted, prohibited, and permitted concomitant medications are described in the following tables (Table 10 and Table 11). Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5).

For gemcitabine and cisplatin, please refer to the local prescribing information with regard to warnings, precautions, and contraindications.

Table 10 Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
Both treatment arms (Arms 1 and 2):	
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment OR during the adjuvant phase study visits for Arm 2 (see Table 3).
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment OR during the adjuvant phase study visits for Arm 2 (see Table 3).
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment OR during the adjuvant phase study visits for Arm 2 (see Table 3). (Concurrent use of hormones for non-cancer-related conditions [eg, insulin for diabetes and hormone replacement therapy] is acceptable.
Live attenuated vaccines	Should not be given through 90 days after the last dose of durvalumab Should not be given through 3 months after the last of chemotherapy (gemcitabine and cisplatin) (Rubin et al 2014)

Table 10 Prohibited concomitant medications

Prohibited medication/class of drug:	Usage:
Experimental arm (Arm 1-durvalumab in neoadjuvant and adjuvant phases):	
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IP-related AEs. • Use prior to imaging procedures in patients with contrast allergies. • Short-term premedication for patients receiving combination chemotherapy agents, in which the prescribing information for the agent requires the use of steroids for documented hypersensitivity reactions. • In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the patient (eg, chronic obstructive pulmonary disease, radiation, nausea, etc). Investigators should attempt to limit the use of steroids for prevention of chemotherapy-induced nausea and vomiting to the day of treatment (ie, Days 1 and 8 only), if possible.
Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs)	Should not be given concomitantly. Should be used with caution in the 90 days post last dose of durvalumab. Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
Herbal and natural remedies that may have immune-modulating effects	Should not be given concomitantly unless agreed by the Sponsor

CTLA-4 cytotoxic T-lymphocyte-associated antigen 4; IP Investigational product; PD-1 Programmed cell death-1; PD-L1 Programmed cell death ligand-1.

Table 11 Supportive medications

Supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management)	Should be used, when necessary, for all patients
Inactivated viruses, such as those in the influenza vaccine	Permitted

6.4.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the patient's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the CRF.

6.4.2 Durvalumab drug-drug interactions

There is no information to date on drug-drug interactions with durvalumab either pre-clinically or in patients. As durvalumab is a mAb and therefore a protein, it will be degraded to small peptides and amino acids and will be eliminated by renal and reticuloendothelial clearance. It is therefore not expected that durvalumab will induce or inhibit the major drug metabolizing cytochrome P450 pathways. As a result, there are no expected PK drug-drug interactions. The MOA of durvalumab involves binding to PD-L1, and therefore significant pharmacodynamic drug interactions with the commonly administered concomitant medications are not expected. Despite this, appropriate clinical monitoring in all of the planned clinical studies will be conducted to evaluate any potential drug-drug interactions.

6.4.3 Rescue medication

As a result of immune-mediated adverse events (imAEs) that could potentially be experienced by patients on durvalumab, immunosuppressant rescue medication has to be made available to this patient population. The 2 products that fall into this category are infliximab (eg, for colitis) and mycophenolate (for hepatitis). AstraZeneca supply chain will be responsible for sourcing these 2 rescue medications to the sites if local regulations prevent the use of infliximab and mycophenolate in this indication, as they are considered off-label for management of immunotherapy related toxicities. These rescue medications must be received, controlled, and administered by the pharmacist and stored according to the labelled storage conditions, with temperature excursions reported accordingly by the pharmacist. If required for use as a result of an imAE, then the IVRS/IWRS will provide to the pharmacists the kit identification number to

be allocated to the patient at the time. Access and notifications will be controlled using the IVRS/IWRS.

6.5 Dose modification

For durvalumab treatment

- Patients may delay dosing under certain circumstances. However, dose reduction is not permitted.
  - Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5.1), due to either an immune or a non-immune-related AE.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible.
  - If there is a dosing delay while on the q3w schedule (neoadjuvant portion), it is advised to skip the durvalumab dose and resume dosing on Day 1 of the subsequent cycle. If there is a dosing delay during the adjuvant portion of therapy, dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy and PRO assessments. Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-life of durvalumab (see current IB for durvalumab).
  - In the event that durvalumab is discontinued or delayed as part of the toxicity management guidance, gemcitabine and cisplatin (G+C) may still be administered as scheduled.

For gemcitabine and cisplatin neoadjuvant treatment

- Patients may delay and subsequently resume dosing per local standard clinical practice. Patients will also be permitted to skip Day 8 chemotherapy per local toxicity management standards for chemotherapy.
  - If dosing must be delayed for reasons other than treatment-related toxicity, dosing will occur as soon as feasible. In the event that Cycle 1 of the chemotherapy schedule is delayed, durvalumab should follow the chemotherapy schedule and should be administered on Day 1 of each cycle.
  - In the event that G+C chemotherapy is discontinued due to treatment-related toxicity, patients should proceed to radical cystectomy when clinically feasible, and the remaining durvalumab monotherapy neoadjuvant doses should be skipped. Adjuvant therapy with durvalumab may continue following radical cystectomy. Note: If the Investigator feels that a patient would benefit from

administering the remaining neoadjuvant durvalumab cycles without chemotherapy, AstraZeneca should be consulted for an exception to this rule.

- In the event that creatinine clearance drops below 60 mL/min, the cisplatin dose may be divided into 2 administrations, as per local practice, for management of renal toxicity.

6.6 Treatment after the end of the study

Patients still on the study following the final DCO and database closure may continue to be followed for OS. Patients will be transitioned to a roll-over or safety extension study for follow-up for OS.

7. DISCONTINUATION OF TREATMENT PHASE OF STUDY AND PATIENT WITHDRAWAL

7.1 Discontinuation of study treatment

An individual patient will not receive any further IP (durvalumab, gemcitabine, or cisplatin) if any of the following occur in the patient in question:

- Withdrawal of consent from further treatment with IP. The patient is, at any time, free to discontinue treatment, without prejudice to further treatment. A patient who discontinues treatment is normally expected to continue to participate in the study (eg, for safety and survival follow-up) unless they specifically withdraw their consent to further participation in any study procedures and assessments (see Section 7.3).

- An AE that, in the opinion of the Investigator or AstraZeneca, contraindicates further dosing

- Any AE that meets criteria for discontinuation as defined in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5) for durvalumab or as defined in the local prescribing information for gemcitabine or cisplatin.

- A radical cystectomy procedure is not performed (see Section 6.1.5) either due to a medical decision by the investigator or a patient refusal, and entry into the noncystectomy extension phase is not applicable

- RECIST 1.1-defined progression that precludes the patient from undergoing a radical cystectomy; local progression during the neoadjuvant phase might not be a precluding event.

  – This is also applicable for patients who enter the noncystectomy extension phase with plans for a delayed cystectomy.

- Proven recurrence, either by RECIST 1.1-defined radiological progression or positive tumor biopsy from suspected recurrence (see Sections 8.1.1.1 and 8.1.1.2) following radical cystectomy.
- Pregnancy or intent to become pregnant
- Non-compliance with the study protocol that, in the opinion of the Investigator or AstraZeneca, warrants withdrawal from treatment with IP (eg, refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent other than treatment described in this protocol. Patients enrolled in Arm 2, which are given treatment outside of the protocol-defined therapy during the adjuvant phase, should continue tumor assessments until progression or recurrence but discontinue all other adjuvant phase visit assessments.

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

Discontinuation of study treatment, for any reason, does not impact the patient's participation in the study. A patient who decides to discontinue IP will always be asked about the reason(s) for discontinuation and the presence of any AE. The patient should continue attending subsequent study visits, and data collection should continue according to the study protocol. If the patient does not agree to continue in-person study visits, a modified follow-up must be arranged to ensure the collection of endpoints and safety information. This follow-up could be a telephone contact with the patient, a contact with a relative or treating physician, or information from medical records. The approach taken should be recorded in the medical records. A patient that agrees to modified follow-up is not considered to have withdrawn consent or to have withdrawn from the study.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment. Patients who are permanently discontinued will enter follow-up (see Table 4).

Patients who permanently discontinue drug for reasons other than disease progression/recurrence should continue to have disease assessments performed every 12 weeks ±7 days after the date of radical cystectomy for the first 24 months, then every 24 weeks ±7 days for 36 months, and then every 52 weeks (annually) thereafter until recurrence either by RECIST 1.1-defined radiologic progression (see Section 8.1.1.1) or a tumor biopsy for suspected new lesions, the end of study, death, study discontinuation, or Sponsor decision, whichever comes first, as defined in Table 1, Table 2, and Table 4.

7.1.2 Procedures for discontinuation of study plan (no radical cystectomy)

For patients with confirmed progression during the neoadjuvant phase outside of the pelvis or patients with cN1 disease at study entry for which the node is no longer considered resectable,

who are therefore precluded from undergoing a radical cystectomy, no additional imaging will be required, and the patient will be entered into the follow-up phase with plans to follow for OS only (see Table 4).

Patients who do not have a radical cystectomy performed for medically excluded reasons will be entered into the follow-up phase. Further disease assessments in these patients are outlined in Section 8.1.1.

Patients who *refuse* to proceed with a radical cystectomy will be managed as follows:

- Patients in either treatment arm who are determined to be in complete response (see Section 6.1.5) and who enter into a noncystectomy extension phase with a plan for a potential delayed cystectomy will be discontinued if they meet progression or medical exclusion criteria, or if they refuse a delayed radical cystectomy, in case of disease recurrence.

- Patients with residual disease will be entered into follow-up with no additional scans and followed for OS only.

All patients will be followed for survival until the end of the study.

Patients who decline to return to the site for evaluations should be contacted by telephone as indicated in the SoAs as an alternative.

Patients who have permanently discontinued from further receipt of IP will need to be discontinued from the IVRS/IWRS.

7.2 Lost to follow-up

Patients will be considered lost to follow-up only if no contact has been established by the time the study is completed (see Section 4.4), such that there is insufficient information to determine the patient's status at that time. Patients who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing patients throughout the study period. If contact with a missing patient is re-established, the patient should not be considered lost to follow-up and evaluations should resume according to the protocol.

In order to support key end point of EFS analysis, the survival status of all patients in the full analysis set (FAS) and the safety analysis set (SAS) should be re-checked; this includes those patients who withdrew consent or are classified as "lost to follow-up."

- Lost to follow-up – site personnel should check hospital records, the patient's current physician, and a publicly available death registry (if available) to obtain a current survival status. (The applicable CRF modules will be updated.)

- In the event that the patient has actively withdrawn consent to the processing of their personal data, the survival status of the patient can be obtained by site personnel from publicly available death registries (if available) where it is possible to do so under

applicable local laws to obtain a current survival status. (The applicable CRF modules will be updated.)

7.3 Withdrawal from the study

Patients are free to withdraw from the study at any time (IP and assessments) without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further IP or further study observation, with the exception of follow-up for survival, which will continue until the end of the study unless the patient has expressly withdrawn their consent to survival follow-up. Note that the patient may be offered additional tests or tapering of treatment to withdraw safely.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

If a patient withdraws consent, they will be specifically asked if they are withdrawing consent to:

- All further participation in the study including any further follow-up (eg, survival contact telephone calls)
- Withdrawal to the use of any samples (see Section 8.8.6)

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoAs (Table 1, Table 2, Table 3, and Table 4). Patients in both Arms 1 and 2 are to follow the assessments, with the exceptions noted.

The Investigator will ensure that data are recorded on the electronic CRFs. The web-based data capture (WBDC) system will be used for data collection and query handling.

The Investigator ensures the accuracy, completeness, legibility, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The Investigator will sign the completed electronic CRFs. A copy of the completed electronic CRFs will be archived at the study site.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue study treatment.

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

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

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

8.1 Efficacy assessments

This study will evaluate the dual primary endpoints of pCR and EFS. Efficacy assessments of pCR (primary) will be derived (by AstraZeneca) using central pathology review of the radical cystectomy sample. The efficacy assessments of EFS (primary) and EFS24 will be derived (by AstraZeneca) using BICR assessments according to RECIST 1.1 or by central pathology review if a biopsy is required for a suspected new lesion.

Additional secondary objectives will be OS, OS5, PFS2 as defined by local standard clinical practice, and proportion of patients who undergo radical cystectomy. The proportion of patients who achieve <P2 will be derived (by AstraZeneca) using local pathology assessments of radical cystectomy samples.

8.1.1 Tumor assessments

pCR efficacy assessment will be done by central pathology review of radical cystectomy samples (Sections 8.1.1.2 and 8.1.1.5). EFS efficacy assessment will be assessed by either RECIST 1.1 on imaging scans (Sections 8.1.1.1 and 8.1.1.6) or by pathology on biopsy samples if required (Sections 8.1.1.2 and 8.1.1.3).

8.1.1.1 Investigator RECIST 1.1 imaging review

Radiological efficacy will be assessed by RECIST 1.1. There will be 2 baseline assessments, the first for the neoadjuvant phase and the second for the adjuvant phase. A first "Neoadjuvant Baseline" scan should be collected during pre-randomization screening (Day -28 to -1) for disease staging and for use as a RECIST 1.1 baseline for the post-neoadjuvant/pre-radical cystectomy follow-up scan (performed upon completion of neoadjuvant chemotherapy prior to surgery; consideration should be given to scheduling this scan as part of the pre-surgical workup, to confirm patient is still eligible for a radical cystectomy) (Table 1).

A second "Adjuvant Baseline" scan should be collected 42 days (±2 weeks) after radical cystectomy and ideally should be performed as close as possible and must be prior to the first date of adjuvant treatment (Table 2). In most instances, no lesions will be observed on the Adjuvant Baseline scans and 'No Evidence of Disease' will be recorded for the Adjuvant Baseline RECIST assessment.

If any radiologically observable tumors are identified, a new selection of Target and/or Non-Target lesions are recorded. A follow-up scan should be performed at least 4 weeks later, as an assessment using RECIST 1.1 criteria and then every 12 weeks, thereafter. The use of an earlier scan is in place to allow early confirmation of a metastatic lesion. Additionally, a new lesion can be evaluated pathologically at any time, when feasible, to confirm metastatic disease.

On-study adjuvant tumor assessments occur every 12 weeks ±7 days after the date of radical cystectomy for the first 24 months, then every 24 weeks ±7 days for 36 months, and then every 52 weeks (annually) thereafter until unequivocal progression, the end of study, death, study discontinuation, or Sponsor decision, whichever comes first. If a new lesion is radiologically equivocal, treatment should continue and the lesion should be assessed at a subsequent scan no earlier than 6 weeks later or at the next scheduled imaging visit to determine if it becomes unequivocal. If measurable, in order for a previously equivocal new lesion to become unequivocal at a subsequent scan, the long axis diameter of the previously new equivocal non-nodal lesion or the short axis diameter of the previously new equivocal nodal lesion should show an increase of at least 5 mm. If the event of progression is confirmed on the subsequent follow-up scan, the date of progression corresponds to the first evidence of progression. Other imaging modalities (eg, bone scan, MRI scan) may be required to define progression in equivocal cases. During adjuvant treatment, the imaging schedule must be followed regardless of any delays in dosing.

Tumor assessment for patients not undergoing a radical cystectomy

For patients with confirmed progression during the neoadjuvant phase outside of the pelvis or progression of a lymph nodein the true pelvis that is determined to be unresectable, and who are therefore precluded from undergoing a radical cystectomy, no additional imaging will be required, and the patient will be entered into the follow-up phase with plans to follow for OS only (see Table 4).

Patients who *refuse* to proceed with a radical cystectomy will have tumor assessments performed as follows:

- Patients in either treatment arm who are determined to be in complete clinical response (see Section 6.1.5) and who enter into a noncystectomy extension phase with a plan for a potential delayed cystectomy will have a scan obtained 12 weeks after the last scan that was performed in the neoadjuvant phase, and then every 12 weeks ±7 days for the first 24 months, then every 24 weeks ±7 days for 36 months, and then every 52 weeks (annually) thereafter until unequivocal progression, the end of the study, death, study discontinuation, or Sponsor decision, whichever comes first. These follow-up scans will use the initial neoadjuvant baseline scan as a baseline scan for RECIST 1.1 assessments. If an unscheduled assessment is performed and the patient has not progressed, every attempt should be made to perform the subsequent assessments according to the original imaging schedule. For patients who discontinue treatment due to toxicity or other reasons in the absence of unequivocal recurrence, tumor assessments should continue according to the schedules of assessments.

  - Patients with local progression during the noncystectomy extension phase, who are not precluded from undergoing a delayed radical cystectomy, will have a post-cystectomy (adjuvant) baseline scan obtained and additional scans performed according to the on-study adjuvant schedule.

  - Patients who are medically precluded from undergoing a delayed radical cystectomy will not undergo any additional scans and will be entered into follow-up for evaluation of OS only.

  - For patients who refuse a delayed radical cystectomy procedure in case of recurrence, no additional scans will be performed, and the patient will be entered into follow-up for evaluation of OS only.

- Patients who refuse a radical cystectomy or are medically excluded and are without confirmation of a complete clinical response will be considered to have at least microscopic residual disease and will have progression (EFS) declared at time of expected surgery.

- Patients who refuse a radical cystectomy and have evidence of residual tumor as per findings on the post-neoadjuvant scan will be considered to have gross macroscopic residual disease and will have progression (EFS) declared at time of expected surgery.

- Patients with residual disease (microscopic or macroscopic) and who refuse radical cystectomy will be entered into follow-up with no additional scans and therefore will not have an "Adjuvant Baseline" scan or adjuvant treatment and will be followed for evaluation of OS only.

8.1.1.2 Local biopsy review

Where possible or feasible, suspected progression/recurrence events should be biopsy proven as soon as feasible. If a biopsy is performed and the histopathological assessment reveals the presence of recurrent tumor, progression will be recorded using the date of biopsy.

8.1.1.3 Local pathology review

Local pathology review of radical cystectomy specimen to assess the pathological stage will be based on American Joint Committee on Cancer tumor-node-metastasis classification of carcinomas of the urinary bladder.

8.1.1.4 Central biopsy review

Where possible or feasible, suspected progression/recurrence events should be biopsy proven as soon as feasible. If a biopsy is performed and the histopathological assessment reveals the presence of recurrent tumor, progression will be recorded using the date of biopsy.

8.1.1.5 Central pathology review

Central pathology review of radical cystectomy specimen to assess the pathological stage will be performed at the discretion of AstraZeneca. Guidelines for sample requirements will be provided in a separate document. A central pathology review will be based on American Joint Committee on Cancer tumor node metastasis classification of carcinomas of the urinary bladder.

8.1.1.6 Central imaging review

All images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed Contract Research Organization (CRO) for quality control and storage. Guidelines for image acquisition, de-identification, storage at the investigative site as source data, and transfer to the imaging CRO will be provided in a separate document. A BICR of images will be performed at the discretion of AstraZeneca. The results of these independent reviews will not be communicated to Investigators, and the results of Investigator RECIST 1.1 assessments will not be shared with the central reviewers. The management of patients will be based in part upon the results of the RECIST 1.1 assessment conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter (also referred to as "Imaging Charter").

Scans obtained for routine clinical management of the patient that are submitted to an imaging Contract Research Organization (iCRO) after investigator assigned RECIST 1.1 progression, may be centrally reviewed.

8.1.2 Survival assessments

Assessments for survival must be made at Months 3, 6, and 9 (±1 week); Month 12 (±2 weeks); and then every 6 months thereafter (±2 weeks) following treatment discontinuation or adjuvant phase study visits (Table 4). Survival information may be obtained via telephone contact with the patient or the patient's family, or by contact with the patient's current physician. The details of first and subsequent therapies for cancer, after discontinuation of treatment, will be collected.

In addition, patients on treatment or in survival follow-up will be contacted following the data cutoff for the primary analysis and all subsequent survival analyses to provide complete survival data. These contacts should generally occur within 7 days of the data cutoff. If patients are confirmed to be alive or if the death date is after the data cutoff date, these patients will be censored at the date of data cutoff. Death dates may be found by checking publicly available death registries, where allowed by local regulations.

8.1.3 Clinical outcome assessments

Patient reported outcome (PRO) is a general term referring to all outcomes and symptoms that are directly reported by the patient. PROs have become important in evaluating the impact of treatment on disease-related symptoms, physical function, and other HRQoL and in assessing treatment-related symptoms. The following PROs will be administered in this study: European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire (EORTC QLQ-C30, core questionnaire), EuroQol 5-Dimension 5-Level health state utility index (EQ-5D-5L), PGIC, PGIS, and selected questions from the PRO-CTCAE items bank. See questionnaires in Appendix H.

The PRO instruments will be completed by the patients using a handheld electronic patient reported outcome (ePRO) device at study sites or at home. It will take approximately 20 to 30 minutes for patients to complete the questionnaires, therefore, the burden to the patient should

be moderate. The PRO questionnaires must be completed by the patient as per the SoAs (Table 1, Table 2, Table 3, and Table 4) to the best of their ability. The PRO questionnaires will be administered on the days specified in the SoAs (Table 1, Table 2, Table 3, and Table 4). The EORTC QLQ-C30 should always be completed prior to the other questionnaires.

Data from the PRO assessments will not be routinely reviewed by the treating physicians throughout the study. Patients will first be informed of this when they fill out the consent form that is required in order to participate in the trial. The form will include information explaining that the PRO information gathered via the device is not routinely reviewed by their healthcare provider and they should therefore report any concerning symptoms directly to their physician. Patients will then be reminded of this each time they complete the assessment on the handheld device. When the patient logs onto the device to complete the assessments, a message screen will show advising the patient to consult their healthcare provider if they have any concerning symptoms. The patient will not be able to continue with the PRO assessments until they have acknowledged that they have read this message. The exact message text states:

“Please Note: If you are having any symptoms, health issues or other concerns, please be sure to discuss these with your doctor or nurse. The answers you provide to the questions are for research purposes only and are not being routinely reviewed by the members of your healthcare team. Please note to always share any and all information with your doctor, including information about the answers you will provide in this questionnaire that may help address your safety concerns.”

Finally, such warning will also be implemented into the training material to the site professionals, who will also verbally pass the message to the patients. It is important that the significance and relevance of the data are explained carefully to participating patients so that they are motivated to comply with data collection.

The following instructions should be followed when collecting PRO data via an electronic device:

- It is vital that the PRO reporting is initiated at randomization, as specified in the SoAs (Table 1, Table 2, Table 3, and Table 4) to capture the effect of study treatment.
- PRO questionnaires should be completed at home or at study sites prior to any other study procedures (following informed consent) and before discussion of disease progression/recurrence to avoid biasing the patient’s responses to the questions.
- When each instrument is due to be completed, the following order should be observed: EORTC QLQ-C30, PGIC, PGIS, EQ-5D-5L, and then PRO-CTCAE.
- The research nurse or appointed site staff must train the patient on how to use the ePRO device using the materials and training provided in the ePRO device. It is important that the ePRO device is charged and fully functional.
- The research nurse or appointed site staff must remind patients that there are no right or wrong answers and avoid introducing bias by not clarifying items.

- Site staff must not read or complete the PRO questionnaires on behalf of the patient. If the patient is unable to read the questionnaire (eg, is blind or illiterate), that patient should be exempted from completing PRO questionnaires but may still participate in the study. Patients exempted in this regard should be flagged appropriately by the site staff in the source documents and in the Review of PRO/Questionnaire/Diary (REVPRDI) eCRF.

- The patient should not receive help from relatives, friends, or clinic staff to answer the PRO questionnaires.

- Site staff must administer questionnaires available in the language that the patient speaks and understands. Questions should not be read in an available language and translated into another language for the patient.

- The research nurse or appointed site staff must monitor compliance since minimizing missing data is a key aspect of study success.

- The research nurse or appointed site staff must check compliance at each study visit (or more frequently to identify problems early). Reminders should be sent to the patient at home as needed to ensure compliance with the assessment schedules.

- If compliance drops to 85% or below, they will be flagged in the routine compliance report generated by the ePRO system, and a check-in call from the study site to ask the patient if he or she has any difficulties is highly recommended. A solution to enhance/resolve compliance should be discussed with the patient. Discussions and compliance review should be reflected in source documents.

- The reason why a patient could not complete assessments will be documented in the source documents and the REVPRDI eCRF.

8.1.3.1 EORTC QLQ-C30

The EORTC QLQ-C30 questionnaire (Appendix H) is included as a well-established instrument for assessing general cancer symptoms, physical functioning, and other HRQoL/health status in cancer clinical studies. It includes 30 items grouped into 9 multi-item scales: 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life (QoL) scale. It also includes 6 single-item symptom measures: dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. For each of the 15 domains, final scores are transformed such that they range from 0 to 100, where higher scores indicate greater functioning, greater HRQoL, or greater level of symptoms (Aaronson et al 1993).

The EORTC QLQ-C30 will be assessed based on the SoAs (Table 1, Table 2, Table 3, and Table 4) using a handheld device at study sites or at home.

8.1.3.2 EQ-5D-5L

The EuroQol 5-dimension, 5-level health state utility index (EQ-5D-5L) is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (EuroQol Group 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as in population health surveys. Since 2009, the EuroQol group has been developing a more sensitive version of the EQ-5D (the EQ-5D-5L), which expands the range of responses to each dimension from 3 to 5 levels of increasing severity (Herdman et al 2011).

The EQ-5D-5L questionnaire (Appendix H) assesses 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 response options (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems) that reflect increasing levels of difficulty.

The patient will be asked to indicate his/her current health state by selecting the most appropriate level in each of the 5 dimensions. The questionnaire also includes a visual analogue scale, where the patient will be asked to rate current health status on a scale of 0 to 100, with 0 being the worst imaginable health state.

The EQ-5D-5L will be assessed based on the SoAs (Table 1, Table 2, Table 3, and Table 4) using a handheld device at study sites or at home.

8.1.3.3 PGIC

The PGIC item (Appendix H) is included to assess how a patient perceives their overall change in health status since the start of study treatment. Patients will be asked, “Overall, how would you rate the change in your health status since starting this Study?” and will choose from seven response options ranging from “Much Better” to “Much Worse.”

The PGIC will be completed based on the SoAs (Table 1, Table 2, Table 3, and Table 4) using a handheld device at study sites or at home.

8.1.3.4 PGIS

The PGIS item (Appendix H) is included to assess how a patient perceives the overall severity of cancer symptoms over the past 1 week. Patients will be asked to choose the response that best describes the severity of their overall cancer symptoms over the past week. The response options are: no symptoms, very mild, mild, moderate, severe, and very severe. This item is included to aid in the interpretation of other PRO measures and to evaluate the overall impact of treatment on the global severity of bladder cancer symptoms.

The PGIS will be completed based on the SoAs (Table 1, Table 2, Table 3, and Table 4) using a handheld device at study sites or at home.

8.1.3.5 PRO-CTCAE

The PRO-CTCAE system has been developed by the National Cancer Institute (NCI). The PRO-CTCAE will only be administered in those countries where a linguistically validated version is available: currently English, Danish, German, Italian, Japanese, Korean, and Spanish. All applicable translations available during the study will be used. PRO-CTCAE is an item bank of symptoms experienced by patients while undergoing treatment of their cancer. It was developed in recognition that collecting symptom data directly from patients using PRO tools can improve the accuracy and efficiency of symptomatic AE data collection. This was based on findings from multiple studies demonstrating that physicians and nurses underestimate symptom onset, frequency, and severity in comparison with patient ratings (Basch et al 2009; Litwin et al 1998; Sprangers et al 1992). To date, 81 symptoms of the CTCAE (version 4) have been identified to be amenable to patient reporting. These symptoms have been converted to patient terms (eg, CTCAE term "myalgia" converted to "aching muscles"). For several symptoms, like fatigue and pain, additional questions are asked about symptom frequency, severity, and interference with usual activities. For other symptoms like rash, additional questions focus on the presence on the body. The items included in the PRO-CTCAE have undergone extensive qualitative review among experts and patients. Using cognitive testing methods, these items and the additional questions for some of the symptoms have been extensively evaluated by cancer patients, so that symptoms of interest are clear, comprehendible, and measurable. Not all items are administered in any one clinical trial. The intention is to only ask patients to complete those items, which are considered relevant for the trial, site of cancer, and cancer treatment.

The items pre-selected for this study are based on analysis of the relevant core symptom set from NCI, treatment-related symptoms of durvalumab monotherapy, and side effects of G+C derived from the literature. Also, 7 of the 8 symptoms (fatigue, diarrhea, cough, shortness of breath, musculoskeletal/muscle pain, rash, pruritus, and fever) associated with immune-related adverse events (irAEs) reported in 5 immunotherapy product labels identified and recommended by the FDA for assessing treatment tolerability in immunotherapy clinical trials (Howie et al 2018) were included. Note that fever is not currently available in the PRO-CTCAE items bank. To minimize patient burden, some items considered too general (abdominal pain and headache) and non-therapy specific in the NCI Core Cancer Symptom list (anxiety, cognitive disturbance, depression, insomnia, neuropathy, painful urination, painful urination, change in usual urine color, urinary frequency, etc) have not been selected. The Free Text item in the PRO-CTCAE instrument is not included in the study, as the utility of this information and the analysis method have not been established. The full list of items is available in Appendix H.

The PRO-CTCAE assessments will be based on the SoAs (Table 1, Table 2, Table 3, and Table 4) using a handheld device at study sites or at home.

8.2 Safety assessments

Planned timepoints for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see the SoAs).

Clinical laboratory safety tests, including serum pregnancy tests, will be performed in a licensed clinical laboratory according to local standard procedures. Sample tubes and sample sizes may vary depending on the laboratory method used and routine practice at the site. Urine pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection, and results (values, units, and reference ranges) will be recorded on the appropriate eCRF.

The laboratory variables to be measured are presented in Table 12 (clinical chemistry), Table 13 (hematology), and Table 14 (urinalysis).

Other safety tests to be performed at screening include assessment for hepatitis B surface antigen, hepatitis C antibodies, and HIV antibodies.

The following laboratory variables will be measured:

Table 12 Clinical chemistry

Albumin	Lipase[b]
Alkaline phosphatase[a]	Magnesium[c]
ALT[a]	Potassium
Amylase[b]	Sodium
AST[a]	Total bilirubin[a]
Calcium	TSH[e]
Creatinine[d]	T3 free[f] (reflex)
Gamma glutamyltransferase[c]	T4 free[f] (reflex)
Glucose	Urea or blood urea nitrogen, depending on local practice
Lactate dehydrogenase	

[a] Tests for ALT, AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2×upper limit of normal (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.

[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured, either lipase or amylase is acceptable.

[c] Gamma-glutamyltransferase, magnesium, testing are to be performed at baseline on Day 1 (unless all screening laboratory clinical chemistry assessments are performed within 3 days prior to Day 1), and if clinically indicated.

[d] Creatinine testing is performed on Day 1 and Day 8 of each treatment cycle and if clinically indicated during the neoadjuvant phase. During the adjuvant phase, creatinine testing is performed according to Table 2 and

Table 3. Laboratory clinical chemistry assessments performed at the beginning of a cycle are obtained within 3 days prior to Day 1. Creatinine clearance will be calculated using Cockcroft-Gault (using actual body weight) at baseline/screening only to ensure initial appropriate treatment assignment based on baseline renal function. Sites are required to determine a creatinine clearance prior to each dose of cisplatin for subsequent cycles.

[e] If TSH is measured within 14 days prior to Day 1 (first infusion day), it does not need to be repeated at Day 1.

[f] Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

AE Adverse event, ALT Alanine aminotransferase; AST Aspartate aminotransferase, T3 Triiodothyronine, T4 Thyroxine, TSH Thyroid-stimulating hormone.

Table 13 Hematology

Absolute neutrophil count[a]	Platelet count
Absolute lymphocyte count[a]	Total white cell count
Hemoglobin	

Note: For coagulation parameters, activated partial thromboplastin time [either as a ratio or as an absolute value, in seconds] and international normalized ratio are to be assessed at baseline on Neoadjuvant Cycle 1 Day 1 (unless all screening laboratory hematology assessments are performed within 3 days prior to Day 1), Adjuvant Cycle 1 Day 1 (for patients in Arm 1 only), and as clinically indicated.

[a] Can be recorded as absolute counts or as percentages. If entered as a percentage, the percentage of neutrophils with total white cell count has to be provided.

Table 14 Urinalysis

Bilirubin	Glucose
Blood	Protein

Note: Urinalysis should be done at screening and then as clinically indicated.
Note: Microscopy should be used as appropriate to investigate white blood cells.

If a patient shows an AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN, refer to Appendix E for further instructions on cases of increases in liver biochemistry and evaluation of Hy's law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed following Table 4 after permanent discontinuation of treatment (Arm 1) or adjuvant phase study visits (Arm 2).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 8.3.7.

All patients with Grade 3 or 4 laboratory values at the time of completion or discontinuation from IP must have further tests performed until the laboratory values have returned to Grade 1 or 2, unless these values are not likely to improve because of the underlying disease.

8.2.2 Physical examinations

Physical examinations will be performed according to the assessment schedules (see the SoAs). Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 8.3.7.

If any PRO assessments occur when the patient is attending a site visit (Section 8.1.3), then the PRO assessments should be completed by the patient prior to the performance of any physical examination.

8.2.3 Vital signs and measurements

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) and height will be assessed according to the SoAs (Table 1, Table 2, Table 3, and Table 4). Body weight is recorded once at each visit when vital signs are evaluated. Body surface area is calculated at the beginning of each cycle in the neoadjuvant phase only, for the purpose of chemotherapy dose calculations.

Situations in which vital sign results should be reported as AEs are described in Section 8.3.7. For any AEs of infusion reactions, the vital sign values should be entered into the CRF.

Neoadjuvant treatment phase

First infusion

On the first infusion day, patients in Arm 1 will be monitored and vital signs collected/recorded in the eCRF prior to, during, and after infusion of durvalumab as presented in the bulleted list below. Patients in Arm 1 will have vital signs monitored and recorded prior to start of chemotherapy per local standards.

Arm 1 only

Vital signs will be collected from patients before, during, and after durvalumab infusion at the following times (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (**halfway** through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

If the infusion takes longer than 60 minutes, then vital signs should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab with monitoring per local standards.

Arm 2

Arm 2 will have vital signs monitored and recorded prior to start of chemotherapy per local standards throughout the neoadjuvant phase.

Subsequent infusions

BP, pulse, and other vital signs should be measured and collected/recorded in the eCRF prior to the start of treatment. Patients should be carefully monitored, and BP and other vital signs should be measured during and post-infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs CRF page.

Adjuvant treatment phase

Arm 1

Patients in Arm 1 will have vital signs collected/recorded in the eCRF prior to the start of durvalumab infusion and should be carefully monitored, and vital signs should be measured per local standards and as clinically indicated.

Arm 2

For patients in Arm 2, vital signs will be collected/recorded in the eCRF once per study visit.

8.2.4 Electrocardiograms

Resting 12-lead ECGs will be recorded at screening and as clinically indicated throughout the study (see the SoAs). ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position.

In case of clinically significant ECG abnormalities, including a QTcF value ≥470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 8.3.7.

8.2.5 WHO/ECOG performance status

WHO/ECOG performance status will be assessed at the times specified in the assessment schedules (see the SoAs) based on the following:

0. Fully active; able to carry out all usual activities without restrictions

1. Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work)

2. Ambulatory and capable of self-care, but unable to carry out any work activities; up and about more than 50% of waking hours.

3. Capable of only limited self-care; confined to bed or chair more than 50% of waking hours

4. Completely disabled; unable to carry out any self-care and totally confined to bed or chair

5. Dead

Any significant change from baseline or screening must be reported as an AE.

8.2.6 Patient follow-up contact (Arm 2 only)

Patients randomized to Arm 2 will be contacted for information regarding ongoing and new AEs and concomitant medications for adjuvant phase visits 2, 4, 6, and 8. Patients are not required to return to the study site for these specified visits but must be contacted and available to provide information regarding AEs and concomitant medications to the Investigator.

8.2.7 Clavien-Dindo assessment

Clavien-Dindo assessment will be utilized for grading surgical complications. The highest grade complication, which occurs within 90 days after the cystectomy (including a partial cystectomy, if performed), will be recorded at the time specified in the SoAs (Table 2 and Table 3). Investigators will indicate which AE resulted in a surgical complication grade reported. The following classification will be used:

Grade	Definition
Grade 0	No events observed.
Grade I	Any deviation from the normal post-operative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. Allowed therapeutic regimens are drugs as anti-emetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside.
Grade II	Requiring pharmacological treatment with drugs other than such allowed for Grade I complications. Blood transfusions and total parenteral nutrition are also included.
Grade III	Requiring surgical, endoscopic, or radiological intervention
Grade IIIa	Intervention not under general anesthesia
Grade IIIb	Intervention under general anesthesia
Grade IV	Life-threatening complication (including CNS complications) requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)

Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

[a] Brain hemorrhage, ischemic stroke, subarrachnoidal bleeding, but excluding transient ischemic attacks.
Source: Dindo et al 2004
CNS central nervous system; IC intermediate care; ICU intensive care unit.

8.2.8 Other safety assessments

If new or worsening pulmonary symptoms (eg, dyspnea) or radiological abnormality suggestive of pneumonitis/ILD is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Section 8.4.5) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography [HRCT], blood and sputum culture, hematological parameters, etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath, and pyrexia, etc) including auscultation for lung field will be assessed.
- Saturation of peripheral oxygen (SpO_2)
- Other items
  - When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:
    - (i) ILD markers (KL-6, SP-D) and β-D-glucan
    - (ii) Additional clinical chemistry: CRP, LDH

8.3 Collection of adverse events

The Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

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

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The Investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow AEs, see Section 8.3.3.

8.3.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

AEs and SAEs will be collected from the time of the patient signing the ICF until the follow-up period is completed (90 days after the last dose of treatment (Arm 1) or adjuvant phase study visits (Arm 2). If an event that starts post the defined safety follow-up period noted above is considered to be due to a late onset toxicity to study drug then it should be reported as an AE or SAE as applicable.

All SAEs will be recorded and reported to the Sponsor or designee within 24 hours, as indicated in Appendix B. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the Investigator learns of any SAE, including a death, at any time after a patient's last visit and he/she considers the event to be reasonably related to the study treatment or study participation, the Investigator may notify the Sponsor.

The method of recording, evaluating, and assessing causality of AEs and SAEs are provided in Appendix B.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All AEs/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the patient' last visit in the study are followed up by the Investigator for as long as medically indicated (this may be beyond the 90 days after the last dose of treatment (Arm 1) or adjuvant phase study visits (Arm 2) but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 Adverse event data collection

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade (report only the maximum CTCAE grade for a calendar day)
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

In addition, the following variables will be collected for SAEs:

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 8.3.5
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the

recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.5 Causality collection

The Investigator will assess causal relationship between the IP and each AE and will answer "yes" or "no" to the question, "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that, for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes."

A guide to the interpretation of the causality question is found in Appendix B.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or the care provider, reported in response to the open question from the study site staff, "Have you had any health problems since the previous visit/you were last asked?," or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

8.3.7 Adverse events based on examinations and tests

The results from the clinical study protocol-mandated laboratory tests and vital signs will be summarized in the clinical study report (CSR). Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible, the reporting Investigator uses the clinical rather than the laboratory term (eg, anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression/recurrence, should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study (see Section 8.3.9).

8.3.8 Hy's law

Cases where a patient shows elevations in liver biochemistry may require further evaluation, and occurrences of AST or ALT ≥3×ULN together with total bilirubin ≥2×ULN may need to be reported as SAEs. Please refer to Appendix E for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

8.3.9 Disease recurrence or progression

Disease recurrence or progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of new metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

8.3.10 New cancers

The development of a new cancer should be regarded as an SAE. New primary cancers are those that are not the primary reason for the administration of the IP and have been identified after the patient's inclusion in this study.

8.3.11 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of treatment (Arm 1) or adjuvant phase study visits (Arm 2), must be reported as follows:

- Death clearly resulting from disease progression/recurrence should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF in the Statement of Death page. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression/recurrence of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the Statement of Death page in the eCRF. The report should contain a comment regarding the co-involvement of PD/recurrence, if appropriate, and should assign main and contributory causes of death.

- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the Statement of Death page in the eCRF. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post mortem results should be forwarded to AstraZeneca Patient Safety or its representative within the usual time frames.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of treatment (Arm 1) or adjuvant phase study visits (Arm 2) should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the

defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

8.3.12 Adverse events of special interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the IP and may require close monitoring. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of the IP.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants, and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated MOA and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regard to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs/imAEs observed with anti PD-L1/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhea/colitis, intestinal perforation, endocrinopathies (hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis and rare/less frequent imAEs including neuromuscular toxicities such as myasthenia gravis and Guillain-Barre syndrome.

Other inflammatory responses that are rare/less frequent with a potential immune-mediated etiology include, but are not limited to, pericarditis, sarcoidosis, uveitis, and other events involving the eye, skin, hematological, rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab IB. More specific guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see Section 8.4.5). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting Investigator.

8.3.13 Safety data to be collected following the final DCO of the study

For patients continuing to receive durvalumab treatment after final DCO and database closure, it is recommended that the patients continue the scheduled site visits and Investigators monitor the patient's safety laboratory results prior to and periodically during treatment with durvalumab in order to manage AEs in accordance with the durvalumab Dose Modification and Toxicity Management Guidelines (see Section 8.4.5). All data after the final DCO and database closure will be recorded in the patient notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in patients still receiving durvalumab treatment (or within the 90 days following the last dose of treatment [Arm 1] or adjuvant phase study visits [Arm 2]) after the final DCO and database closure must be reported as detailed in Section 8.4.1.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within 1 calendar day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site staff how to proceed. Investigators or other site personnel send relevant CRF modules by fax to the designated AstraZeneca representative.

For further guidance on the definition of a SAE, see Appendix B.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the patient has received any study drug

- Pregnancies in the partner of male patients (see Section 5.3 for lifestyle restrictions for male patients with a female partner of childbearing potential and Section 8.4.2.2 for restrictions on male patients fathering a child)

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

8.4.2.1 Maternal exposure

If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day (ie, immediately but **no later than 24 hours** of when he or she becomes aware of it).

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 8.4.1) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy, and the PREGOUT is used to report the outcome of the pregnancy.

8.4.2.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab. Please follow the local prescribing information relating to contraception and the time limit for such precautions for gemcitabine and cisplatin.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose of durvalumab should, if possible, be followed-up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Independent Ethics Committees/Institutional Review Boards (IECs/IRBs) prior to use.

Patients who are permanently discontinued from further receipt of IP, regardless of the reason, will be identified as having permanently discontinued treatment and will enter follow-up (see the SoAs).

8.4.3 Overdose

8.4.3.1 Durvalumab

Use of durvalumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event of overdose of durvalumab, and possible symptoms of overdose are not established.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.3.2 Gemcitabine and cisplatin

For patients receiving neoadjuvant gemcitabine and cisplatin, refer to the local prescribing information for treatment of cases of overdose. If any overdose is associated with an AE or SAE record the AE/SAE diagnosis or symptoms in the relevant AE modules only of the eCRF.

8.4.4 Medication error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day, ie, immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an SAE

associated with the medication error (see Section 8.3.2) and within 30 days for all other medication errors.

The definition of a medication error can be found in Appendix B.

8.4.5 Management of IP-related toxicities

The following general guidance should be followed for management of toxicities:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity if required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of the assigned IP along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression/recurrence, concomitant medications, or infections). This includes gemcitabine- or cisplatin-induced toxicity. In the event that toxicities are clearly attributed to chemotherapy, both chemotherapy and durvalumab should be delayed.
- In the absence of a clear alternative etiology, all events should be potentially immune related and the TMGs should be followed (see Section 8.4.5.1).
- In the event that the AE has clear immune-related etiology, G+C chemotherapy may still be administered as scheduled while durvalumab administration is delayed per TMGs (see Section 8.4.5.1).
- In the event that G+C chemotherapy is discontinued due to treatment-related toxicity, patients should proceed to radical cystectomy when clinically feasible, and the remaining durvalumab monotherapy neoadjuvant doses should be skipped. Adjuvant therapy with durvalumab may continue following radical cystectomy. Note: If the Investigator feels that a patient would benefit from administering the remaining neoadjuvant durvalumab cycles without chemotherapy, AstraZeneca should be consulted for an exception to this rule.

All toxicities will be graded according to NCI CTCAE, version 5.0.

8.4.5.1 Specific toxicity management and dose modification information – durvalumab

Comprehensive TMGs have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors, durvalumab (MED4736; PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these 2 compounds, these TMGs are

applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and is administered concurrently or sequentially with other anticancer drugs (ie, antineoplastic chemotherapy, targeted agents) are as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised, however, to use local practice guidelines and consult local references for the management of toxicities observed with other anticancer treatment (see Section 8.4.5.2).

The most current version of the TMGs is provided to the investigative site as an Annex to Protocol document entitled, "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy)," and is maintained within the Site Master File.

Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 7.1 of this protocol and the Dosing Modification and Toxicity Management Guidelines).

Following the first dose of the IP, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy by the reporting Investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

8.4.5.2 Specific toxicity management and dose modification information - gemcitabine and cisplatin

Chemotherapy- related toxicity management and dose adjustments, including dose delays and reductions, should be performed and follow standard clinical practice.

In the event that an AE can reasonably be attributed to chemotherapy, dose adjustment of chemotherapy should be attempted before modifying the administration of durvalumab.

In the event that chemotherapy is delayed, durvalumab should also be delayed. Every effort should be made to ensure patients receive at least 4 cycles of neoadjuvant therapy across all

treatment arms in the study, if conditions allow. In the event of unfavorable tolerability, patients who are unable to complete the study specified number of neoadjuvant treatment cycles patients may receive less than 4 cycles.

8.5 Pharmacokinetics

8.5.1 Collection of samples

Blood samples for the determination of durvalumab concentration in serum will be obtained according to the SoAs.

Samples for determination of durvalumab concentration in serum will be analyzed by a designated third party on behalf of AstraZeneca. Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate bioanalytical validation report.

8.5.1.1 Collection of samples to measure for the presence of ADAs

The presence of ADA will be assessed in serum samples taken according to the SoAs.

Samples will be measured for the presence of ADAs and ADA-neutralizing antibodies for durvalumab using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive-negative cut points previously statistically determined from drug-naïve validation samples will be employed.

8.5.2 Storage and destruction of pharmacokinetic/ADA samples

Durvalumab PK and ADA samples will be destroyed within 5 years of CSR finalization.

PK and ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical validation report.

Any residual backup PK samples may be used for future exploratory biomarker research (in this case, residual backup PK samples will be shipped to AstraZeneca-designated Biobank; see details in the Laboratory Manual).

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

8.7.1 Optional exploratory genetic sample

If the patient agrees to participate in the optional genetic research study, a blood sample will be collected. Participation is optional. Patients who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the patient. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix D for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in Appendix D or in the Laboratory Manual.

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.7.2 Storage and destruction of genetic samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples may be stored for a maximum of 15 years or as per local regulations from the date of the last patient's last visit, after which they will be destroyed. DNA is a finite resource that may be used up during analyses. The results of any further analyses will be reported either in the CSR itself or as an addendum or separately in a scientific report or publication.

No personal details identifying the individual will be available to AstraZeneca or designated organizations working with the DNA.

8.8 Biomarkers

By participating in this study, the patient consents to the mandatory collection and use of donated biological samples as described here. Tissue samples will be obtained from all screened patients.

Mandatory tumor and blood biomarkers to be evaluated to support the exploratory objectives of the study are described in Section 8.8.2. Alternative biomarkers may be evaluated as determined by additional data associated with disease progression/recurrence or response to durvalumab.

Biomarker assessments that may have the potential to identify patients likely to respond to treatment with durvalumab (determined from other durvalumab studies) will be investigated to determine a patient's biomarker status and for possible correlation with efficacy endpoints.

Pre-randomization tumor PD-L1 expression will be evaluated in all patients. Putative associations with clinical endpoints will be assessed. Baseline tumor requirements are briefly described in Section 8.8.1. Based on availability of tissue, additional exploratory biomarkers may also be evaluated as described in Section 8.8.2.

Comparisons of PD-L1 expression in tumor will be made between arms to determine if PD-L1 status is prognostic or predictive of outcomes associated with durvalumab + G+C combination therapy and/or G+C. The results may be pooled with biomarker data from other durvalumab studies to evaluate biological responses across indications and to compare results in monotherapy versus combination settings.

Samples will be taken at the times presented in the study plans in Table 1 and Table 2. For sample requirement, refer to the Laboratory Manual.

Details for collection, volumes, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

All samples collected for biomarker analyses will be stored at the study site, a reference laboratory, or at AstraZeneca facilities and may be used for subsequent research relevant to evaluating biological and/or clinical response to immunotherapy as described in the exploratory analyses section.

8.8.1 Collection of tissue samples for central pathology review, stratification by PD-L1 expression, and biomarker research

There are 2 mandatory requirements for the provision of tissue samples:

- MANDATORY (screening stage): Provision of a FFPE tumor biopsy for the purpose of PD-L1 expression analyses and for enabling exploratory analyses as described in the proceeding section. A newly acquired tumor biopsy is strongly preferred; however, if not feasible with an acceptable clinical risk, an archival MIBC tumor sample taken ≤3 months prior to screening can be submitted. A tumor tissue block is preferred. If a tissue block is unavailable, unstained sections from the tissue block may be submitted. This sample must be shipped to the central laboratory prior to dosing. The collection of tumor tissue is mandated when the patient has MIBC, which is defined as tumor invasion into the muscularis propria and must be submitted with the local pathology report confirming invasion into the muscular propria. Please refer to the Laboratory Manual for detailed instructions and guidelines regarding sections.
  - Samples should be collected during cystoscopy or transurethral resection of bladder tumor and placed in formalin and processed to a single paraffin-embedded block, as described in the Laboratory Manual. Whenever feasible, additional samples beyond those mandated for PD-L1 analyses should be obtained and processed as described in the Laboratory Manual.
  - Newly acquired or archived specimens with limited tumor content and fine needle aspirates are inadequate for defining tumor PD-L1 status, hence, are not accepted.
- MANDATORY (treatment stage): The collection of the radical cystectomy specimen at radical cystectomy to assess the pathological stage and to determine the rate of down-staging. Please refer to the Pathology Manual for detailed instructions and guidelines regarding this section.

- OPTIONAL: The collection of additional tumor biopsies upon progression or recurrence of patients in Arm 1 and Arm 2 is strongly encouraged. If the biopsy is performed, the tumor biopsy must be submitted to centrally confirm histopathological finding. Please see Covance laboratory manual for detailed instructions and guidelines.

Patients will be permitted, upon discussion with the study team, to be provided their PD-L1 status if requested after an event that is considered an EFS event.

Please refer to the Laboratory Manual for further details of requirements including sample quality control and shipping.

A brief description of exploratory tumor markers likely to be explored by IHC or RNA analysis is provided in Section 8.8.2.

To meet the requirement for FDA approval of a companion diagnostic, sections of the tumor will be retained at Ventana or Ventana-approved laboratory for potential additional studies, as requested by the FDA, to support potential test approval.

8.8.2 Exploratory biomarkers

Blood, tumor, and urine samples for exploratory biomarker analyses will be obtained according to the schedules presented in the SoAs. Details for collection, volume, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

Baseline measures will be correlated with outcomes. Note that samples will be obtained from patients randomized to each treatment arm. Comparisons will be made between baseline measures to determine if biomarkers (or combination of markers) are prognostic or predictive of outcomes associated with Arm 1 versus Arm 2, subgrouped by histology.

Additional sample collections and analyses may be completed at select study sites by site-specific amendment. All samples collected for such exploratory analyses will be stored at the site, at a reference laboratory, or at AstraZeneca's facilities and may be used for subsequent research relevant to evaluating response to immunotherapy.

The exploratory biomarker plan is described by sample type below.

Tumor markers (in FFPE tumor block)

Tissue obtained as part of screening procedures for establishing PD-L1 status at radical cystectomy and/or progression/recurrence may be analyzed for additional markers by IHC. Markers evaluated may change based on the best available information at the time of the biomarker analysis. Markers of special interest include, but are not limited to, Ox40, GITR, PD-L2, Tim-3, CD137, CD8, and Lag3-.

Tissues obtained may also be assessed for somatic mutations, microsatellite instability, TMB, neo-antigen prediction, T-cell receptor clonality and/or for an IFN-γ gene expression signature (eg, -IFN-γ, *CXCL9*, *LAG3*, and *CD274*) and other RNA biomarkers by targeted RNAseq and/or other gene expression methodologies.

For genomic DNA that has been extracted, genotyping of immunomodulatory genes such as PD-1, PD-L1, CTLA-4, and human leukocyte antigen loci may be completed to determine whether natural variation within such genes is associated with the likelihood of clinical benefit and/or with the likelihood of drug-related AEs. Genes associated with solid tumor development, disease progression/recurrence, or likelihood of tumor response to chemotherapy may likewise be investigated. Genotyping will occur retrospectively, data will not be shared with patients, and results will not impact treatment decisions.

Whole blood gene expression (PaxGene-RNA)

Whole blood samples will be obtained from all patients at the timepoints described in Table 1, Table 2, and Table 3. RNA will be prepared for quantification of RNA and/or micro-RNA expression using reverse transcription-quantitative polymerase chain reaction, microarray, sequencing, or similar technology.

Focus is likely to be given to the expression of immunomodulatory genes. Correlations with outcome data will be completed on select candidates and predictive markers, with the aim of identifying useful expression thresholds for identifying patients likely to receive benefit.

Other biomarkers

Plasma, serum, and urine samples will be taken at the timepoints described in Table 1, Table 2, and Table 3 for additional exploratory plasma (ctDNA/circulating soluble factors), serum biomarkers, and urine biomarkers.

Urine-based markers

Urine must be obtained at the timepoints described in Table 1. These samples will be used to evaluate urine cytology, exploratory biomarkers, which may be predictive of pathological response prior to radical cystectomy, or other clinical endpoints.

Serum-based markers

Serum will be obtained to explore the expression of cytokines and chemokines, including but not limited to IFN-γ, interleukin (IL)-18, CXCL9, and CXCL10.

Similarly, the concentrations of a battery of IC ligands, receptors, or other soluble factors may be assessed. Proteins of special interest include CTLA-4, PD-1, B7-1, B7-2, and IL-6R.

Plasma-based markers (ctDNA, circulating soluble factors)

Plasma will be obtained from all patients as described in the SoAs. The concentrations of a panel of relevant cytokines, chemokines, and other immune-related markers may be assessed. Plasma may also be used to evaluate mutant circulating tumor DNA. Overall mutational burden and/or somatic mutations/genomic alterations in plasma may be assessed using next generation or similar technologies. Such measurements may be correlated with response.

Management of biomarker data

The biomarker data will have unknown clinical significance. AstraZeneca will not provide biomarker research results to patients, their family members, any insurance company, an employer, clinical study Investigator, general physician, or any other third party unless required to do so by law. The patient's samples will not be used for any purpose other than those described in the study protocol.

Individual patients will not be identified in any report or publication resulting from this work. The data and results of this research may be reviewed with collaborators and published, but neither the patient's name nor any other personal identifiers will appear in any publication nor report.

8.8.3 Storage, re-use, and destruction of biomarker samples

Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report. The results of this biomarker research may be pooled with biomarker data from other studies involving durvalumab to generate hypotheses to be tested in future research.

8.8.4 Labeling and shipment of biological samples

The Principal Investigator at each center will ensure that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B, Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria); see Appendix C "IATA 6.2 Guidance Document."

Any sample identified as Infectious Category A materials will not be shipped, and no further samples will be taken from the involved patients unless agreed upon with AstraZeneca and appropriate labeling, shipment, and containment provisions are approved.

8.8.5 Chain of custody of biological samples

A full chain of custody will be maintained for all samples throughout their life cycle (Appendix C).

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and will keep documentation of sample shipment.

The sample receiver will keep full traceability of the samples while in storage and during use until used or disposed of or until further shipment and will keep documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers.

Samples retained for further use will be stored in the AstraZeneca-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

8.8.6 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of or destroyed and the action documented. If samples have already been analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator will:

- Ensure that AstraZeneca is immediately notified of the patients' withdrawal of informed consent to the use of donated samples
- Ensure that biological samples from that patient, if stored at the study site, are immediately identified, disposed of, or destroyed and the action documented
- Ensure that the organization(s) holding the samples is/are immediately informed about the withdrawn consent and that samples are disposed of or destroyed, the action is documented.
- Ensure that the patient and AstraZeneca are informed about the sample disposal

AstraZeneca ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or destroyed and the action documented and the study site is informed.

8.8.7 German biomarker sub-study

In addition to planned biomarker analyses performed for the overall study patient population, a biomarker sub-study will be performed at select sites (approximately 15) in Germany to assess additional immune, mutational and/or molecular subtyping biomarkers from tumor samples collected at baseline and again at the time of cystectomy (Appendix L 1). Association and correlation with biomarker results and clinical responses (therapy response, outcomes) will be investigated. The sub-study is intended to collect samples from approximately 50 patients (if feasible), recruited from participating NIAGARA sites located in Germany only. Participation in this sub-study for these patients is optional and will require a separate consent process.

Analysis of the exploratory biomarker data within this sub-study will be analyzed and reported independently from the NIAGARA study. Prioritization is given to the biomarker analyses required for the parent NIAGARA study. Additional sub-study analyses will only be performed if there is sufficient tissue available.

9. STATISTICAL CONSIDERATIONS

All statistical analyses will be performed by AstraZeneca or its representatives.

A comprehensive statistical analysis plan (SAP) will be prepared and finalized within 3 months of the first randomized patient and any subsequent amendments will be documented, with final amendments completed prior to reporting of data.

The dual primary objectives of this study are to assess the efficacy of Arm 1 versus Arm 2 (neoadjuvant/adjuvant) in terms of EFS as assessed per BICR or by central pathology review if a biopsy is required for a suspected new lesion and pCR rate (neoadjuvant) as assessed per central pathology review in ITT. To achieve these objectives, the multiple testing procedure (MTP) for controlling the type I error rate will be utilized (see Section 9.4.1.1).

Depending on the extent of any impact, summaries of data related to patients diagnosed with COVID-19 and impact of COVID-19 on study conduct (in particular, missed visits, delayed or discontinued IP, and other protocol deviations) may be generated. More detail will be provided in the SAP.

9.1 Sample size determination

This study will plan to enroll and screen approximately 1400 patients at approximately 150 sites in order to randomize approximately 1050 eligible patients in a 1:1 ratio to receive either durvalumab + G+C combination therapy (neoadjuvant)/durvalumab alone (adjuvant) in Arm 1 or G+C combination therapy (neoadjuvant)/no adjuvant treatment in Arm 2.

The study is sized to characterize the pCR rate and EFS benefit of Arm 1 versus Arm 2 in MIBC patients who have not received prior systemic chemotherapy.

Statistical assumptions are made using a pCR rate of 35% and 50% for patients enrolled on the control arm and experimental arms, respectively, (see below) for ITT.

Non-uniform accrual of patients (with k=2) is assumed when estimating the analysis times. The total proportion of patients randomized at time t [t ≤22 months] following the start of the study is assumed to be $(t/22)^2$.

The final analysis of the primary pCR will be performed approximately 6 months after the last patient is randomized to the study.

The final analysis of the dual-primary endpoint of EFS will be performed when approximately 451 EFS events in ITT have occurred across the 2 arms (43% maturity) or June 2025 (approximately 45 months after the last patient is randomized), whichever occurs first.

Arm 1 versus Arm 2 (pCR in ITT)

It is assumed that the pCR for patients (ITT) in Arm 2 is 35% (Grossman et al 2003). Under the alternative hypothesis, pCR is assumed to be 50% for Arm 1. With 525 patients in each arm, the study will have at least 95% power to demonstrate a statistically significant difference at a 2-

sided alpha level of 0.1%. Assuming a pCR rate of 35% in Arm 2, the smallest pCR rate that could be observed as being statistically significant at the time of pCR analysis is a 10-percentage point increase to 45% in Arm 1.

Arm 1 versus Arm 2 (EFS in ITT)

The assumed EFS treatment effect under the alternative hypothesis is an average HR of 0.733 for Arm 1 versus Arm 2. This is based on the following assumptions:

An exponential model was assumed for EFS such that in patients who are assigned to the Arm 1, the overall median EFS is 38.0 months and the EFS rate at 24 months is 64.5%.

For Arm 2, an exponential model was assumed for EFS such that patients who are assigned to Arm 2, the overall median EFS is 27.8 months and the EFS rate at 24 months is 55%.

Based on a blinded event prediction an estimated 451 EFS events (43% maturity) are expected to be observed at 45 months after the date of the last patient randomized. With 451 EFS events, the study will have at least 90% power to demonstrate a statistically significant difference at a 2-sided overall alpha level of 4.90%, allowing two interim analyses to be conducted at approximately 67% and 91% of the target events. The smallest treatment difference that could be statistically significant will be an average HR of 0.82.

Arm 1 versus Arm 2 (OS in ITT)

The assumed OS treatment effect under the alternative hypothesis is an average HR of 0.76 for Arm 1 versus Arm 2. This is based on the following assumptions:

- An exponential model was assumed for OS such that in all patients who are assigned to Arm 1, the overall median OS is 8.6 years (103 months), and the OS rate at 5 years is 66.7%.

- For Arm 2, an exponential model was assumed for OS such that in all patients who are assigned to Arm 2, the overall median OS is 6.5 years (78 months) and the OS rate at 5 years is 58.7%.

The final analysis of OS based on approximately 428 OS events for the comparison of Arm 1 versus Arm 2 (41% maturity, 428/1050), from ITT, is expected to occur approximately 5 years (60 months) after the last patient is randomized to the study and will provide at least 80% power to demonstrate a statistically significant difference in OS at a 2-sided alpha level of 4.9%, allowing two interim analysis to be conducted at approximately 67% and 74% of the target events. The smallest treatment difference that could be statistically significant will be an HR of 0.82.

Arm 1 versus Arm 2 (OS5 in ITT)

The statistical model assumptions for OS5 in the ITT of each arm are stated above.

The analysis of OS5 that is performed at the time of the final analysis of OS will provide at least 77% power to demonstrate a statistically significant difference in OS5 at a 2-sided alpha level of 4.9%.

9.2 Populations for analyses

Definitions of the analysis sets for each outcome variable are provided in Table 15.

Table 15 Summary of outcome variables and analysis populations

Outcome variable	Populations
Efficacy data	
pCR rate	Full analysis set (ITT population) PD-L1-high analysis set
EFS	Full analysis set (ITT population) PD-L1-high analysis set
Proportion of patients who achieve <P2, EFS24, MFS, DSS, OS, OS5, PFS2, proportion of patients who undergo radical cystectomy	Full analysis set (ITT population)
PROs	Full analysis set (ITT population)
DFS	Cystectomy population
Demography	Full analysis set (ITT population)
PK data	PK analysis set
Safety data	
Exposure	Safety analysis set
AEs	Safety analysis set
ECOG performance status	Safety analysis set
Laboratory measurements	Safety analysis set
Vital signs	Safety analysis set

AE Adverse event; DFS Disease-free survival; DSS Disease-specific survival; ECOG Eastern Cooperative Oncology Group; EFS Event-free survival; EFS24 Proportion of patients alive and event free at 24 months; ITT Intent-to-treat; MFS Metastasis-free survival; OS5 Proportion of patients alive at 5 years; pCR Pathologic complete response; PFS2 Time from the date of randomization to the earliest date of progression which occurs on subsequent therapy following an EFS event or death; PK Pharmacokinetic; PRO Patient-reported outcome.

9.2.1 Full analysis set (ITT population)

The FAS will include all randomized patients. Unless otherwise specified, the FAS will be used for all efficacy analyses (including PROs). Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received. Patients who were randomized but did not subsequently go on to receive study treatment are included in the analysis in the treatment arm to which they were randomized.

9.2.2 Cystectomy population

The Cystectomy population will include all patients in FAS who undergo radical cystectomy. Unless otherwise specified, the analysis set will be used for DFS only. Treatment arms will be compared on the basis of randomized study treatment, regardless of the treatment actually received.

9.2.3 PD-L1-high analysis set

The PD-L1-high analysis set will include the subset of patients in the FAS whose PD-L1 status is PD-L1-high as defined by Ventana SP263 assay in Table 6.

9.2.4 Safety analysis set

The SAS will consist of all patients who received at least 1 dose of study treatment. Safety data will not be formally analyzed but summarized according to the treatment received, that is, erroneously treated patients (eg, those randomized to treatment A but actually given treatment B) will be summarized according to the treatment they actually received.

9.2.5 PK analysis set

All patients who receive at least 1 dose of IP per the protocol for whom any post-dose data are available and who do not violate or deviate from the protocol in ways that would significantly affect the PK analyses will be included in the PK analysis set. The population will be defined by the Study Physician, Pharmacokineticist, and Statistician prior to any analyses being performed.

9.3 Outcome measures for analyses

9.3.1 Calculation or derivation of efficacy variables

9.3.1.1 Dual Primary endpoint: pathologic complete response (pCR)

The dual primary endpoint of pCR is the pCR assessment in ITT per central pathology review.

pCR rate is defined as the proportion of patients whose pathological staging was T0N0M0 as assessed using specimens obtained via radical cystectomy following the neoadjuvant treatment. pCR will be assessed per central pathology review and local pathology review. The denominators for pCR in the ITT will be MIBC patients in the ITT.

9.3.1.2 Dual Primary endpoint: event-free survival (EFS)

The dual primary endpoint of EFS is the EFS assessment in ITT per BICR or by central pathology review if a biopsy is required for a suspected new lesion.

EFS is defined as the time from randomization to the first recurrence of disease after radical cystectomy, the time of first documented progression in patients who are medically precluded from a radical cystectomy, or time of expected surgery in patients who refuse to undergo a radical cystectomy or failure to undergo a radical cystectomy in participants with residual disease, or the time of death due to any cause, whichever occurs first.

- A recurrence of disease includes local (pelvic) recurrence of UC, urinary tract recurrence of UC, or distant metastasis of UC. In the event that progression is confirmed via biopsy or subsequent scans (the confirmation of suspected new lesions initially identified in the scans if applicable), the date of recurrence will be the earliest date among the initial detection of radiological unequivocal new lesion, or the pathological confirmation of new lesion if biopsy is performed to confirm suspected new lesion post cystectomy, or the death due to any causes.

- Patients who are suspected of having microscopic disease (ie, no evidence on imaging) or who have documented macroscopic disease (confirmed by imaging) at the completion of neoadjuvant therapy and who refuse to proceed with a radical cystectomy, are declared as progressed, with EFS being declared at the time of expected surgery

- For patients who fulfill criteria for a complete clinical response, refuse an initial radical cystectomy and are entered in a noncystectomy extension phase, EFS is defined as time to the first recurrence of disease following a delayed radical cystectomy (if performed). For patients who are medically precluded from or refuse a delayed radical cystectomy, EFS is confirmed at time of unequivocal progression.

EFS will be assessed using CT/MRI and pathology testing performed according to local standards and as clinically indicated.

Patients who take subsequent therapy prior to their last evaluable RECIST assessment or progression or death will not be censored at their last evaluable RECIST assessment prior to taking the subsequent therapy. Patients who have not progressed or experienced recurrent disease or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable disease assessment. If the patient has no evaluable visits or does not have baseline disease assessment (ie, a baseline scan) prior to neoadjuvant treatment, they will be censored at Day 1 unless they die within 112 days of randomization.

The EFS time will always be derived based on assessment dates and not visit dates.

9.3.1.3 Secondary endpoints

Proportion of patients alive and event free at 24 months after randomization

The EFS24 will be defined as the Kaplan-Meier estimate of EFS at 24 months after randomization, as assessed per BICR or by central pathology review if a biopsy is required for a suspected new lesion and per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion.

Proportion of patients who achieve <P2

The proportion of patients who achieve <P2 is defined as the proportion of patients whose pathological staging at radical cystectomy was P0 (T0N0M0)/Pa/P1/Cis as assessed per local pathology review using specimens obtained via radical cystectomy following the neoadjuvant treatment.

The denominator for this endpoint will be the number of patients in the ITT population (MIBC patients).

Overall Survival (OS)

OS is defined as the time from the date of randomization until death due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. In order to minimize confounding of OS, patients randomized to Arm 2 will not be allowed to cross over to Arm 1.

Note: Survival calls will be made following the date of data cutoff for the analysis (these contacts should generally occur within 7 days of the data cutoff date). If patients are confirmed to be alive or if the death date is after the data cutoff date, these patients will be censored at the date of data cutoff. Death dates may be found by checking publicly available death registries, where allowed by local regulations.

Proportion of patients alive at 5 years after randomization (OS5)

The OS5 will be defined as the Kaplan-Meier estimate of OS at 5 years after randomization.

Metastasis-free survival

MFS is defined as the time from date of randomization until the first recognition of distant metastases or death, whichever occurs first. Patients who were alive and free from metastases were censored at the time of the latest date of assessment from their last evaluable disease assessment.

Disease-specific survival

DSS is defined as the time from the date of randomization until death due to BC. Any patient not known to have died due to BC at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive.

Disease-free survival

DFS is defined as the time from the date of radical cystectomy to the first recurrence of disease post radical cystectomy, or death due to any cause, whichever occurs first. DFS will be assessed in patients who undergo radical cystectomy and are disease free at adjuvant baseline visit per BICR assessment.

Proportion of patients who undergo cystectomy

Proportion of patients who undergo cystectomy is defined as the proportion patients who undergo radical cystectomy after the neoadjuvant treatment. The denominator will be patients in the ITT population.

Time from randomization to subsequent progression or recurrence post-EFS event (PFS2)

PFS2 will be defined as the time from the date of randomization to the earliest date of progression which occurs on subsequent therapy following an EFS event or death.

The date of subsequent progression will be recorded by the Investigator in the eCRF and defined according to local standard clinical practice and may involve any of the following: objective radiological imaging, symptomatic progression, or death. Patients who are alive and for whom a subsequent disease progression post-EFS event has not been observed should be censored at the last time known to be alive and without a subsequent disease progression.

9.3.2 Calculation or derivation of safety variables

9.3.2.1 Adverse events

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of Medical Dictionary for Regulatory Activities [MedDRA] preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with durvalumab will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of any IP may be included in the AE summaries, but the majority of those summaries will omit the AEs observed after a patient has received further therapy for cancer. Supporting AE summaries for any AE occurring within 90 days of completion of adjuvant visit and for any AE occurring from radical cystectomy to 90 days post-radical cystectomy, including Clavien-Dindo assessment, will also be provided to support the above AE summaries. Further details will be provided in the SAP. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of durvalumab) will be flagged in the data listings. The SAS will be used for reporting of safety data.

A separate data listing of AEs occurring more than 90 days after discontinuation of IP will be produced. These events will not be included in AE summaries.

9.3.2.2 Other significant adverse events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant adverse events (OAEs) and reported as such in the CSR. A similar review of laboratory/vital signs/ECG data and physical examinations will be performed for identification of OAEs. Examples of these are marked hematological and other laboratory abnormalities and certain events that lead to intervention (other than those already classified as serious) or significant additional treatment.

9.3.2.3 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, and physical examinations, the baseline value will be the latest result obtained prior to the start of study treatment.

QTcF will be derived during creation of the reporting database using the reported ECG values (RR and QT) using the following formula:

- QTcF = $QT/RR^{(1/3)}$ where RR is in seconds

Corrected calcium product will be derived during creation of the reporting database using the following formulas:

- Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – albumin (G/L)] × 0.02)

The denominator used in laboratory summaries will only include evaluable patients, ie, those who had sufficient data to have the possibility of an abnormality.

For example:

- If a CTCAE criterion involves a change from baseline, evaluable patients would have both a pre-dose and at least 1 post-dose value recorded.
- If a CTCAE criterion does not consider changes from baseline to be evaluable, the patient need only have 1 post-dose value recorded.

The denominator in vital signs data should include only those patients with recorded data.

9.3.3 Calculation or derivation of patient-reported outcome variables

All items/questionnaires will be scored according to published scoring guidelines listed in the SAP. All PRO analyses will be based on the FAS.

EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that can be combined into 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea/vomiting), and global health status/QoL scale. The EORTC QLQ-C30 will be scored according to the EORTC QLQ-C30 Scoring Manual (Fayers 2001). An outcome variable consisting of a score from 0 to 100 will be derived for each of the symptom scales, each of the functional scales, and the global measure of health status scale in the EORTC QLQ-C30 according to the EORTC QLQ-C30 Scoring Manual. Higher scores on the global health status and functional scales indicate better health status/function, but higher scores on symptom scales represent greater symptom severity.

Definition of clinically meaningful changes - Visit Response and Best Overall Response

Definition of clinically meaningful changes in score compared with baseline will be evaluated. A clinically meaningful change is defined as an absolute change in the score from baseline of ≥10 for scales from the EORTC QLQ-C30 (Osoba et al 1998). For example, a clinically meaningful improvement in physical functioning (as assessed by EORTC QLQ-C30) is defined as an increase in the score from baseline of ≥10, whereas a clinically meaningful deterioration is defined as a decrease in the score from baseline of ≥10. A clinically meaningful deterioration or worsening in pain (as assessed by EORTC QLQ-C30) may be defined as an increase in the score from baseline of ≥10. At each post-baseline assessment, the change in global health status/QoL,

symptoms, and functioning score from baseline will be categorized as improvement, no change, or deterioration as shown in Table 16.

Table 16 Mean change and clinically meaningful change - EORTC QLQ-C30

Score	Change from baseline	Visit response
EORTC QLQ-C30 global health status/quality of life scale score	≥10 point increase from baseline (ie, increase of at least 10)	Improvement
	≥10 point decrease from baseline (ie, decrease of at least 10)	Deterioration
	Otherwise	No change
EORTC QLQ-C30 symptom scales	≥10 point increase from baseline (ie, increase of at least 10)	Deterioration
	≥10 point decrease from baseline (ie, decrease of at least 10)	Improvement
	Otherwise	No change
EORTC QLQ-C30 functional scales	≥10 point increase from baseline (ie, increase of at least 10)	Improvement
	≥10 point decrease from baseline (ie, decrease of at least 10)	Deterioration
	Otherwise	No change

A patient's best overall response in symptoms, function, or global health status/QoL will be derived as the best response the patient achieved, based on evaluable PRO data collected during the study period. The criteria in Table 17 will be used to assign a best response in symptoms or function or global health status/QoL.

Table 17 Best response in EORTC QLQ-C30 scores: FAS population

Overall score response	Criteria
Improved	Patient meets 1 of the following criteria: 1. Has 2 consecutive visit responses of "improvement" at least 21 days apart 2. Has 1 visit response of "improvement" and no further assessments
No Change	Patient does not qualify for an overall score response of "improved" and meets 1 of the following criteria: 1. Has 2 consecutive visit responses of "no change" 2. Has 1 visit response of "no change" and no further assessments The 2 responses should be at least 21 days apart.

Overall score response	Criteria
Deterioration	Patient does not qualify for an overall score response of "improved" or "no change" and meets 1 of the following criteria: 1. Has 2 consecutive visit responses of "deterioration" at least 21 days apart 2. Has 1 visit response of "deterioration" and no further assessments 3. Has 1 visit response of "improvement", "no change", or "deterioration" followed by death within 2 PRO assessment visits
Other	Patient meets 1 of the following criteria: 1. Does not qualify for one of the above. 2. Has either no baseline or no post-baseline evaluable PRO assessments
Missing	Patient has no baseline and no post baseline evaluable PRO assessments

Time to definitive/sustained clinically meaningful deterioration in health-related QoL, functioning or symptoms

Time to definitive or sustained clinically meaningful deterioration in global health status/QoL and functioning as measured by EORTC QLQ-C30 scales/items will be defined as the time from the date of randomization until the date of the first observation with ≥10-point decrease in score with no subsequent observations with <10-point decrease from baseline. Similarly, time to definitive clinically meaningful deterioration in symptoms as measured by EORTC QLQ-C30 scales/items will be defined as the time from the date of randomization until the date of the first observation with ≥10-point increase in score with no subsequent observations with <10-point increase from baseline. Sensitivity analysis will be performed by including death (by any cause) in the absence of a clinically meaningful deterioration, regardless of whether the patient discontinues study drug(s) or receives another anticancer therapy prior to global health status/QoL, function or symptom deterioration. Such deaths will be included as an event in the sensitivity analysis only if it occurs within 2 PRO assessment visits from the last available PRO assessment. Patients whose global health status/QoL, functioning, or symptoms (as measured by EORTC QLQ-C30) has not shown a clinically meaningful deterioration and who are alive at the time of the analysis will be censored at the time of their last PRO assessment where the global health status/QoL, function, or symptom could be evaluated.

The at-risk population for the analysis of time to global health status/QoL or functioning deterioration is defined as the subset of the FAS having baseline scores of ≥10. The at-risk population for the analysis of time to symptom deterioration is defined as the subset of the FAS having baseline scores ≤90.

Improvement rate – global health status/QoL, functioning, symptoms

Responses in symptoms for each visit (improvement, deterioration, and no change based on Table 16) as well as the best overall response will be calculated for each patient. The symptom improvement rate will be defined as the number (%) of patients with a best overall score response of "improved" in symptoms. The denominator will consist of a subset of the FAS who

have a baseline symptom score ≥10. Global health status/QoL or function improvement rate. The global health status/QoL or function improvement rate will be defined as the number (%) of patients with best overall response of "improved" in QoL or function. The denominator will consist of a subset of the FAS who have a baseline global health status/QoL or function score ≤90.

EQ-5D-5L

The EQ-5D-5L index comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, respondents select which statement best describes their health on that day from a possible 5 options of increasing levels of difficulty (no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems). A unique EQ-5D-5L health state is referred to by a 5-digit code, allowing for a total of 3125 health states. For example, state 11111 indicates no problems on any of the 5 dimensions. These data will be converted into a weighted health state index by applying scores from EQ-5D-5L value sets elicited from general population samples (the base case will be the United Kingdom valuation set, with other country value sets applied in scenario analyses and described in detail in the SAP).

In addition to the descriptive system, respondents also assess their health on the day of assessment on a visual analogue scale, ranging from 0 (worst imaginable health) to 100 (best imaginable health). This score is reported separately.

PGIC

The PGIC question is "Overall, how would you rate the change in your health status since starting this Study?" with response options for the PGIC as follows: Much Better (+3), Moderately Better (+2), A Little Better (+1), About the Same (0), A Little Worse (-1), Moderately Worse (-2), and Much Worse (-3). No scoring will be done using the assigned numerical values.

PGIS

PGIS assesses the overall severity of disease-related symptoms (eg, general cancer symptoms). The response options of the PGIS are as follows: No Symptoms = 0, Very Mild = 1, Mild = 2, Moderate =3, Severe = 4, and Very Severe = 5.

PRO-CTCAE

Refer to Appendix H for details on the PRO-CTCAE questions and responses.

PRO-CTCAE items are not combined into summary scores, and individual items will be descriptively summarized (eg, proportion of patients endorsing each response option). Further details will be provided in the SAP.

9.3.4 Calculation or derivation of pharmacokinetic variables

9.3.4.1 Population pharmacokinetics and exposure-response/safety analysis

A population PK model may be developed using a non-linear mixed-effects modeling approach. If performed, the impact of physiologically relevant patient characteristics (covariates) and disease on PK will be evaluated. The relationship between the PK exposure and the effect on safety and efficacy endpoints may be evaluated. The results of such an analysis will be reported in a separate report. The PK, pharmacodynamics, demographic, safety, and efficacy data collected in this study may also be combined with similar data from other studies and explored using population PK and/or PK-pharmacodynamic methods.

9.3.4.2 Pharmacokinetic analysis

The non-compartmental analysis will not be conducted for this study due to sparse sampling. PK concentration data will be listed and summarized by visit using descriptive statistics.

9.3.4.3 Immunogenicity analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADAs against durvalumab. The immunogenicity titer and presence of neutralizing ADAs will be reported for samples confirmed positive for the presence of ADAs. The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow.

9.3.5 Calculation or derivation of biomarker variables

Biomarker status, as defined in the secondary objectives, will be assessed for evaluable patients in each cohort according to prespecified criteria that will be detailed in the SAP.

9.3.6 Calculation or derivation of pharmacogenetic variables

In the case of genetic data, only the date that the patient gave consent to participation in the genetic research and the date the blood sample was taken from the patient will be recorded in the eCRF and database. The genetic data generated from the study will be stored in the AstraZeneca Laboratory Information Management System (LIMS) database or other appropriate system. This database is a secure database, which is separate from the database used for the main study. Some or all of the dataset from the main study may be duplicated within the AstraZeneca LIMS database for exploratory genetic analysis. Data will be reported outside the CSR (see Appendix D).

9.4 Methods for statistical analyses

In ITT, the following formal statistical analysis of pCR and EFS (as dual primary endpoints) will be performed:

- H0: No difference between Arm 1 and Arm 2
- H1: Difference between Arm 1 and Arm 2

The study has been sized to characterize the pCR rate and EFS benefit of Arm 1 versus Arm 2 in ITT.

The final analysis of the primary pCR will be performed approximately 6 months after the last patient is randomized.

The final analysis of the primary EFS will be performed when 451 EFS events (43% maturity) in ITT are reached across both arms or in June 2025, whichever occurs first. This is expected approximately 45 months after the last patient is randomized.

Descriptive statistics will be used for all variables, as appropriate, and will be presented by treatment arm. Continuous variables will be summarized by the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency counts and percentages for each category. Unless otherwise stated, percentages will be calculated out of the population total for the corresponding treatment arm.

Baseline will be the last assessment of the variable under consideration prior to the intake of the first dose of IP, except for efficacy variables. For efficacy variables except DFS (including pCR rate, EFS, EFS24, proportion of patients who achieve <P2, MFS, DSS, OS, OS5, PFS2, proportion of patients who undergo radical cystectomy, PRO, demography, and PK data), baseline is defined as the last visit prior to randomization. A second ("adjuvant") baseline scan will be performed 42 days (±2 weeks) following the date of radical cystectomy and prior to the start of adjuvant therapy for radiological assessments. Efficacy assessments of pCR will be derived (by AstraZeneca) using central pathology review of the radical cystectomy sample.

All data collected will be listed. Efficacy and PRO data will be summarized and analyzed based on the FAS. PK data will be summarized and analyzed based on the PK analysis set. Safety data will be summarized on the safety analysis set.

Results of all statistical analyses will be presented using a 95% CI and 2-sided p-value, unless otherwise stated.

Table 18 details which endpoints are to be subjected to formal statistical analysis, together with pre-planned sensitivity analyses, making it clear which analysis is regarded as primary for that endpoint. Note, all endpoints compare Arm 1 versus Arm 2 in all randomized patients (ITT population), unless otherwise indicated.

Table 18 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
pCR rate	Stratified logistic regression for: Primary analysis using central pathology review: • Arm 1 versus Arm 2 (ITT population) Secondary analysis using Investigator assessment: • Arm 1 versus Arm 2 (ITT population) • Arm 1 versus Arm 2 (PD-L1-high population)

Table 18 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
EFS	Stratified log-rank test for: Primary analysis using BICR or by central pathology review if a biopsy is required for a suspected new lesion: • Arm 1 versus Arm 2 (ITT population) Sensitivity analysis for the primary analysis using BICR or by central pathology review if a biopsy is required for a suspected new lesion: • Using a Kaplan-Meier plot of time to censoring where the censoring indicator of the primary analysis is reversed - attrition bias (ITT) • Interval censored analysis - evaluation-time bias (, ITT) • Analysis where subjects who take subsequent anti-cancer therapy prior to the EFS event will be censored at their last evaluable assessment prior to taking the subsequent therapy – attrition bias (ITT) • Analysis using the 2 missed visit censoring rule - attrition bias (ITT) Secondary analysis per local Investigator or local biopsy review if a biopsy is required for a suspected new lesion: • Arm 1 versus Arm 2 (ITT population) • Arm 1 versus Arm 2 (PD-L1-high population).
EFS24	Hazard ratio using the Kaplan-Meier estimates of EFS24: • Arm 1 versus Arm 2 (ITT population)
Proportion of patients who achieve <P2	Stratified logistic regression using central pathology review: • Arm 1 versus Arm 2 (ITT population)
OS	A stratified log-rank test: • Arm 1 versus Arm 2 (ITT population)
OS5	Hazard ratio using the Kaplan-Meier estimates of OS5: • Arm 1 versus Arm 2 (ITT population)
Proportion of patients who undergo radical cystectomy	Point estimate and 95% CI • Arm 1 versus Arm 2 (ITT population)
DFS	A stratified log-rank test based on BICR data: • Arm 1 versus Arm 2 (Cystectomy population)
MFS	A stratified log-rank test based on Investigator data: • Arm 1 versus Arm 2 (ITT population)
DSS	A stratified log-rank test based on Investigator data: • Arm 1 versus Arm 2 (ITT population)
EORTC QLQ-C30	Average change from baseline using a MMRM analysis

Table 18 Pre-planned statistical and sensitivity analyses to be conducted

Endpoints analyzed	Notes
Time to definitive/sustained clinically meaningful deterioration (EORTC QLQ-C30)	Stratified log-rank test

BICR Blinded Independent Central Review; CI Confidence interval; DFS Disease-free survival; DSS Disease-specific survival; EFS Event-free survival; EFS24 Proportion of patients alive and event free at 24 months; EORTC QLQ-C30 European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire; ITT Intent-to-treat; MFS Metastasis-free survival; MMRM Mixed-model for repeated-measures; OS5 Proportion of patients alive at 5 years; pCR Pathologic complete response.

9.4.1.1 Multiple testing strategy

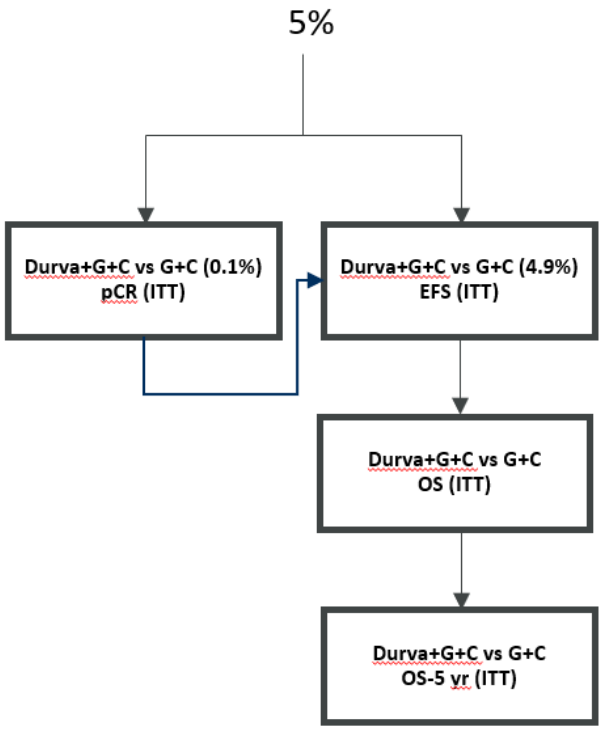
In order to strongly control the type I error at the 5% 2-sided alpha level, an MTP with gatekeeping strategy will be used across the dual primary endpoints (pCR rate and EFS). If the higher level hypothesis in the MTP is rejected for superiority, the following hypothesis will then be tested as shown in Figure 3.

Hypotheses will be tested using a multiple testing procedure with an alpha-exhaustive recycling strategy (Burman et al 2009). With this approach, hypothesis will be tested in a pre-defined order by first splitting the 5% alpha into 0.1% and 4.9% for pCR and EFS for Arm 1 versus Arm 2, respectively, in the ITT population as outlined in Figure 3.

According to alpha (test mass) splitting and alpha recycling, the test mass that becomes available after each rejected hypothesis is recycled to secondary hypotheses not yet rejected. Since the EFS in the ITT is tested at multiple timepoints (ie, 2 interims and final analysis), the EFS tests for the same comparison/population (ie, shown in first box in the MTP) will be considered as 1 test family. As long as 1 test in the family can be rejected, the family is rejected; thus, the assigned total alpha to the family can be recycled to the next MTP level. This testing procedure stops when the entire test mass is allocated to non-rejected hypotheses. Implementation of this predefined ordered testing procedure, including recycling, will strongly control type I error at the 5% (2-sided) alpha level among all key hypotheses. Figure 3 shows the multiple testing framework for the dual primary endpoints and key secondary endpoint. The details of the complete MTP and the alpha-exhaustive recycling procedure will be provided in the SAP.

The alpha level allocated to pCR and EFS (dual primary endpoints) will be controlled at the superiority interim and final timepoints by using the Lan DeMets (Lan and DeMets 1983) spending function that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends on the proportion of information available.

Figure 3 Multiple testing procedure for controlling the type I error rate



Durva Durvalumab; EFS Event-free survival; G+C Gemcitabine+cisplatin; ITT Intention to treat; OS5 Proportion of patients alive at 5 years; pCR Pathologic complete response; vs versus.

9.4.1.2 Pathologic complete response (pCR)

The primary analysis of pCR will be based on assessment per central pathology review. The pCR will be compared between Arm 1 and Arm 2 in ITT using logistic regression models adjusted for the stratification factors: clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively; renal function (adequate renal function versus borderline renal status); and PD-L1 status (high versus low/negative). The results of the analysis will be presented in terms of an odds ratio together with its corresponding 99.9% CI and p-value.

Pathological response data will be listed and summarized over time for patients with adequate renal function.

A secondary analysis, using pCR rate per local Investigator assessment, will be performed using the same methodology as for the analysis described above.

9.4.1.3 Event-free survival (EFS)

The primary EFS analysis will be based on assessments per the BICR or by central pathology review if a biopsy is required for a suspected new lesion. The analysis will be performed in ITT

using a stratified log-rank test adjusted for the stratification factors: clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively; renal function (adequate renal function versus borderline renal status); and PD-L1 status (high versus low/negative). The effect of treatment will be estimated by the HR together with its corresponding ([1-adjusted alpha] × 100%) CI and p-values.

The HR and CI will be estimated from the stratified Cox proportional hazards model (Cox 1972).

All of the secondary analyses will be performed using the same methodology as for the primary analyses described above.

Kaplan-Meier plots of EFS will be presented by treatment arm. Summaries of the number and percentage of patients experiencing an EFS event and the type of event (progression, recurrence, or death) will be provided along with median EFS for each treatment.

Subgroup analyses will be conducted comparing EFS (per disease assessment using BICR assessments) between Arm 1 versus Arm 2 in the following subgroups of patients in ITT (but not limited to):

- Sex (male versus female)
- Age at randomization (<65 versus ≥65 years of age)
- Pathologic lymph node metastasis found at radical cystectomy (N0 versus N+)
- All visible tumor removed during the TUBRT procedure prior to study entry (Yes versus No)

PD-L1 status (high versus low/negative), other baseline variables may also be assessed if there is clinical justification or an imbalance is observed between the treatment arms. The purpose of the subgroup analyses is to assess the consistency of treatment effect across expected prognostic and/or predictive factors. Forest plot will be performed.

No adjustment to the significance level for testing of the subgroup and sensitivity analyses will be made since all these analyses will be considered supportive of the analysis of EFS.

Cox proportional hazards modelling will be employed to assess the effect of covariates on the HR estimate. A model will be constructed, containing treatment and the stratification factors, to ensure that any output from the Cox modelling is likely to be consistent with the results of the stratified log-rank test.

Additionally, for each subgroup, the HR (Arm 1: Arm 2) and 95% CI will be calculated from a Cox proportional hazards model, with treatment as the only covariate. These will be presented on a forest plot including the HR and 95% CI from the overall population.

The secondary analysis of EFS will be performed using the same methodology as for the primary analysis described above.

If there are too few events available for a meaningful analysis of a particular subgroup (it is not considered appropriate to present analyses where there are less than 20 events in a subgroup), the relationship between that subgroup and EFS will not be formally analyzed. In this case, only descriptive summaries will be provided.

9.4.2 Analysis of secondary endpoints

9.4.2.1 Proportion of patients alive and event free at 24 months after last randomization (EFS24)

EFS24 will be summarized (using the Kaplan-Meier curve) and presented by treatment arm and will be compared between treatments by using the KM estimator of EFS at 24 months for each treatment to obtain the HR. Note: 24 months equates to study day 731.

9.4.2.2 Proportion of patients who achieve <P2

The primary analysis for proportion of patients who achieve <P2 will be based on assessment per local pathology review. The proportion of patients who achieve <P2 will be compared between Arm 1 and Arm 2 using logistic regression models adjusted for the stratification factors. The results of the analysis will be presented in terms of an odds ratio together with its corresponding 95% CI and p-value.

9.4.2.3 Overall Survival (OS)

OS will be analyzed using stratified log-rank tests, using the same methodology as described for the primary EFS endpoint (see Section 9.4.1.3).

9.4.2.4 Proportion of patients alive at 5 years after randomization (OS5)

OS5 will be summarized using the same methodology as EFS24 (see Section 9.4.2.1).

9.4.2.5 Metastasis-free survival (MFS)

MFS will be analyzed using stratified log-rank tests, using the same methodology as described for the primary EFS endpoint (see Section 9.4.1.3). The effect of treatment will be estimated by the HR together with its corresponding 95% CI for the ITT population.

9.4.2.6 Disease-specific survival (DSS)

DSS will be analyzed using the same methodology as described for MFS (see Section 9.4.2.5 9.4.2.5).

9.4.2.7 Disease-free survival (DFS)

DFS will be analyzed using the same methodology as described for MFS (see Section 9.4.2.5 9.4.2.5).

9.4.2.8 Proportion of patients who undergo radical cystectomy

The proportion of patients who undergo radical cystectomy will be presented together with its corresponding 95% CI.

9.4.2.9 Patient-reported outcomes

EORTC QLQ-C30

The main PRO measures identified in the secondary objectives are global health status/QoL, physical functioning, fatigue, and pain subscales of the EORTC QLQ-C30. However, separate analysis will be conducted for global health status/QoL, functions (physical, role, cognitive, social, and emotional), fatigue, and pain. PROs are not part of the main MTP and will be analyzed as supportive endpoints.

Summaries for compliance (the number of evaluable forms divided by the number of expected forms) for each treatment arm will be produced.

The primary assessment of global health status/QoL, functioning, and symptoms will be focused on the adjusted mean change from baseline using a mixed-model for repeated-measures (MMRM) analysis of all the post-baseline scores for each visit. The model will include treatment, visit, treatment by visit interaction, and stratification variables as explanatory variables, and the baseline score as a covariate. Adjusted mean change from baseline estimates per treatment arm and corresponding 95% CIs will be presented along with an overall estimate of the treatment difference, 95% CI, and p-value.

Supportive analysis of global health status/QoL, functioning, and symptoms will be time to definitive or sustained clinically meaningful deterioration analyzed using a stratified log-rank test as described for the primary EFS endpoint. Separate analysis will be conducted for global health status/QoL, functions, fatigue, and pain. The effect between Arm 1 and Arm 2 will be estimated by the HR together with its corresponding CI and p-value. Kaplan-Meier plots will be presented by treatment arm. Summaries of the number and percentage of patients who have an event as well as who were censored will be provided along with the medians for each treatment.

Summary tables of visit responses for each EORTC QLQ-C30-scale/item score (global health status/QoL, 5 functions and all symptoms) and for each visit (improvement, deterioration, and no change) will be presented by treatment arm. In addition, summary tables of the best overall response will be provided for the following domains by treatment arm: global health status/QoL, functions (physical, role, cognitive, emotional and social), fatigue and pain. Occurrence of symptom and QoL/function improvement based on the best overall response will be compared between treatment arms using a logistic regression model. The odds ratio, p-value, and 95% CI will be presented graphically on a forest plot.

Summaries of absolute and unadjusted change from baseline values of each EORTC QLQ-C30 scale/item will be reported by visit for each treatment arm. Graphical presentations may also be produced as appropriate.

Alternative thresholds for meaningful change in the EORTC QLQ-C30 scales will be derived from anchor-based methods using the PGIS and/or PGIC. The analyses will be supplemented with empirical cumulative distribution function and probability density function curves as necessary. Details will be described further in the SAP.

EQ-5D-5L

Descriptive statistics, graphs, and listings will be reported for health state utility index values (United Kingdom base case) and visual analogue scale by visits as well as the change in these scores from baseline. To support future economic evaluations of the study treatment, additional appropriate analyses may be undertaken, for example, mean health state utility pre- and post-treatment and pre- and post-progression/recurrence.

PGIC

PGIC data will be presented using summaries and descriptive statistics based on the FAS. The proportion of patients in each response category at each visit will be presented by treatment arm. Further details will be provided in the SAP.

PGIS

PGIS data will be presented using summaries and descriptive statistics based on the FAS. The proportion of patients in each response category at each visit will be presented by treatment arm. Also, the change from baseline in the severity of general cancer symptoms will be presented as the proportion of patients with no change (eg, mild to mild), 1 category improvement (eg, mild to none), ≥2 category improvement (eg, severe to mild), 1 category deterioration (eg, none to mild), and ≥2 category deterioration (eg, mild to severe) at each visit by treatment arm. The data may be analyzed based on the following re-grouped categories: None (no symptoms), Mild (very mild and mild), Moderate, and Severe (very severe and severe). Further details will be provided in the SAP.

PRO-CTCAE

The PRO-CTCAE data will be presented using summaries and descriptive statistics based on the FAS. Further details will be provided in the SAP.

PRO compliance

Summary measures of visit and overall compliance rates will be derived for each PRO questionnaire (EORTC QLQ-C30, PGIC, PGIS, EQ-5D-5L, and PRO-CTCAE, respectively). These will be based upon the following criteria:

- Expected: Number of patients still under PRO follow-up expected to complete a questionnaire at a scheduled assessment time. For patients whose disease has progressed/recurred, the latest of progression/recurrence and safety follow-up will be used to assess whether the patient is still under PRO follow-up at the specified assessment time. Date of study discontinuation will be mapped to the nearest visit date to define the number of expected patients/forms.

- Received: Number of patients from whom a completed questionnaire with at least 1 item completed was received plus those recorded as “subject too heavily affected by symptoms of disease under investigation” is answered as a reason for not completing the questionnaire.

- Evaluable: Number of patients for whom at least 1 subscale (eg, single-item subscale) can be determined or "subject too heavily affected by symptoms of disease under investigation" is answered as a reason for not completing the form.

Compliance rate (visit): Compliance will be calculated separately for each visit, including baseline, for each treatment arm as (Evaluable ÷ Expected) × 100.

Evaluable rate: Evaluability rate will be calculated separately for each visit, including baseline, for each treatment arm as (Evaluable ÷ Received) × 100.

Overall compliance rate: Patients are counted as Received/Evaluable if they have a Received/Evaluable baseline and at least 1 Received/Evaluable post-baseline questionnaire. Rates are expressed in percentages.

Missing values

Missing data will be handled based on the EORTC QLQ-C30 scoring manual.

9.4.3 Safety analyses

Safety and tolerability data will be presented by treatment arm using the SAS.

Data from all cycles of treatment will be combined in the presentation of safety data. AEs (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient. The number of patients experiencing each AE will be summarized by treatment arm and CTCAE grade. Additionally, data presentations of the rate of AEs per person-years at risk may be produced.

Other safety data will be assessed in terms of physical examination, laboratory assessments, vital signs, and ECGs. Exposure to durvalumab and G+C will be summarized. Time on study and durvalumab and G+C dosing delays will also be summarized. At the end of the study, appropriate summaries of all safety data will be produced, as defined in the SAP.

9.4.4 Pharmacokinetic data

PK concentration data will be listed for each patient and each dosing day, and a summary will be provided for all evaluable patients using the PK analysis set.

9.4.5 Immunogenicity data

Immunogenicity results will be listed by patient, and a summary will be provided by the number and percentage of patients who develop detectable ADAs against durvalumab. The immunogenicity titer and neutralizing ADA data will be listed for samples confirmed positive for the presence of anti-durvalumab antibodies.

The effect of immunogenicity as well as the effect of its neutralizing properties on PK, pharmacodynamics, efficacy, and safety will be evaluated, if the data allow. A detailed plan will be written by the AstraZeneca Clinical Pharmacology group or designee.

9.4.6 Pharmacokinetic/pharmacodynamic relationships

If the data are suitable, the relationship between PK exposure and efficacy/safety parameters may be investigated graphically or using an appropriate data modeling approach.

9.4.7 Biomarker data

The relationship of PD-L1 expression and, if applicable, of exploratory biomarkers to clinical outcomes (including but not restricted to) of pCR, EFS, EFS24, proportion of patients who achieve <P2, OS, OS5, MFS, DSS, and proportion of patients who undergo radical cystectomy may be presented.

PD-L1 expression determined by IHC will be reported in the CSR. Summaries and analyses for exploratory biomarkers will be documented in a separate analysis plan and will be reported outside the CSR in a separate report.

9.5 Interim analyses

EFS

EFS will be tested at two interim time points and a final time point.

For the dual-primary EFS endpoint in MIBC patients (Arm 1 versus Arm 2), two superiority interim analyses for EFS will be conducted: the first when the pCR analysis is conducted and the second based on a data cut-off when approximately 410 EFS events have occurred (39% maturity, 410/1050) across the 2 arms in ITT, or in April 2024 whichever occurs first (approximately 31 months after the last patient is randomized). The final analysis will be conducted when approximately 451 EFS events have occurred (43% maturity, 451/1050) across Arm 1 and Arm 2 or in June 2025 (approximately 45 months after the last patient is randomized), whichever occurs first.

The alpha level allocated to the EFS will be controlled at the interim and final time points using the Lan DeMets spending function that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends on the proportion of information available. The first interim analysis has been performed with 301 events and the 2-sided alpha of 0.69% (calculated assuming 509 total events as stated in the previous protocol) has been spent. Applying this alpha spent at the first interim analysis and considering the revised total of 451 events, if exactly 91% of the target 451 events are available at the time of the second interim analysis, with overall 2-sided alpha level of 4.9%, the 2-sided alpha to be applied at the second interim analysis, and final analysis would be, 3.5%, and 3.9%, respectively. However, the derivation of actual rejection boundary for any interim analysis will use the observed number of events at the interim analysis and the number of events planned for the final analysis. For the planned final analysis, the rejection boundaries will be derived based on the observed number of events and previous rejection boundaries using the generalized Haybittle-Peto method (SAS manual), exhausting any remaining alpha for the analysis.

OS

OS will be tested at 2 interim time points and a final time point in accordance with the hierarchical multiple testing strategy.

The first interim analysis of OS will be conducted at the time when the second interim EFS analysis is conducted (but will only be tested if EFS is positive via the MTP). A second interim analysis will be conducted at the time when the final EFS analysis is conducted. At the time of the first interim analysis, approximately 288 OS events are estimated to occur (27% maturity, 288/1050) across Arm 1 and Arm 2. At the time of the second interim analysis, approximate 318 OS events are estimated to occur (30% maturity, 318/1050) across Arm 1 and Arm 2. The final analysis will be conducted when approximately 428 OS events have occurred (41% maturity, 428/1050) across Arm 1 and Arm 2, which is expected to be approximately 60 months after the last participant is randomized.

The alpha level allocated to the OS will be interim and final time points using the Lan DeMets spending function that approximates an O'Brien Fleming approach, where the alpha level applied at the interim depends on the proportion of information available. If exactly 67% (288/428) and 74% (318/428) of the target events are available at the time of the first interim analysis and the second interim analysis, with overall 2-sided alpha level of 4.9%, the smallest treatment difference that could be statistically significant will be an average HR of 0.82, and the 2-sided alpha to be applied at the first, the second interim analysis, and final analysis would be 1.2%, 1.5%, 4.3 %, respectively.

The derivation of actual rejection boundary for any interim analysis will use the observed number of events at the interim analysis and the number of events planned for the final analysis. For the planned final analysis, the rejection boundaries will be derived based on the observed number of events and previous rejection boundaries using the generalized Haybittle-Peto method (SAS manual), exhausting any remaining alpha for the analysis. The interim analyses will be assessed by an IDMC. Details of the plan and communication process will be provided in the SAP and in the IDMC charter.

9.6 Independent data monitoring committee

A data monitoring committee will be utilized for this study.

The safety of all AstraZeneca clinical studies is closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

An IDMC comprised of independent experts will be convened and will meet approximately 6 months after the study has started or after the first 90 patients have been randomized, whichever occurs first, to review safety assessments and make recommendations to continue, amend, or stop the study based on safety findings. The IDMC will separately assess the safety of durvalumab + gemcitabine/cisplatin in Japanese patients for the initial data review meetings and make recommendation if additional separate safety reviews are required. The committee will

meet approximately every 6 months thereafter. For the interim analysis, the IDMC will review interim data and inform the Sponsor whether the interim boundaries specified in Section 9.4.3 are crossed. Full details of the IDMC procedures, processes, and interim analyses can be found in the IDMC Charter.

Interim safety monitoring will be conducted by an IDMC. Details of the plan and communication process will be provided in an IDMC Charter.

The recommendations from the IDMC will not reveal the results of the analyses but will take the form of "Continue/Modify/Recommend early submission/Stop."

10. REFERENCES

Aaronson et al 1993
Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. JNCI 1993;85(5):365-76.

Abdelhafez and Williams 2017
Abdelhafez M, Williams M. Safety and efficacy of gemcitabine-cisplatin split dose as a neoadjuvant chemotherapy for muscle invasive bladder cancer. J Urol 2017;197(4S):e1194.

AJCC Cancer Staging Manual, 8th Edition
Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, et al, editors. AJCC Cancer Staging Manual, Eighth Edition. American Joint Committee on Cancer (AJCC); 2017. Available upon request.

Alexandrov et al 2013
Alexandrov LB, Nik-Zainal S, Wedge DC, Aparicio SAJR, Behjati S, Blankin AV, et al. Signatures of mutational processes in human cancer. Nature 2013;500:415-21.

Babjuk et al 2014
Babjuk M, Böhle A, Burger M, Compérat E, Kaasinen E, Palou J, et al. Guidelines on non muscle-invasive bladder cancer (Ta, T1, and CIS). EAU Guidelines Office, Arnhem, The Netherlands. European Association of Urology; 2014.

Bajorin et al 2021
Bajorin DF, Witjes JA, Gschwend JE, Schenker BP, Valderrama BP, Tomita Y, et al. Adjuvant Nivolumab versus Placebo in Muscle-Invasive Urothelial Carcinoma. N Engl J Med 2021;384(22):2102-2114.

Balar et al 2017
Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389(10064):67-76.

Basch et al 2009
Basch E, Jia X, Heller G, Barz A, Sit L, Fruscione M, et al. Adverse symptom event reporting by patients vs clinicians: relationship with clinical outcomes. Journal of National Cancer Institute 2009;101:1624-1632.

BAVENCIO [package insert] 2017
BAVENCIO [package insert]. New York, USA. 2017.

Bellmunt et al 2007
Bellmunt J, Paz-Ares L, Cuello M, Cecere FL, Albiol S, Guillem V, et al. Gene expression of ERCC1 as a novel prognostic marker in advanced bladder cancer patients receiving cisplatin-based chemotherapy. Ann Oncol 2007;18(3):522-8.

Bellmunt et al 2017
Bellmunt J, Powles T, Vogelzang N. A review on the evolution of PD-1/PD-L1 immunotherapy for bladder cancer: The future is now. Cancer Treat Rev 2017;54:58-67.

Bellmunt et al 2021
Bellmunt J, Hussain M, Gschwend J, Albers P, Oudard S, Castellano D, et al. Adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma (IMvigor010): a multicentre, open-label, randomized, phase 3 trial. Lancet Oncol. 2021;22(4):525-37

Birgitte et al 2008
Birgitte A, Sengelov L, Von der Maase H, et al. Gemcitabine and cisplatin in locally advanced and metastatic bladder cancer; 3 or 4 week schedule? Acta Oncologica 2008;47:110-9.

Boccardo and Palmeri 2006
Boccardo F, Palmeri L. Adjuvant chemotherapy of bladder cancer. Ann Oncol 2006;17(Supplement 5):v129-32.

Brahmer et al 2012
Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366(26):2455-65.

Burger et al 2013
Burger M, Catto JWF, Dalbagni G, Grossman HB, Herr H, Karakiewicz P, et al. Epidemiology and Risk Factors of Urothelial Bladder Cancer. European Urology 2013;63(2):234-241.

Burman et al 2009
Burman CF, Sonesson C, Guilbaud O. A recycling framework for the construction of Bonferroni based multiple tests. Stat Med 2009;28:739-61.

Cancer Genome Atlas Research Network 2014
Cancer Genome Atlas Research Network. Comprehensive molecular characterization of urothelial bladder carcinoma. Nature 2014;507(7492):315-22.

Cathomas et al 2022
Cathomas R, Rothschild S, Hayoz S, Spahn M, Özdemir B, Kiss B, et al. Perioperative chemoimmunotherapy with durvalumab for operable muscle-invasive urothelial carcinoma (MIUC): Primary analysis of the single arm phase II trial SAKK 06/17. J Clin Oncol, 2022 ASCO Annual Meeting Abstracts;40(16s): (suppl; abstr 4515).

Chang et al 2017
Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/ASTRO/SUO guideline. American Urological Association 2017;1-42.

Cox 1972
Cox DR. Regression models and life tables. J Royal Stst Society 1972;Series B 34(2):187-220.

Criteria Committee NYHA 1964
Criteria Committee, New York Heart Association, Inc. Diseases of the heart and blood vessels. Nomenclature and criteria for diagnosis, 6th ed. Boston (MA), Little, Brown and Co.; 1964. (Available upon request).

Dash et al 2006
Dash A, Galsky MD, Vickers AJ, Serio AM, Koppie TM, Dalbagni G, et al. Impact of renal impairment on eligibility for adjuvant cisplatin based chemotherapy in patients with urothelial carcinoma of the bladder. Cancer 2006;107(3):506-13.

Dash et al 2008
Dash A, Pettus JA, Herr HW, Bochner BH, Dalbagni G, Donat SM, et al. A role for neoadjuvant gemcitabine plus cisplatin in muscle-invasive urothelial carcinoma of the bladder: a retrospective experience. Cancer 2008;113(9):2471-77.

Desai et al 2016
Desai NB, Scott SN, Zabor EC, Cha EK, Hreiki J, Sfakianos JP, et al. Genomic characterization of response to chemoradiation in urothelial bladder cancer. Cancer 2016;122(23):3715-23.

Dindo et al 2004
Dindo D, Demartines N, Clavien P. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients results of a survey. Ann Surg 2004;240(2):205-213.

Dunn et al 2004
Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004;22:329-60.

European Medicines Agency 2013
Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man; Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials. 2012. Available at URL: https://www.ema.europa.eu/en/appendix-1-guideline-evaluation-anticancer-medicinal-products-man-methodological-consideration-using-progression-free-survival-pfs-or-disease-free-survival-dfs-confirmatory-trials-scientific-guideline.

EuroQol Group 1990
EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208.

Fairman et al 2014
Fairman D, Narwal R, Liang M, Robbins PB, Schneider A, Chavez C, et al. Pharmacokinetics of durvalumab, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumours. J Clin Oncol, 2014 ASCO Annual Meeting Abstracts;32(5s): (suppl; abstr 2602).

Fayers 2001
Fayers PM. Interpreting quality of life data: population-based reference data for the EORTC QLQ-C30. Eur J Cancer 2001;37(11):1331-4.

Ferlay et al 2015
Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.

Flaig et al 2018
Flaig TW, Spiess PE, Agarwal N, Bangs R, Boorjian SA, Buyyounouski MK et al. Bladder Cancer, Version 5.2018: Featured update to the NCCN guidelines. J Nat Comp Cancer Network 2018; 16(9): 1041-1053

Fleischer et al 2011
Fleischer F, Gaschler-Markefski B, Bluhmki E. How is retrospective independent review influenced by investigator-introduced informative censoring: a quantitative approach. Stat Med 2011;30(29):3373-86.

Galsky et al 2015
Galsky MD, Pal SK, Chowdhury S, Harshman LC, Crabb SJ, Wong Y-N, et al. Comparative effectiveness of gemcitabine plus cisplatin versus methotrexate, vinblastine, doxorubicin, plus cisplatin as neoadjuvant therapy for muscle-invasive bladder cancer. Cancer 2015;121(15):2586-93.

Gill et al 2017
Gill DM, Sonpavde G, Pal SK, Agarwal N. Which checkpoint inhibitor? An embarrassment of riches for bladder cancer. Immunotherapy. 2017;9(6):463-466.

Grossman et al 2003
Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003;349:859-66.

Herdman et al 2011
Herdman M, Gudex C, Lloyd A et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res: 1–10; 2011 Dec;20(10):1727-36.

Hirano et al 2005
Hirano F, Kaneko K, Tamura H, Dong H, Wang S, Ichikawa M, et al. Blockade of B7-H1 and PD-1 by monoclonal antibodies potentiates cancer therapeutic immunity. Cancer Res 2005;65(3):1089-96.

Horn et al 2018
Horn L, Mansfield AS, Szcaesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolimab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379(23):2220-2229.

Howie et al 2018
Howie LJ, Singh H, King-Kallimanis B, Roydhouse J, Theoret MR, Blumenthal GM, et al. Patient-reported outcomes in PD-1/PD-L1 inhibitor registration trials: FDA analysis of data

submitted and future directions. J Clin Oncol, 2018 ASCO-SITC Clinical Immuno-Oncology Symposium, 36 (suppl 5S; abstr 134).

Hussain et al 2012
Hussain SA, Palmer DH, Lloyd B, Collins SI, Barton D, Ansari J, et al. A study of split-dose cisplatin-based neoadjuvant chemotherapy in muscle-invasive bladder cancer. Oncology Letters 2012;3:855-59.

IMFINZI [package insert] 2017
IMFINZI [package insert]. Cambridge, England: AstraZeneca; 2017.

Inman et al 2007
Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, Frank I, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. Cancer 2007;109(8):1499-5.

International Collaboration of Trialists 2011
International Collaboration of Trialists, Medical Research Council Advanced Bladder Cancer Working Party (now the National Cancer Research Institute Bladder Cancer Clinical Studies Group), European Organisation for Research and Treatment of Cancer Genito-Urinary Tract Cancer Group, Australian Bladder Cancer Study Group, National Cancer Institute of Canada Clinical Trials Group, Finnbladder, Norwegian Bladder Cancer Study Group, et al. International phase III trial assessing neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: long-term results of the BA06 30894 trial. J Clin Oncol 2011; 29(16):2171-7.

Iwai et al 2002
Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc Natl Acad Sci USA 2002;99:12293-7.

Iyer et al 2016
Iyer G, Price J, Bourgeois S, Armstrong E, Huang S, Harari PM. Insulin growth factor 1 like receptor (IGF-1R). BMC Cancer 2016;16(1):773.

Jan et al 2016
Jan A, Dolan D, Lombardi K and Gupta S. Tolerability of Gemcitabine Plus Cisplatin for Treatment of Urothelial Cancer in the Elderly Population. Clin Genitourin Cancer 2016;14.3:257-263.

Keir et al 2008
Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008;26:677-704.

KEYTRUDA [package insert] 2018
KEYTRUDA [package insert]. New Jersey, USA. 2018.

Kim et al 2015
Kim PH, Cha EK, Sfakianos JP, Iyer G, Zabor EC, Scott SN, et al. Genomic predictors of survival in patients with high-grade urothelial carcinoma of the bladder. Eur Urol 2015;67(2):198-201.

Kim et al 2017
Kim HS, Jeong CW, Kwak C, Kim HH, Ku JH. Adjuvant chemotherapy for muscle-invasive bladder cancer: a systematic review and network meta-analysis of randomized clinical trials. Oncotarget 2017;8(46):81204-14. Available at URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5655275/.

Klein et al 2007
Klein JP, Logan B, Harhoff M, Andersen PK. Analyzing survival curves at a fixed point in time. Stat Med 2007;26(24):4505-19.

Kodumudi et al 2010
Kodumudi KN, Woan K, Gilvary DL, Sahakian E, Wei S, Djeu JY. A novel chemoimmunomodulating property of docetaxel: suppression of myeloid-derived suppressor cells in tumor bearers. Clin Cancer Res 2010;16(18):4583-94.

Kroemer et al 2013
Kroemer G, Galluzzi L, Kepp O, Zitvogel L. Immunogenic cell death in cancer therapy. Annu Rev Immunol 2013;31:51-72.

Lan and DeMets 1983
Lan KKG, DeMets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.

Langer et al 2016
Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomized, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol 2016;17(11):1497-1508.

Leow et al 2014
Leow JJ, Martin-Doyle W, Rajagopal PS, Patel CG, Anderson EM, Rothman AT, et al. Adjuvant chemotherapy for muscle-invasive bladder cancer: a 2013 updated systematic review and meta-analysis of randomized trials. Eur Urol 2014;66(1):42-54.

Lerner et al 2016
Lerner SP, Bajorin DF, Dinney CP, Efstathiou JA, Groshen S, Hahn NM, et al. Summary and Recommendations from the National Cancer Institute's Clinical Trials Planning Meeting on Novel Therapeutics for Non-Muscle Invasive Bladder Cancer. Bl Cancer 2016;2(2):165-202.

Litwin et al 1998
Litwin MS, Lubeck DP, Henning JM, et al. Differences in urologist and patient assessments of health related quality of life in men with prostate cancer: Results of the CaPSURE database. J Urol 1998;159:1988-92.

Liu et al 2010
Liu WM, Fowler DW, Smith P, Dalgleish AG. Pre-treatment with chemotherapy can enhance the antigenicity and immunogenicity of tumours by promoting adaptive immune responses. Br J Cancer 2010;102(1):115-23.

Massard et al 2016
Massard C, Gordon M, Sharma S, Rafii S, Wainberg Z, Luke J, et al. Safety and efficacy of durvalumab (MEDI4736), an anti-programmed cell death ligand-1 immune checkpoint inhibitor, in patients with advanced urothelial bladder cancer. J Clin Oncol 2016;34(26):3119-25.

Mellman et al 2011
Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480(7378):480-9.

Mullane et al 2016
Mullane SA, Werner L, Guancial EA, Lis RT, Stack EC, Loda M, et al. Expression levels of DNA damage repair proteins are associated with overall survival in platinum-treated advanced urothelial carcinoma. Clin Genitourin Cancer 2016;14(4):352-9.

Narwal et al 2013
Narwal R, Roskos LK, Robbie GJ. Population pharmacokinetics of sifalimumab, an investigational anti-interferon-α monoclonal antibody, in systemic lupus erythematosus. Clin Pharmacokinet 2013;52:1017–27.

National Comprehensive Cancer Network 2019
National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Bladder Cancer. 2019. Available from: https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf. Accessed 06 March 2019.

Necchi et al 2018
Necchi A, Briganti A, Bianchi M, Raggi D, Giannatempo P, Luciano R, et al. Preoperative pembrolizumab (pembro) before radical cystectomy (RC) for muscle-invasive urothelial bladder carcinoma (MIUC): Interim clinical and biomarker findings from the phase 2 PURE-01 study. J Clin Oncol 2018;36(15_suppl):4507.

Ng et al 2006
Ng CM, Lum BL, Gimenez V, Kelsey S, Allison D. Rationale for fixed dosing of pertuzumab in cancer patients based on population pharmacokinetic analysis. Pharm Res 2006;23(6):1275–84.

Okazaki and Honjo 2007
Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int Immunol 2007;19(7):813-24.

Okudaira et al 2009
Okudaira K, Hokari R, Tsuzuki Y, Okada Y, Komoto S, Watanabe C, et al. Blockade of B7-H1 or B7-DC induces an antitumor effect in a mouse pancreatic cancer model. Int J Oncol 2009;35(4):741-9.

Osoba et al 1998
Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. J Clin Oncol 1998;16(1):139-44.

Pardoll 2012
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 2012;12:252-64.

Powles et al 2014
Powles T, Eder JP, Fine GD, Braiteh FS, Loriot Y, Cruz C, et al. MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. Nature 2014;515(7528):558-62.

Powles et al 2017
Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol 3(9): doi: 10.1001/jamaoncol.2017.2411. Epub 2017 Sep 14.

Powles et al 2018
Powles T, Rodriguez-Vida A, Duran I, Crabb SJ, Van Der Heijden MS, Pous AF, et al. A phase II study investigating the safety and efficacy of neoadjuvant atezolizumab in muscle invasive bladder cancer (ABACUS). J Clin Oncol 36(15_suppl):4506.

Qin et al 2016
Qin A, Coffey DG, Warren EH, Ramnath N. Mechanisms of immune evasion and current status of checkpoint inhibitors in non-small cell lung cancer. Cancer Med 2016; 9:2169–70.

Rizvi et al 2015
Rizvi N, Brahmer J, Ou S-H, Segal NH, Khleif SN, Hwu WJ. Safety and clinical activity of MEDI4736, an anti-programmed cell death-ligand-1 (PD-L1) antibody, in patients with nonsmall cell lung cancer (NSCLC). J Clin Oncol 2015;33:Abstract 8032.

Rizvi et al 2016
Rizvi NA, Hellmann MD, Brahmer JR, Juergens RA, Borghaei H, Gettinger S, et al. Nivolumab in Combination With Platinum-Based Doublet Chemotherapy for First-Line Treatment of Advanced Non-Small-Cell Lung Cancer. JCO 2016;34:2969-79.

Rosenberg et al 2016
Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387(10031):1909-20.

Rubin et al 2014
Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, et al. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis 2014;58(3):e44-100.

SAS manual
https://documentation.sas.com/doc/en/pgmsascdc/9.4_3.4/statug/statug_seqdesign_details31.htm.

Segal et al 2015
Segal NH, Ou S-HI, Balmanoukian AS, Fury MG, Massarelli E, Brahmer JR, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol 2015;33:Abstract 3011.

Sonpavde et al 2009
Sonpavde G, Goldman BH, Speights, VO, Lerner SP, Wood DP, Vogelzang NJ, et al. Quality of pathologic response and surgery correlate with survival for completely resected bladder cancer following neoadjuvant chemotherapy. Cancer 2009;115(18):4104-09.

Sprangers et al 1992
Sprangers MA, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease: A review. J Clin Epidemiol. 1992;45:743-760.

Stewart et al 2015
Stewart R, Morrow M, Hammond SA, Mulgrew K, Marcus D, Poon E, et al. Identification and characterization of MEDI4736, an antagonistic anti-PD-L1 monoclonal antibody. Cancer Immunol Res 2015;3(9):1052-62.

Sun and Chen 2010
Sun X, Chen C. Comparison of Finkelstein's Method with the conventional approach for interval-censored data analysis. Stat Biopharm Res 2010;2(1):97-108.

TECENTRIQ [package insert] 2018
TECENTRIQ [package insert]. California, USA. 2018.

Teo et al 2017
Teo MY, Bambury RM, Zabor EC, Jordan E, Al-Ahmadie H, Boyd ME, et al. DNA damage response and repair gene alterations are associated with improved survival in patients with platinum-treated advanced urothelial carcinoma. Clin Cancer Res 2017;23(14):3610-8.

Topalian et al 2012
Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366:2443-54.

Torre et al 2015
Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.

U.S. Department of Health and Human Services et al 2018
U.S. Department of Health and Human Services Food and Drug Administration Oncology Center of Excellence Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER), Clinical trial endpoints for the approval of cancer drugs and biologics: Guidance for industry. 2018. Available at URL: https:// www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics. 2018

VENTANA PD-L1 (SP263) Assay Package Insert
VENTANA PD-L1 (SP263) Assay. Ventana Medical Systems, Inc. Tucson, Arizona, USA. 2017. Available at: https://www.accessdata.fda.gov/cdrh_docs/pdf16/p160046c.pdf.

Von der Maase et al 2000
Von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, Phase III study. J Clin Oncol 2000;18:3068–77.

Wang et al 2009
Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol 2009;49(9):1012–24.

Whitehead and Whitehead 1991
Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. Stat Med 1991;10(11):1665-77.

Witjes et al 2016
Witjes JA, Comperat E, Cowan NC, De Santis M, Gakis G, Lebret T, et al. EAU Guidelines on muscle-invasive and metastatic bladder cancer. European Association of Urology (EAU) Guidelines. 2016.

Zhang et al 2008
Zhang C, Wu S, Xue X, Li M, Qin X, Li W, et al. Antitumor immunotherapy by blockade of the PD-1/PD-L1 pathway with recombinant human PD-1-IgV. Cytotherapy 2008;10(7):711-9.

Zhang et al 2012
Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed dosing versus body size-based dosing of therapeutic peptides and proteins in adults. J Clin Pharmacol 2012;52(1):18–28.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

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

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements

relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

- For all studies except those utilizing medical devices investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

Regulatory Reporting Requirements for Serious Breaches

- Prompt notification by the investigator to the sponsor of any (potential) serious breach of the protocol or regulations is essential so that legal and ethical obligations are met.
- A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.
- If any (potential) serious breach occurs in the course of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives immediately after he or she becomes aware of it.
- In certain regions/countries, the sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about such breaches.
- The sponsor will comply with country-specific regulatory requirements relating to serious breach reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators. If EU Clinical Trials Regulation 536/2014 applies, the sponsor is required to enter details of serious breaches into the European Medicines Agency (EMA) Clinical Trial Information System (CTIS). It is important to note that redacted versions of serious breach reports will be available to the public via CTIS.
- The investigator should have a process in place to ensure that:
- the site staff or service providers delegated by the investigator/institution are able to identify the occurrence of a (potential) serious breach
- a (potential) serious breach is promptly reported to the sponsor or delegated party, through the contacts (e-mail address or telephone number) provided by the sponsor

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.

Patients must be informed that their participation is voluntary. Patients or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

If a patient declines to participate in any voluntary exploratory genetic research component of the study, there will be no penalty or loss of benefit to the patient and he/she will not be excluded from other aspects of the study.

If a patient's partner becomes pregnant during or within 90 days after the last dose of durvalumab, the partner is asked to sign the "Adult Study Informed Consent Form for Pregnant Partners of Study Patients" and provide information about the pregnancy accordingly.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. The patient will give a separate agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will indicate this in the ICF. If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples already have been analyzed at the time of the request, AstraZeneca will not be obliged to destroy the results of this research

A 4 Data protection

The ICF will incorporate wording that complies with relevant data protection and privacy legislation. In some cases, such wording will be in a separate accompanying document. AstraZeneca will not provide individual genotype results to patients, their family members, their

general physician, any insurance company, any employer, or any other third party, unless required to do so by law.

Precautions are taken to preserve confidentiality and prevent genetic data from being linked to the identity of the patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, an AstraZeneca Physician or an Investigator might know a patient's identity and might also have access to his or her genetic data. Also, regulatory authorities may require access to the relevant files. Even so, the patient's medical information and the genetic files would remain physically separate.

Each patient will be assigned a unique identifier by the Sponsor. Any patient records or data sets transferred to the Sponsor will contain only the identifier; patient names or any information which would make the patient identifiable will not be transferred.

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

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

A 5 Committees structure

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 6 Dissemination of clinical study data

Any results both technical and lay summaries for this trial, will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries, due to scientific reasons as otherwise statistical analysis is not relevant.

A description of this clinical trial will be available on *http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov* as will the summary of the *main* study results when they are available. The clinical trial and/or summary of *main* study results may also be available on other websites according to the regulations of the countries in which the *main* study is conducted.

A 7 Data quality assurance

All patient 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 is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

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.

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 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 patients 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 signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a minimum of 25 years after study archiving or as required by local regulations, according to the AstraZeneca Global retention and Disposal (GRAD) Schedule. No records may be destroyed during the retention period without the written approval of AstraZeneca. No records may be transferred to another location or party without written notification to AstraZeneca.

A 8 Source documents

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

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

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study are defined as source documents. Source data are contained in source documents (original records or certified copies).

A 9 Study and site closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/ IEC or local health authorities, the Sponsor's procedures, or the GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

A 10 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, 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.

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.

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

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event (AE) is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (eg, an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

B 2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the patient or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

‘Life-threatening’ means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient’s death. ‘Life-threatening’ does not mean that had an AE occurred in a more severe form it might have caused death (eg, hepatitis that resolved without hepatic failure).

B 4 Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (eg, bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

B 6 CTCAE grade

The grading scales found in the revised National Cancer Institute CTCAE Version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the criteria recommended in the CTCAE manual that converts severity levels into CTCAE grades should be used. A copy of the CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov). The applicable version of CTCAE should be described clearly.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix B 2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix B 2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix B 2.

B 7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred

- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error (eg, medication prepared incorrectly, even if it was not actually given to the participant)
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated (eg, tablet dissolved in water when it should be taken as a solid tablet)
- Drug not stored as instructed (eg, kept in the fridge when it should be at room temperature)
- Wrong participant received the medication (excluding IVRS/IWRS errors)
- Wrong drug administered to participant (excluding IVRS/IWRS errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
- Participant accidentally missed drug dose(s), eg, forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

Appendix C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each center keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

Samples retained for further use will be stored in the AZ-assigned biobanks and will be registered by the AstraZeneca Biobank Team during the entire life cycle.

If required, AstraZeneca will ensure that remaining biological samples are returned to the site according to local regulations or at the end of the retention period, whichever is sooner.

C 2 Withdrawal of Informed Consent for donated biological samples

AstraZeneca ensures that biological samples are returned to the source or destroyed at the end of a specified period as described in the informed consent.

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an integral part of the study, then the patient is withdrawn from further study participation.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient
- temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix D Genetics

D 1 Use/analysis of DNA

Genetic variation may impact a patient's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.

AstraZeneca intends to collect and store DNA for genetic research to explore how genetic variations may affect clinical parameters, risk and prognosis of diseases, and the response to medications. Genetic research may lead to better understanding of diseases, better diagnosis of diseases or other improvements in health care and to the discovery of new diagnostics, treatments or medications.

In addition, collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Genetic research may consist of the analysis of the structure of the subject's DNA, ie, the entire genome.

The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on durvalumab continues but no longer than 15 years or other period as per local requirements.

D 2 Genetic research plan and procedures

Selection of genetic research population

Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

Inclusion criteria

- For inclusion in this genetic research, subjects must fulfil all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**: Provide informed consent for the genetic sampling and analyses.

Exclusion criteria
Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Withdrawal of consent for genetic research:
Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary withdrawal will not prejudice further treatment. Procedures for withdrawal are outlined in Appendix C 2 of the main Clinical Study Protocol.

Collection of samples for genetic research
The blood sample for genetic research will be obtained from the patients pre-dose at the first dosing visit. Although DNA is stable, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an AE, such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at the first dosing visit, it may be taken at any visit until the last study visit. Only one sample should be collected per patient for genetics during the study. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples
The processes adopted for the coding and storage of samples for genetic analysis are important to maintain subject confidentiality. Samples will be stored for a maximum of 15 years, from the date of last subject last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

An additional second code will be assigned to the blood either before or at the time of DNA extraction replacing the information on the sample tube. Thereafter, the sample will be identifiable only by the second, unique number. This number is used to identify the sample and corresponding data at the AstraZeneca genetics laboratories, or at the designated organisation. No personal details identifying the individual will be available to any person (AstraZeneca employee or designated organisations working with the DNA).

The link between the subject enrolment/randomisation code and the second number will be maintained and stored in a secure environment, with restricted access at AstraZeneca or designated organisations. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit, and permit tracing of samples for destruction in the case of withdrawal of consent.

Ethical and regulatory requirements
The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Appendix B.

Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Copies of both signed and dated consent forms must be given to the subject and the original filed at the study centre. The Principal Investigator(s) is responsible for ensuring that consent is given freely and that the subject understands that they may freely withdrawal from the genetic aspect of the study at any time.

Patient data protection

AstraZeneca will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician unless required to do so by law.

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, an AstraZeneca Physician or an investigator might know a subject's identity and also have access to his or her genetic data. In addition, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored at a secure system at AstraZeneca and/or designated organizations to analyse the samples.

AstraZeneca and its designated organisations may share summary results (such as genetic differences from groups of individuals with a disease) from this genetic research with other researchers, such as hospitals, academic organisations or health insurance companies. This can be done by placing the results in scientific databases, where they can be combined with the results of similar studies to learn even more about health and disease. The researchers can only use this information for health related research purposes. Researchers may see summary results but they will not be able to see individual subject data or any personal identifiers.

Some or all of the clinical datasets from the main study may be merged with the genetic data in a suitable secure environment separate from the clinical database.

Statistical methods and determination of sample size

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A Statistical Analysis Plan may be prepared where appropriate.

Appendix E Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

E 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries. Specific guidance on managing liver abnormalities can be found in Section 8.2.1 of the Clinical Study Protocol.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug induced liver injury (DILI) caused by the investigational medicinal product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

E 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3× upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2×ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 ×ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (ie, on the same day) the elevation in TBL, but there is no specified time frame within which the elevations in transaminases and TBL must occur.

E 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN

- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

For studies using central laboratories:

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (and also to the AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

For studies using local laboratories:

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Appendix E 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

E 4 Follow-up

E 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

E 4.2 Potential Hy's Law criteria met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting Study treatment (See Section 8.4 Safety Reporting)

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the Hy's law lab kit should be used.

- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

E 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay of over 3 weeks in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

E 6 Actions required when potential Hy's Law criteria are met before and after starting study treatment

This section is applicable to patients who meet PHL criteria on Study treatment having previously met PHL criteria at a study visit prior to starting Study treatment.

At the first on-study treatment occurrence of PHL criteria being met, the Investigator will determine if there has been a significant change in the subjects' condition[#] compared with the last visit where PHL criteria were met.[#]

- If there is no significant change, no action is required
- If there is a significant change, notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in Appendix B 5.
- A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the

discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

E 7 Actions required for repeat episodes of potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment, and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review, and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study (eg, chronic or progressing malignant disease, severe infection or liver disease), or did the subject meet PHL criteria prior to starting study treatment and at first on-study treatment visit, as described in Appendix E 6?

If **No**: Follow the process described in Appendix E 4.

If **Yes**: Determine if there has been a significant[#] change in the subject's condition compared with when PHL criteria were previously met.

If there is no significant change, no action is required.

If there is a significant change, follow the process described in Appendix E 4.

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

Appendix F Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

Introduction

This appendix details the implementation of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this Appendix.

Imaging modalities and acquisition specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumor assessment of target lesions (TLs), non-target lesions (NTLs), and new lesions (NLs) is provided in Table 19.

Table 19 Summary of methods of assessment

Target Lesions	Non-Target Lesions	New Lesions
CT (preferred)	CT (preferred)	CT (preferred)
MRI	MRI	MRI
	Plain X-ray	Plain X-ray
	Chest X-ray	Chest X-ray
		Bone scan
		FDG-PET/CT

CT Computed tomography; FDG-PET/CT ^{18}F-Fluoro-deoxyglucose positron emission tomography/CT; MRI Magnetic resonance imaging.

CT and MRI

Computed tomography (CT) with intravenous (IV) contrast is the preferred imaging modality (although magnetic resonance imaging [MRI] with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumor assessments (ie, for measurement of TLs, assessment of NTLs, and identification of NLs). It is essential that the same correct imaging modality, image acquisition parameters (eg, anatomic coverage, imaging sequences, etc), imaging facility, tumor assessor (eg, radiologist), and method of tumor assessment (eg, RECIST 1.1) are used consistently for each patient throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumor assessment schedule as closely as possible (refer to the schedules of activities [SoAs]), and this on-study imaging schedule MUST be followed regardless of any delays in dosing or missed imaging visits. If an unscheduled assessment is performed (eg, to investigate clinical signs/symptoms of progression) and the patient has not progressed, every attempt should be made to perform the subsequent scan acquisitions at the next scheduled imaging visit.

Due to its inherent rapid acquisition (seconds), CT is the imaging modality of choice. Body scans should be performed with breath-hold scanning techniques, if possible. Therefore, CT of the chest is recommended over MRI due to significant motion artifacts (eg, heart, major blood

vessels, breathing) associated with MRI. MRI has excellent contrast and spatial and temporal resolutions; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. The modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. In general, local oncology diagnostic imaging parameters are applied for scan acquisition. It is beyond the scope of this appendix to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases.

The most critical CT and MRI image acquisition parameters for optimal tumor evaluation are *anatomic coverage, contrast administration, slice thickness, and reconstruction interval.*

a. Anatomic coverage: Optimal anatomic coverage for most solid tumors is the chest-abdomen (-pelvis). Coverage should encompass all areas of known predilection for metastases in the disease under evaluation and should additionally investigate areas that may be involved based on signs and symptoms of individual patients. Because a lesion later identified in a body part not scanned at baseline would be considered as an NL representing disease progression, careful consideration should be given to the extent of imaging coverage at baseline and at subsequent follow-up timepoints. This will enable better consistency not only of tumor measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumor burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these timepoints are specified in the SoAs. Examples include the following:

- IV contrast-enhanced CT of chest-abdomen (including the entire liver and both adrenal glands) (-pelvis)
- Non-contrast CT of chest and IV contrast-enhanced abdomen (including the entire liver and both adrenal glands) (-pelvis)
- IV contrast-enhanced CT or MRI of the head and neck
- IV contrast-enhanced MRI (preferred) or CT of the brain

For chest-abdomen (-pelvis) imaging, the following are scanning options in decreasing order of preference, with additional options (2 to 4) for consideration when patients have sensitivity to IV contrast or have compromised renal function:

1. Chest-abdomen (-pelvis) CT with IV CT contrast (most preferred)
2. Chest CT without IV contrast + abdomen (-pelvis) MRI with IV MRI contrast, if CT IV contrast (iodine based) is medically contraindicated at any time during the study
3. Chest-abdomen (-pelvis) CT without IV contrast, if both IV CT and MRI contrast are medically contraindicated or the patient has compromised renal function

4. Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study

Specifically for this study in UC, staging and surveillance of malignancy in the upper urinary tract (renal pelvis, ureters) by CT urography may be applied according to local practice. Various techniques and scanning protocols for CT urography have been described (Potenta et al 2015; Zhang et al 2007).

b. IV contrast administration: Optimal visualization and measurement of metastases in solid tumors requires consistent administration (dose and rate) of IV contrast as well as timing of scanning. An adequate volume of a suitable contrast agent should be given so that the tumor lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given patient. Oral contrast is recommended to help visualize and differentiate structures in the abdomen and pelvis.

c. Slice thickness and reconstruction interval: It is recommended that CT or MRI scans be acquired/reconstructed as contiguous (no gap) with ≤5 mm slice thickness for optimal lesion measurements. Exceptionally, particular institutions may perform medically acceptable scans at slice thicknesses >5 mm. If this occurs, the minimum size of measurable lesions at baseline should be twice the slice thickness of the baseline scans.

For CT scans, all window settings should be included in the assessment, particularly in the thorax where lung and soft tissue windows should be considered. When measuring lesions, the TL should be measured on the same window setting for repeated examinations throughout the study.

Chest X-ray

Chest X-ray assessment will not be used for assessment of TLs. Chest X-ray can, however, be used to assess NTL and to identify the presence of NLs. However, there is preference that a higher resolution modality such as CT be used to confirm the presence of NLs.

Plain X-ray

Plain X-ray may be used as a method of assessment for bone NTLs and to identify the presence of new bone lesions.

Isotopic bone scan

Bone lesions identified on an isotopic bone scan at baseline and confirmed by CT, MRI, or X-ray at baseline should be recorded as NTLs and followed by the same method per baseline assessment (CT, MRI, or X-ray).

Isotopic bone scans may be used as a method of assessment to identify the presence of new bone lesions at follow-up visits. NLs may be recorded in case positive hot-spots appear on a bone scan that were not present on a previous bone scan; however, a newly observed equivocal hot-spot on a bone scan that cannot be verified with correlative imaging (CT, MRI, or X-ray) of the same anatomical region shall not be the only trigger for a progressive disease (PD) assessment at that timepoint.

FDG-PET/CT

^{18}F-Fluoro-deoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scans may be used as a method for identifying new extrahepatic lesions (but not intrahepatic lesions) for RECIST 1.1 assessments according to the following algorithm: NLs will be recorded where there is positive ^{18}F-fluoro-deoxyglucose uptake[1] not present on baseline or prior FDG-PET scan or in a location corresponding to an NL on a companion CT/MRI collected close in time to the FDG-PET scan. The PET portion of the PET/CT introduces additional data that may bias an Investigator if it is not routinely or serially performed. Therefore, if there is no baseline or prior FDG-PET scan available for comparison and no evidence of NLs on companion CT/MRI scans, then follow-up CT/MRI assessments should continue as per the regular imaging schedule to verify the unequivocal presence of NLs.

At present, low-dose or attenuation correction CT portions of a combined FDG-PET/CT scan are of limited use in anatomically based efficacy assessments, and it is therefore suggested that they should not substitute for dedicated diagnostic contrast-enhanced CT scans for tumor measurements by RECIST 1.1. In exceptional situations, if a site can document that the CT performed, as part of a PET/CT examination, is of identical diagnostic quality (with IV contrast) to a dedicated diagnostic CT scan, then the CT portion of the PET/CT can be used for RECIST 1.1 tumor assessments. Caution that this is not recommended because the PET portion of the CT introduces additional (PET) data that may bias an Investigator if it is not routinely or serially performed.

Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumors as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation and may not provide an accurate assessment of true tumor size. Tumors identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

Other Tumor Assessments

Clinical examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumors identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

Endoscopy and laparoscopy

Endoscopy and laparoscopy will not be used for tumor assessments as they are not validated in the context of tumor assessment.

Histology and cytology

Histology or tumor markers on tumor biopsy samples will not be used as part of the tumor response assessment as per RECIST 1.1.

1 A positive FDG-PET scan lesion should be reported only when an uptake (eg, SUV) greater than twice that of the surrounding tissue or liver is observed.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, pleural effusion) that appears or worsens during the study will not be used as part of the tumor response assessment as per RECIST 1.1.

Furthermore, an overall assessment of complete response (CR; all other disease disappears/reverts to normal) would be changed to partial response (PR) if an effusion remains present radiologically.

Measurability of tumor lesions at baseline

RECIST 1.1 measurable lesions at baseline:

A tumor lesion that can be accurately measured at baseline as ≥10 mm in the longest diameter for non-nodal lesions or ≥15 mm in short axis[2] diameter for lymph node lesions with IV contrast-enhanced CT or MRI and that is suitable for accurate repeated measurements. Please see additional RECIST 1.1 guidance below on measurability of intrahepatic hepatocellular carcinoma lesions and porta hepatic lymph nodes.

Non-measurable lesions at baseline:

- Truly non-measurable lesions include the following:
  - Bone lesions (see exception below for soft tissue component)
  - Leptomeningeal disease
  - Ascites, pleural, or pericardial effusion
  - Inflammatory breast disease
  - Lymphangitic involvement of skin or lung
- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis diameter at baseline[3]).
- Previously irradiated lesions[4]
- Brain metastasis

Special considerations regarding lesion measurability at baseline:

- Bone lesions

[2] The short axis is defined as the longest in-plane axis perpendicular to long axis
[3] Lymph nodes with <10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.
[4] Localized post-radiation changes that affect lesion sizes may occur. Therefore, lesions that have been previously irradiated are typically considered non-measurable and as NTL at baseline and followed up as part of the NTL assessment.

  - Bone scan, PET scan or plain X-ray are not considered adequate imaging techniques to measure bone lesions; however, these techniques can be used to confirm the presence or disappearance of bone lesions.

  - Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, can be considered measurable if the soft tissue component meets the definition of measurability.

  - Blastic bone lesions are considered non-measurable.

- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the criteria for measurability from a radiological point of view, but if non-cystic lesions are present in the same patient, these should be selected over cystic lesions as TLs.

RECIST 1.1 TL selection at baseline:

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes collectively considered as a single organ), representative of all lesions involved should be identified as TL at baseline. TLs should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis diameter for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected.

Lymph nodes, in any location (local/regional and distant), are collectively considered as a single organ, with a maximum of 2 lymph nodes as TLs. A bilateral organ (eg, adrenal glands), a segmented organ (eg, liver), or a multilobed organ (eg, lung) is each considered as a single organ.

The site and location of each TL should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all TLs will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all TLs will be calculated and reported as the follow-up sum of diameters.

Special cases for TL assessment at baseline:

- For TL measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis diameter.

- When lymph nodes are coalesced and no longer separable in a conglomerate mass, the vector of the longest diameter should be used to determine the perpendicular vector for the maximal short axis diameter of the coalesced mass. Non-nodal lesions that coalesce should similarly be assessed by the longest axis diameter.

- Tumor lesions selected for fresh screening biopsy should not be selected as TLs, unless imaging occurred at least approximately 2 weeks after biopsy, allowing time for healing.

- If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.

RECIST 1.1 NTL selection at baseline:

All other lesions, including non-measurable lesions and surplus measurable lesions not recorded as TLs should be identified as NTLs at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

Evaluation of tumor response and progression

RECIST 1.1 TL assessment at follow-up

This section defines the criteria used to determine objective tumor visit response for RECIST 1.1-defined TLs. The imaging modality, location, and scan date of each TL identified previously at baseline should be documented at follow-up visits with the long axis diameter for non-nodal lesions or short axis diameter for lymph node lesions. All measurements should be recorded in millimeters. The sum of the diameters for all TLs at each follow-up visit will be compared to the baseline sum of diameters (for response or stable disease [SD]) or to the smallest prior (nadir) sum of diameters (for progression).

Special cases for TL assessment at follow-up:

- If a lesion has completely disappeared, the diameter should be recorded as 0 mm. If a lesion appears in the same location on a subsequent scan, it will be recorded as an NL.

- If a TL splits into two or more parts, the sum of the diameters of those parts should be recorded.

- If two or more TLs merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s). If the merged TLs are non-nodal lesions, record the long axis diameter of the merged lesion. If pathologic lymph nodes coalesce and are no longer individually separable within a conglomerate mass, the vector of the longest diameter of the coalesced mass should be used to determine the perpendicular vector for the maximal short axis diameter.

- If a TL is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

- If a TL cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. The choice of "too large to measure" in the CRF will trigger an overall visit response of PD.
- When a TL has had any intervention, the following apply:
    - Target Lesion Intervention may include radiotherapy, embolization, excisional biopsy, surgery, etc. that is not a part of study treatment and might adversely affect the size of that Target lesion
    - If an Intervention on a Target Lesion is ticked in the case report form, the diameter of the lesion is still recorded (0mm if no longer present) and is included in the sum of diameters.
    - If a Target Lesion Intervention is ticked, the Intervention must be reported for all subsequent assessments of that Target lesion.
    - If a Target Lesion has an Intervention, the only Overall Visit Responses allowed to be recorded by the Investigator are NE or PD, with PD if the sum of diameters exceeds a 20% increase and at least a 5mm absolute increase in the visit sum of diameters compared to the previous minimum (nadir) sum of diameters.
    - No visit with a recorded Target Lesion Intervention can be used as the minimum (nadir) sum of diameters.

Table 20 RECIST 1.1 evaluation of target lesions

Complete response (CR)	Disappearance of all TLs since baseline. Any pathological lymph nodes selected as TLs must have a reduction in short axis diameter to <10 mm.
Partial response (PR)	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
Stable disease (SD)	Neither sufficient decrease in sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
Progression of disease (PD)	At least a 20% increase in the sum of diameters of TLs, taking as reference the smallest previous sum of diameters (nadir) – This includes the baseline sum if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm from nadir.
Not evaluable (NE)	Only relevant if any of the TLs at follow-up were not assessed or not evaluable (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the progressive disease criteria, progressive disease overrides not evaluable as a TL response.
Not applicable (NA)	Only relevant if no TLs present at baseline.

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; SD Stable disease; TL Target lesion.

RECIST 1.1 NTL assessment at follow-up

All other lesions (or sites of disease) not recorded as TLs should be identified as NTLs at baseline. Measurements are not required for these lesions, but their status should be followed at subsequent visits. At each visit an overall assessment of the NTL response should be recorded by the Investigator.

To achieve "unequivocal progression" on the basis of NTLs, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in TLs, the overall tumor burden has increased sufficiently to merit unequivocal progression by NTLs. A modest "increase" in the size of 1 or more NTLs is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PD of target disease will therefore be extremely rare.

Table 21 RECIST 1.1 evaluation of non-target lesions

Complete response (CR)	Disappearance of all NTLs since baseline. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/non-PD	Persistence of one or more NTLs.
Progression (PD)	Unequivocal progression of existing NTLs. Unequivocal progression may be due to an important progression in one lesion only or in several lesions. In all cases the progression MUST be clinically significant for the physician to consider changing (or stopping) therapy.
Not evaluable (NE)	Only relevant when one or some of the NTLs were not assessed and, in the Investigator's opinion, they are not able to provide an evaluable overall NTL assessment at this visit. Note: For patients without TLs at baseline, this is relevant if any of the NTLs were not assessed at this visit and the progression criteria have not been met.
Not applicable (NA)	Only relevant if no NTLs present at baseline

CR Complete response; PR Partial response; PD Progression of disease; NE Not evaluable; NTL Non-target lesion; TL Target lesion.

RECIST 1.1 NL identification at follow-up

Details including the imaging modality, the date of scan, and the location of any NLs will be recorded in the CRF. The presence of 1 or more NLs is assessed as progression. The finding of an NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor. If an NL is radiologically equivocal, for example, because of its small size, the treatment and tumor assessments should continue, and the lesion should be assessed at a subsequent scan no earlier than 6 weeks later to determine if it becomes unequivocal. If measurable, in order for a previously equivocal new lesion to become unequivocal at a subsequent scan, the long axis diameter of the previously new equivocal non-nodal lesion or the short axis diameter of the

previously new equivocal nodal lesion should show an increase of at least 5 mm. If a previously equivocal NL is assessed as unequivocal at a follow-up visit, then the progression date should be declared using the date of the initial scan when the NL first appeared.

A lesion identified at a follow-up assessment in an anatomical location that was not scanned at baseline is considered an NL and will indicate disease progression.

RECIST 1.1 evaluation of overall visit response at follow-up

Derivation of overall visit response as a result of the combined assessment of TLs, NTLs, and NLs is identical between RECIST 1.1 and RECIST 1.1 using the algorithm shown in Table 22.

Table 22 RECIST 1.1 overall visit response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE or NA	No	PR
SD	Non-PD or NE or NA	No	SD
NA	Non-CR/Non-PD	No	SD (Non-CR/non-PD)
NE	Non-PD or NE	No	NE
NA	NE	No	NE
NA	NA	No	NED
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR Complete response, PR Partial response, SD Stable disease, PD Progression of disease, NE Not evaluable, NED No evidence of disease (only relevant if there were neither target lesions nor non-target lesions at baseline); NA Not applicable (only relevant if there were no target and/or non-target lesions at baseline),
RECIST 1.1 Response Evaluation Criteria in Solid Tumors, version 1.1.
Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.

The following overall visit responses are possible depending on the extent of tumor disease at baseline:

- For subjects with TLs (at baseline): CR, PR, SD, PD, or not evaluable (NE)
- For subjects with NTLs only (at baseline): CR, non-CR/non-PD, PD, or NE

- For subjects with no disease at baseline: no evidence of disease (NED; available as an option in the eCRF), PD, or NE

Central imaging

Images, including unscheduled visit scans, will be collected on an ongoing basis and sent to an AstraZeneca-appointed iCRO for quality control, storage, and for Blinded Independent Central Review (BICR). Digital copies of all original scans should be stored at the Investigator site as source documents. Electronic image transfer from the sites to the iCRO is strongly encouraged. A BICR of images will be performed at the discretion of AstraZeneca. Results of these independent reviews will not be communicated to Investigators, and results of Investigator tumor assessments will not be shared with the central reviewers. The management of patients will be based solely upon the results of the tumor assessments conducted by the Investigator. Further details of the BICR will be documented in the Independent Review Charter, (also referred to as 'Imaging Charter').

References

Eisenhauer et al 2009
Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Potenta et al 2015
Potenta SE, D'Agostino R, Sternberg KM, Tatsumi K, Perusse K. CT urography for evaluation of the ureter. RadioGraphics 2015;35:709-26.

Zhang et al 2007
Zhang J, Gerst S, Lefkowitz RA, Bach A. Imaging of bladder cancer. Radiol Clin N Am 2007;45:183-205.

Appendix G International Airline Transportation Association (IATA) 6.2 Guidance Document

Labelling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories. For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging
- Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable
- Samples routinely transported by road or rail are patient to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix H Patient-reported outcomes

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: ____
Your birthdate (Day, Month, Year): __ __ / __ __ / __ __ __ __
Today's date (Day, Month, Year): 31 __ __ / __ __ / __ __ __ __

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent

Health Questionnaire

English version for the UK

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

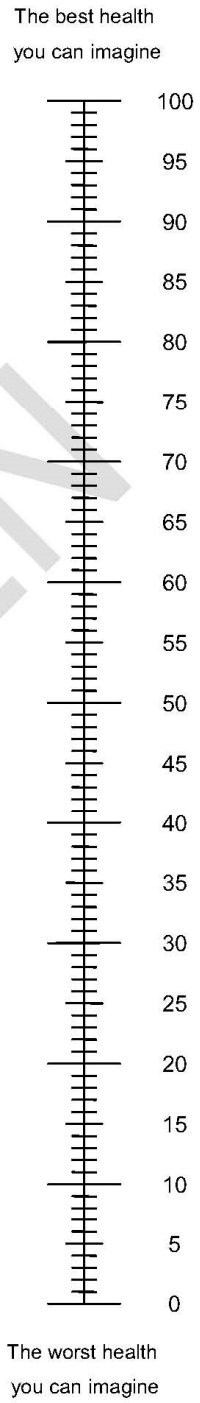
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



PATIENT GLOBAL IMPRESSION OF CHANGE (PGIC)

Overall, how would you rate the change in your health status since starting this Study?
Please tick (✓) one box only:

- ☐ Much Better
- ☐ Moderately Better
- ☐ A Little Better
- ☐ About the Same
- ☐ A Little Worse
- ☐ Moderately Worse
- ☐ Much Worse

PATIENT GLOBAL IMPRESSION OF SEVERITY (PGIS)

Please choose the response below that best describes the severity of your overall cancer symptoms over the past 7 days.

- ☐ No Symptoms
- ☐ Very Mild
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very Severe

PRO-CTCAE

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an ⊠ in the one box that best describes your experiences over the past 7 days...

1. In the last 7 days, what was the SEVERITY of your PROBLEMS WITH TASTING FOOD OR DRINK at their WORST?

   ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

2. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?

   ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

   In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?

   ○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

3. In the last 7 days, how OFTEN did you have NAUSEA?

   ○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

   In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?

   ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

4. In the last 7 days, how OFTEN did you have VOMITING?

   ○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

   In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?

   ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

5. In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?

   ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

6. In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?

   ○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

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7. In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?

   ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

   In the last 7 days, how much did your SHORTNESS OF BREATH INTERFERE with your usual or daily activities?

   ○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

8. In the last 7 days, what was the SEVERITY of your COUGH at its WORST?

   ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

   In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?

   ○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

9. In the last 7 days, did you have any RASH?

   ○ Yes ○ No

10. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?

    ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

11. In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?

    ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

    In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?

    ○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

12. In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?

    ○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

    In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?

    ○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

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13. In the last 7 days, how OFTEN did you have ACHING MUSCLES?

○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your ACHING MUSCLES at their WORST?

○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did ACHING MUSCLES INTERFERE with your usual or daily activities?

○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

14. In the last 7 days, how OFTEN did you have ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS)?

○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) at their WORST?

○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did ACHING JOINTS (SUCH AS ELBOWS, KNEES, SHOULDERS) INTERFERE with your usual or daily activities?

○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

15. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?

○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?

○ Not at all ○ A little bit ○ Somewhat ○ Quite a bit ○ Very much

16. In the last 7 days, how OFTEN did you have SHIVERING OR SHAKING CHILLS?

○ Never ○ Rarely ○ Occasionally ○ Frequently ○ Almost constantly

In the last 7 days, what was the SEVERITY of your SHIVERING OR SHAKING CHILLS at their WORST?

○ None ○ Mild ○ Moderate ○ Severe ○ Very severe

Appendix I Abbreviations

Abbreviation or special term	Explanation
1L	first line
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BC	bladder cancer
BCG	Bacillus Calmette Guerin
BICR	Blinded Independent Central Review
BP	blood pressure
CD	cluster of differentiation
CI	confidence interval
CIS	carcinoma in situ
CMV	cisplatin, methotrexate, and vinblastine
CR	complete response
CrCl	creatinine clearance
CRF	case report form (electronic/paper)
CRO	Contract Research Organization
CSA	clinical study agreement
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
ctDNA	circulating tumor DNA
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DCO	data cutoff
DDR	DNA damage response and repair
DFS	disease-free survival
DoR	duration of response
DSS	disease-specific survival
ECG	electrocardiogram

Abbreviation or special term	Explanation
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EFS24	proportion of patients alive and event free at 24 months
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire
ePRO	electronic patient reported outcome
EQ-5D-5L	EuroQol 5-dimension, 5-level health state utility index
FA	final analysis
FAS	full analysis set
FDA	Food and Drug Administration
FDG-PET	^{18}F-fluoro-deoxyglucose positron emission tomography
FFPE	formalin-fixed, paraffin-embedded
G+C	gemcitabine and cisplatin
GCP	Good Clinical Practice
GI	gastrointestinal
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
IB	Investigator Brochure
IC	immune cell
ICF	informed consent form
ICH	International Conference on Harmonisation
iCRO	imaging Contract Research Organization
IDMC	independent data monitoring committee
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
Ig	immunoglobulin

Abbreviation or special term	Explanation
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
imAE	immune-mediated adverse event
IMP	investigational medicinal product
IP	investigational product
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
LIMS	Laboratory Information Management System
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MFS	metastasis-free survival
MIBC	muscle-invasive bladder cancer
MMRM	mixed-model for repeated-measures
MOA	mechanism of action
MRI	magnetic resonance imaging
MTP	multiple testing procedure
MVAC	methotrexate, vinblastine, adriamycin, and cisplatin
NCI	National Cancer Institute
NL	new lesion
NMIBC	non-muscle-invasive bladder cancer
NSCLC	non-small-cell lung cancer
NTL	non-target lesion
OAE	other significant adverse event
ORR	objective response rate
OS	overall survival
OS5	proportion of patients alive at 5 years
pCR	pathologic complete response
PD	progressive disease

Abbreviation or special term	Explanation
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PFS	progression-free survival
PFS2	Time from the date of randomization to the earliest date of progression which occurs on subsequent therapy following an EFS event or death
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PK	pharmacokinetic(s)
PR	partial response
PRO	patient-reported outcome
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
PS	performance status
q3w	every 3 weeks
q4w	every 4 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
REVPRDI	Review of PRO/Questionnaire/Diary
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	stable disease
SoA	schedule of activities
SoC	Standard of care
TC	tumor cell
TCC	transitional cell carcinoma
TKI	tyrosine kinase inhibitors
TL	target lesion
TMB	tumor mutational burden
TMG	toxicity management guidelines
UC	urothelial carcinoma

Abbreviation or special term	Explanation
ULN	upper limit of normal
US	United States
WBDC	web based data capture
WHO	World Health Organization

Appendix J Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 5 (22-Jun-2023)

Overall Rationale for the Amendment:

Following a review of the literature, there is a growing body of evidence that there is a slow down of progression events after 2 years in MIBC treated with chemotherapy and/or checkpoint-inhibitors, with the majority of events occurring within 12 months after radical surgery (Bajorin et al 2021Bajorin et al 2021Bajorin et al 2021, Bellmunt et al 2021, Cathomas et al 2022). As such, to ensure study completion, the statistical assumptions in terms of number of events and timing of these events have been updated. Hence, the protocol has been amended to reduce the total number of expected events at final analysis (FA) from 509 to 451 across the two arms with a corresponding reduction in the power from 93% to 90%. Calendar based data cut-offs for the second interim and final EFS analyses, which are set up based on the latest blinded event predictions, have also been introduced in case of further slowing down of the events. An interim analysis (IA) of OS has also been added at EFS IA2 (but will only be formally tested if EFS is statistically significant via the MTP).

This and other changes incorporated in this amendment are described in the following table. Administrative and formatting changes were made throughout the protocol.

Section # and name	Description of change	Brief rationale	Substantial/ non-substantial
Title Page – EU CTR Number	Added EU CTR Number	EU CTR applicable for studies transitioning to EU CTR.	Non-substantial
Section 1.2 Synopsis, Study period	Updated text of the estimated date of last patient completed from Q4 2025 to Q2 2026	To update estimated dates based on the actual date of the last patient enrolled	Non-substantial
Section 1.2 Synopsis, Statistical methods, Section 9.1 Sample Size Determination, Section 9.4 Methods for Statistical Analyses, Section 9.5 Interim Analyses	Changed number of events for final EFS analysis and also added calendar-based assessment timepoints for EFS IA2 and FA. In accordance with these changes, the study power and critical value were also updated, as were the information fraction values at the interim analyses	To account for the slowing down of EFS events after 2 years	Substantial
Section 1.2 Objectives and Endpoints, Section 8.9, Section 9.3.4, Table 1, Table 2, Table 3, Table 4, Table 5	Removal of calculation of healthcare resource use (HOSPAD)	Collection of HOSPAD data was de-prioritized by AstraZeneca as assessment of health economics and hospital burden is no longer required for the submission	Non-substantial
Section 1.2 Synopsis, Section 9.1 Sample size determination	The calculation method of the timing of targeted events has been changed.	A blinded event prediction has been used to provide a more accurate prediction	Non-substantial
Section 4.4	End of Study definition updated	EU CTR requirement. To distinguish between US and EU end of the study definitions	Non-substantial
8.1.1.6 Central Imaging Review	Clarification regarding scans taken for routine clinical management after RECIST 1.1 progression	Clarification concerning any post progression scans submitted to vendor which may, in some instances, be centrally reviewed	Non-substantial

8.2.8 Other safety assessments	Removal of Tumor markers for Pneumonitis investigation	No specific tumor markers associated with metastatic bladder cancer presenting in the lung that would be relevant for ILD investigation have been identified	Non-substantial
Section 9.3.1.2 (Dual primary endpoint for event-free survival [EFS])	Updated text to clarify EFS censoring rules 1) at the time of radical cystectomy, patients will now be censored if the general 2 missed visit rule applies rather than considering only the scan immediately after cystectomy 2) patients with no evaluable visits or baseline disease assessment prior to neoadjuvant treatment will not be censored at Day 1 if they die within **112** days of randomization (rather than 2 visits	Simplification of the censoring rules. Change to calendar days due to there only being 1 visit in the neoadjuvant phase	Non-substantial
Section 9.5 Interim Analyses	Additional interim analysis of OS at EFS IA2 added	To allow a formal test of OS if EFS at EFS IA2 is positive.	Substantial
Section 9.5 Interim Analyses	Predicted OS events at the time of EFS IA2 have been added and predicted OS events at the EFS final analysis have been revised	Updated blinded prediction with EFS IA2 added	Non substantial
Section 9.5 Interim Analyses	Text has been added to state that the actual alpha level will be based on the observed number of events and as such the final analysis alpha will be derived using the generalized Haybittle-Peto method	Clarification	Non substantial

Appendix A1	Serious breach wording added	Insertion of required EU CTR language to define how to identify and report serious breaches.	Non-substantial
Appendix A6	Dissemination of Clinical Study Data	Insertion of required EU CTR language to define when study results will be available	Non-substantial
Appendix A7	Data Quality Assurance	Insertion of required EU CTR language" to update document retention period	Non-substantial
Appendix F	Deletion of "Evaluation of scans subsequent to RECIST 1.1-defined progression" paragraph	Treatment through progression is not applicable in this study	Non-substantial
Appendix L	Specific Country Requirements	Insertion of required EU-CTR language to capture applicable EU/EEA local CSP and country specific requirements that were previously approved by the respective country	Non-substantial

Amendment 4 (01-Jun-2021)

Overall Rational for the Amendment: Primary analysis, study objective and changes to the multiple testing plan now reflects the intention-to-treat (ITT) population rather than patients with adequate renal function, based on evolving data demonstrating no difference in outcomes for patients receiving a full or split cisplatin-dose regimen as part of a gemcitabine-cisplatin neoadjuvant regimen.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 (Schedule of Activities [SoAs]), Table 1, Table 2, Table 3, and Table 4	Clarified footnotes to reflect collection of samples for ctDNA and PaxGene RNA.	Samples for ctDNA and PaxGene only need to be collected at the time of a clinical event, defined as the time of progression or recurrence, occurring at any time during the study (neoadjuvant, adjuvant or follow-up). No additional samples are required beyond a progression or recurrence event. Language indicating collection 'for any other reason or at end of the study' has been removed.	Non-substantial
Section 1.1 (Schedule of Activities [SoAs]), Table 2 and Table 3 Section 8.2.7 (Clavien-Dindo Assessments)	Updated language to reflect requirement for Clavien-Dindo assessment at 90 days, for all cystectomy procedures	Clavien-Dindo assessments, performed at 90 days following a cystectomy procedure, are to be determined for all surgical procedures, including both a radical and a partial cystectomy (performed either due to medical contraindication or investigator's decision)	Non-substantial
Section 2.2 (Background)	Removal of Urothelial Carcinoma (UC) indication language, reflecting FDA approval in the US for locally advanced or metastatic disease	AstraZeneca has voluntarily withdrawn the conditionally approved indication of durvalumab in the US for locally advanced or metastatic UC after platinum-containing chemotherapy with consultation and guidance of the FDA.	Non-substantial
Section 2.3.2.1 (Durvalumab)	Updated text to reflect additional risks for durvalumab, based on current safety language.	The following risks have been added for Durvalumab: pemphigoid [reflected as rash/dermatitis (pemphigoid)] and immune thrombocytopenia	Non-substantial

Section 3 (Objective and Endpoints) Section 4.2.2. (Rationale for efficacy study endpoints) Section 9.2 (Table 18) (Population Analyses)	Updated study objectives and study population	Primary analysis for pCR and EFS will be performed on the ITT population instead of patients in the adequate renal function cohort; now reflected as the primary study objective Reference to the adequate renal function population has been removed from all the secondary objectives.	Substantial
1.2 Synopsis 8.1 Efficacy Assessments 9. Statistical Considerations (And throughout protocol, where applicable, except in Appendix J - Protocol Amendment History)	Regarding pCR and EFS endpoints, updated "co-primary" endpoint(s) language to "dual primary" endpoint(s)	Dual primary endpoints is more appropriate than co-primary endpoints in the context of study's statistical considerations.	Non-substantial
Section 8.4.5.1 (Specific toxicity management and dose modification information – durvalumab)	Removal of text referencing toxicity management guidelines (TMG) link to the WebPortal	The on-line TMG WebPortal has been decommissioned due to lack of use. The TMGs for the management of Durvalumab (and Tremelimumab) are continued to be provided to sites as a separate Annex document	Non-substantial
Section 9.3.1.2 (Dual primary endpoint for event-free survival [EFS])	Updated text to clarify window for post-cystectomy scan,	Censoring rules for patients with scans 42 to 120 days post-cystectomy (adjuvant baseline) are as follows: If this scan is obtained during this interval and prior to the first study treatment (Arm 1) and within the 120 days, regardless of timing relative to the first study visit (Arm 2), the patient will not be censored	Non-substantial

		This interval aligns with text in section 6.1.2 (Dose and Treatment regimens)	
Section 9.3.1.3 (Secondary Endpoints) Section 3 (Objectives and Endpoints)	Updated text to clarify additional survival endpoint	Overall survival (OS) added as a secondary endpoint (and also reflected in the secondary objective)	Substantial
Section 9.4 (Method of Statistical Analyses) Section 1.2 (Synopsis)	Updated text to reflect population for primary analysis and also modified statistical analysis plan	Primary analysis is to be performed on ITT, to align with updated study objectives; changes to multiple testing plan and modified schedule for interim analyses have been added.	Substantial
Appendix K (Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis)	Added language describing COVID-19 assessment for patients receiving durvalumab	Guidance provided for recruitment of new patients, management of existing patients, administration of study treatment, and considerations for COVIV-19 vaccination.	Non-substantial

Amendment 3 (20-July-2020)

Overall Rational for the Amendment: The primary reason for this amendment is to modify the patient population to include patients with clinical node-positive disease, specifically patients with cN1 disease. In addition to existing patients with node-negative disease (cT2-4aN0M0), patients with cT2-4aN1M0 are now included in the study population. In this context, the T2 cap is being clarified to only restrict enrollment of patients with cT2N0M0 disease; patients with cT2N1M0 disease are permitted to enroll onto the study.

Additionally, study mitigation language has been added which will provide sites with measures that may be implemented if a participant is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the participant, maintaining compliance with GCP, and minimizing risks to the study integrity.

This and other changes incorporated in this amendment are described in the following table. In addition, minor text clarifications, administrative changes, and changes for consistency across the durvalumab program have been made; as these changes were minor, they are not listed in detail in the table below.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 (Schedule of activities [SoAs]), Table 1 to Table 4	Clarified requirement for conducting QLQ and CTCAE assements in the timeframe between radical cystectomy and start of adjuvant phase	Clarification	Non-substantial
Section 1.1 (Schedule of activities [SoAs]), Table 1 to Table 4	Added footnote to tables 1-3 to clarify requirement for collection of PaxGene-RNA and ctDNA/circulating soluble factor samples	For patients who are discontinued early from either the neoadjuvant or adjuvant phase due to recurrence, progression, or any other reason, PaxGene-RNA and ctDNA/circulating soluble factor samples are also to be collected	Non-substantial
Section 1.1 (Schedule of activities [SoAs]), Table 1 to Table 4	Added language to indicate that patients who are discontinued from the neoadjuvant phase and will not enter into adjuvant phase, even if a	It is recognized that for patients who discontinue from study treatment either during or at the completion of the neoadjuvant phase and have not undergone a cystectomy, or do not enter adjuvant phase, the time	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	cystectomy is performed, 30 and 60-day follow up visits may be waived; however, a comprehensive 90-day visit must be performed	between the last dose of study drug and the first visit will often be longer than 30 and even 60 days, as required in the follow-up phase. For these patients, the 30 Day and Month 2 follow-up visits can be waived; however, the Month 3 (90 day) visit is required to ensure comprehensive assessments (safety, concomitant medications and PK) are documented	
Figure 1 Section 2.1 (Study rationale)	Updated footnote to reflect T2 cap limiting only enrollment of T2N0 patients	The figure is updated to reflect that only T2N0 patients will be limited to enrollment.	Substantial
Section 1.2 (Synopsis) Section 4.1 (Overall design)	Updated text to clarify current stratification to accommodate cN1 patients	. Randomization will be stratified by clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively.	Substantial
Section 2.1 (Study rationale)	Added language to reflect modification to study population to now include patients with cN1 disease	In accordance with current NCCN guidelines, patients with stage IIIa disease are now considered for neoadjuvant chemotherapy/radical cystectomy. Therefore, randomization will be stratified by clinical tumor stage T2N0 versus >T2N0 (including T2N1, T3 and T4a) to reflect prognostic stage II versus IIIa, respectively	Substantial
4.1.1 Study conduct mitigation during study disruptions due to cases of civil crisis, natural disaster, or public health crisis	New wording was added which would give guidance on how the study could continue in the event of a serious disruption with details of mitigation that could be	The impact of COVID-19 has highlighted the risk to continuity of clinical trials during times of study disruption, whether by civil crisis, natural disaster or public health crisis. This section details the measures that may be implemented if	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Appendix K	employed to ensure study continuity.	a patient is not able to visit a study site to ensure that the clinical trial can continue whilst minimizing risk to the patient, maintaining compliance with GCP, and minimizing risks to study integrity. These changes will only be initiated at a time of study disruption.	
Section 5.1 (Inclusion criteria) Section 6.1.5 (Surgical plan)	Updated text to reflect inclusion of patients with N1 disease	Patients with T2-T4aN1, in addition to patients with T2-T4aN0 patients, are now included in the patient population. Definition of clinical N1 is provided. The single regional pelvic lymph node, in the opinion of the investigator, must be considered resectable per the surgical plan.	Substantial
Section 5.2 (Exclusion criteria)	Updated text to reflect N2 and N3 patients are excluded	Only node-positive patients with N1 disease are considered eligible. Modified exclusion reflects patients with N2 and N3 disease are not eligible	Substantial
Section 5.2 (Exclusion criteria)	Updated exclusion #9	Removed requirement for a prior prostatectomy	Non-substantial
Section 6.1.5 (Surgical plan)	Updated text to reflect recommendation for PET-scan for N1 patients	For patients with N1 disease at study entry who are being considered for the non-cystectomy extension phase, a PET-CT is recommended in addition to a pelvic CT scan, as a confirmatory assessment, to confirm a complete clinical response (cCR)	Non-substantial
Section 6.2.1 (Patient enrollment and randomization)	Updated text to reflect requirement of PD-L1 sample to collected ≤ 3 months prior to screening	Clarification	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 7.1.2 (Procedure for discontinuation of study plan-no radical cystectomy) Section 8.1.1. (Investigator RECIST 1.1 imaging review)	Updated text to discontinuation procedure for non-cystectomy patients with N1 disease	Patients who have N1 disease at study entry who are subsequently found to have an unresectable regional lymph node after randomization, will follow the procedures described for non-cystectomy patients.	Non-substantial
Section 8.1.1. (Investigator RECIST 1.1 imaging review)	Updated text to reflect initial neoadjuvant baseline scan is the reference scan for patients entering into the extended noncystectomy phase	Clarification	Non-substantial

Amendment 2 (09-December-2019)

Overall Rationale for the Amendment: The primary reason for this amendment was the addition of language to accommodate patients who have no radical cystectomy performed. This and other changes incorporated in this amendment are described in the following table. In addition, minor text clarifications, administrative changes, and changes for consistency across the durvalumab program have been made; as these changes were minor, they are not listed in detail in the table.

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 1.1 (Schedule of activities [SoAs]), Table 1 to Table 4 Section 1.2 (Synopsis) Section 4.2.2 (Rationale for efficacy study endpoints)	Added language addressing patients who have no radical cystectomy performed	More details provided in the SoA tables and CSP sections outlining requirements for tumor assessment and EFS determinations, specifically for patients who do not undergo a radical cystectomy	Substantial
Section 1.1 (Schedule of activities [SoAs]), Table 1	Added footnote “u” to indicate that the sample for genetic research may be obtained at any point during the study	To alleviate the burden of activities on Cycle 1 Day 1, and to align with standard practice in this program	Non-substantial
Section 1.1 (Schedule of activities [SoAs]), Table 1	Added language to footnote “w” (now “x”) and respective text in Section 8.1.1.1 to indicate that sites should consider scheduling the	No specific timeframe is defined in the CSP as to when the post-neoadjuvant scan needs to be obtained relative to the last dose of neoadjuvant treatment; guidance	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	post-neoadjuvant scan as part of the pre-surgical work-up	provided to suggest timing should coincide with pre-surgery work-up, if applicable	
Section 1.1 (Schedule of activities [SoAs]), Table 1 and Table 2 Section 8.2.1 (Clinical safety laboratory assessments)	Added language requiring activated partial thromboplastin time and international normalized ratio be assessed on Cycle 1 Day 1 of both the neoadjuvant and adjuvant phases.	Assessment at adjuvant Cycle 1 Day 1 is added as coagulation and hepatic function may have changed due to intervening procedures, including cystectomy.	Substantial
Section 1.2 (Synopsis) Section 3 (Objective and endpoints) Section 4.2.2 (Rationale for study endpoints) Section 9.2 (Populations for analyses) Section 9.2.4 (PD-L1-high analysis set) Section 9.4 (Methods for statistical analyses)	Added language to reflect efficacy objective for pCR and EFS for patients in the PD-L1-high subgroup	Emerging clinical data from other studies using neoadjuvant PD/PD-L1 inhibitors have demonstrated improved response rates in PD-L1 high patients; this objective is also being incorporated into this study	Substantial
Section 1.2 (Synopsis) Section 4.1 (Overall design)	Added language indicating a limit on recruitment of patients with T2 disease to approximately 40%, in both treatment arms	This limit is in place to align with previously published studies describing the distribution of patients with T2 and > T2 disease (and their corresponding pCR rates) for patients receiving neoadjuvant chemotherapy and thereby, to ensure that the statistical assumptions for pCR rates between the experimental and control groups are maintained, as reflected in Section 9.1 (Sample size determination).	Substantial
Section 1.2 (Synopsis) Section 6.1.3 (Duration of treatment and criteria for treatment through progression)	Clarified progression events that would or would not preclude patient from undergoing a radical cystectomy	Additional language provided to clarify progression events, in the context of both medical reasons and confirmed progression that would or would not preclude a patient from proceeding with a radical cystectomy.	Substantial
Section 5.1 (Inclusion criteria)	Added language to clarify that clinical tumor staging is a composite assessment of results obtained from imaging,	Clarification that a single clinical tumor stage needs to be derived based on all available data, regardless of the order in which	Non-substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	pathology, and physical exam, to derive a single tumor stage at study entry	that information is being reviewed. A single tumor stage needs to be documented in the eCRF and IXRS at the time of randomization.	
Section 5.2. (Exclusion criteria)	• Exclusion Criterion 2: added language to clarify that additional work-up of a large lymph node, confirming a benign lesion, is acceptable for eligibility • Exclusion Criterion 14: removal of QTcF requirement at baseline due to low risk of QTc-prolonging effects with study treatment	• Language added to allow sites to work-up a large nodal mass (short-axis between 10 and <15 mm), either pathologically (biopsy) or by PET-CT scan, to confirm the presence of a benign mass and allow the patient to be enrolled • Requirement for documentation of normal QTcF was initially retained due to concerns related to ECG effects related to gemcitabine; further assessment is that QTc-prolonging effects is not a risk with any of the study treatments, and therefore is being removed.	Non-substantial
Section 6.1.2 (Dose and treatment regimens)	Added language describing the noncystectomy extension phase for patients who meet specific criteria	New provision added to allow patients in either treatment arm who have a complete clinical response at the completion of neoadjuvant treatment and refuse a radical cystectomy to transition into the noncystectomy extension phase, with approval from AZ, with assessments mirroring those in the adjuvant phase. For patients in Arm 1, this would include additional cycles of durvalumab monotherapy.	Substantial
Section 6.1.5 (Surgical Plan):	• Added language indicating that AZ should be consulted for a patient who is unable to undergo a radical cystectomy within the 56-day timeframe, specifically for delays extending beyond 70 days (10 weeks) • Added language indicating that if a patient is confirmed to have a complete clinical response (by multi-modal	• Provision added to encourage sites to contact AZ if a radical cystectomy may be delayed beyond 10 weeks (the outer limit supported by guidelines), secondary to a medical issue. • New provision being added to allow patients who are determined to have a complete clinical response at the completion of neoadjuvant treatment and refuse a radical	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
	assessment) and refuses a radical cystectomy, transition into the noncystectomy extension phase (instead of the follow-up phase) is permitted with approval by the Sponsor.	cystectomy to transition into a noncystectomy extension phase, with approval from Sponsor.	
Section 6.2.1 (Patient enrollment and randomization)	Added language to clarify that clinical tumor staging should be determined at screening Updated text to reflect timeframe for collection of sample for PD-L1 testing is ≤3 months (instead of 56 days)	Clarification Clarification	Non-substantial
Section 6.4 (Concomitant therapy)	Added language clarifying the requirements for recording concomitant medications/therapy administered during the surgical procedure	Medications routinely used to perform the surgery (eg, pre- and peri-operative medications) are now exempt from recording as a concomitant medication unless specific criteria are met, predominately related to the management or cause of an unexpected event occurring peri-or post-operatively.	Substantial
Section 7.1 (Discontinuation of study treatment)	Added language clarifying criteria for study treatment discontinuation for patients who have no radical cystectomy performed	Specific guidance provided describing disposition of patients who do not have a radical cystectomy performed	Substantial
Section 8.1.1 (Investigator RECIST 1.1 imaging review)	• Added language indicating a modified imaging plan for patients with a new tumor (target and non-target lesion) detected on initial post-cystectomy (adjuvant baseline) scan • Added language to clarify tumor assessment (imaging plan) for patients who are precluded from or refuse a radical cystectomy	Clarification provided to indicate evaluation of a new lesion, detected at the adjuvant baseline scan Clarification of tumor assessment and EFS determination provided for patients who are medically preclude from or refuse a radical cystectomy	Substantial
Section 8.8.7 (German biomarker sub-study)	Added text describing a biomarker sub-study being performed at NIAGARA sites within Germany	Language added to reference a substudy being conducted evaluating additional exploratory immune, mutational, and/or molecular subtyping biomarkers	Substantial

Section # and Name	Description of Change	Brief Rationale	Substantial/ Non-substantial
Section 9.3.1.2 (Co-primary endpoint: event-free survival (EFS))	Added language clarifying definition of EFS for patients who refuse a radical cystectomy procedure, specifically for patients with residual disease and for those achieving a complete response.	EFS definition has been updated, to align with updates on the definition provided by the FDA	Substantial
Appendix A (Regulatory, ethical and study oversight considerations)	Added text regarding study termination and reporting requirements for SAEs as per TransCelerate protocol template	Language explaining requirements for SAE reporting and reasons for study termination, added per program-wide template language	Non-substantial
Appendix B (Adverse event definitions and additional safety information)	Added text regarding AEs for malignant tumors as per TransCelerate protocol template	Language describing AEs for malignant tumors added per program-wide template language	Non-substantial
Appendix F (Guidelines for Evaluation of Objective Tumor Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)	Removal of text describing requirement for obtaining a confirmatory scan once unequivocal progression is confirmed Additionally updated text to be consistent with latest TransCelerate protocol template	Once unequivocal progression has been confirmed by imaging, no additional scans are required. Additional updates added per program-wide template language.	Substantial Non-substantial

Amendment 1 (Version 2.0): 23-April-2019

Overall Rationale for the Amendment: Protocol version 2 (dated 23Apr19) was created based on feedback from investigators and regulatory agencies. The main drivers for the amendment included:

- Clarification that the adjuvant phase is required for both treatment (Arm 1) and control arm (Arm 2)
- Modification of adjuvant schedule to retain patients in Arm 2 by allowing for visits to alternate between in clinic visits and phone contacts
- Primary/secondary endpoints updated to reflect EFS assessments by BICR AND central pathology review
- Modification of Imaging Schedule for Control and Experimental Arms (Arms 1 and 2)
- Change of International Coordinating Investigator (ICI)

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Schedules of activities (SoAs): Table 1 (Schedule of assessments for screening and neoadjuvant treatment [all treatment arms]):	• Extended the assessment time for concomitant medications, urinalysis, adverse event (AE)/serious adverse event (SAE) assessment, and patient-reported outcome (PRO)/hospital resource use module (HOSPAD) endpoints to include the pre-radical cystectomy and radical cystectomy dates • Added row for coagulation parameters for clarification on time of collection • Changed tumor sample age from ≤3 years to ≤3 months for programmed cell death-ligand 1 (PD-L1) testing • Moved urine biomarker and cytology from screening to Cycle 1 Day 1 (pre-dose) • Removed Cycle 3 Day 1 urine sample for biomarker and cytology • Removed blood sample for PaxGene-RNA analysis from screening • Moved serum sample for biomarkers from screening to Cycle 1 Day 1 • Clarified patient global impression of change (PGIC) timepoint • For footnote "c," added section link for vital signs • Clarified creatinine clearance requirements for cisplatin • Added row and footnote for urine biomarker to clarify what laboratories would perform the tests • Added row and footnote for urine cytology to clarify what laboratories would perform the tests • Changed timing for urine collection for biomarker and cytology for pre-cytology visit from within 2 days to within 7 days immediately prior to radical cystectomy • For footnote "g," added details for collection of coagulation parameters at baseline	To reflect the changes to the study based on this amendment and to provide clarification on adjuvant phase visits for treatment Arm 1 and Arm 2

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Schedules of activities (SoAs): Table 2 (Schedule of assessments for the adjuvant treatment phase [Arm 1]):	• Renamed as schedule of assessments for the adjuvant treatment phase (Arm 1) • Baseline adjuvant scan time frame changed from 35 to 42 days to allow patients a longer period to recover from cystectomy prior to the baseline adjuvant scan • Extended the assessment time for electrocardiograms, concomitant medications, urinalysis, AE/SAE assessment, and PRO/HOSPAD to include 42 days after radical cystectomy • Removed urine biomarker and cytology laboratory assessments • Added Clavien-Dindo assessment 90 days following radical cystectomy to collect surgical complications • Updated the patient-reported outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) assessment timing to be completed at Cycle 1 Day 1 and every 2 weeks up to Week 13 (instead of Week 12) then every 4 weeks thereafter • For footnote "g," added text to indicate that AEs and medications related to the radical cystectomy will be recorded to provide clarification that AEs and concomitant medications related to the surgery need to be documented • For footnote "a," added section link for vital signs • Updated adjuvant assessment to reflect change to every 24 weeks for 36 months, then every 52 weeks (annually) thereafter	Table added to clarify adjuvant phase schedule for patients randomized to Arm 1
Section 1.1 Schedules of activities (SoAs): Table 3 (Schedule of assessments for the adjuvant phase visits [Arm 2]):	• Incorporated all relevant changes from Table 2 (adjuvant schedule for Arm 1) • Clarified that for patients in Arm 2, pregnancy test will only be required for Cycle 1 and Cycle 3	Table added to clarify adjuvant phase schedule for patients randomized to Arm 2, which modified the adjuvant schedule of assessments to decrease the burden of on-site visits for patients randomized to Arm 2
Section 1.1 Schedules of activities (SoAs): Table 4 (Schedule of assessments for patients who have discontinued treatment or completed study visits/treatment):	• Removed Months 4 and 8, as no assessments are scheduled for these dates • Added footnote "a" at Month 2 to indicate patients in Arm 2 will have a follow-up call only at this visit • Removed weight from follow-up assessment at Month 6 • Updated tumor assessment to reflect change to every 24 weeks for 36 months, then every 52 weeks (annually) thereafter	

Section # and Name	Description of Change	Brief Rationale
Section 1.2 (Synopsis - International Coordinating Investigator):	Updated the International Coordinating Investigator from PPD to PPD	
Section 2.3.1.2 (Durvalumab in combination with chemotherapy):	New section	Section added for completeness of potential benefit for use of durvalumab in combination with chemotherapy
Section 2.3.2.2 (Durvalumab in combination with chemotherapy):	New section	Section added for completeness of potential risk for use of durvalumab in combination with chemotherapy
Table 5 (Section 3 [Objectives and Endpoints]):	• Updated event-free survival (EFS) using assessments per Blinded Independent Central Review (BICR) endpoint to include "or by central pathology review if a biopsy is required for a suspected new lesion" to ensure that biopsy results can be incorporated into the EFS endpoint • Updated EFS and proportion of patients alive and event free at 24 months (EFS24) using assessments per local Investigator endpoints to include "or Investigator biopsy review if a biopsy is required for a suspected new lesion" to ensure that biopsy results can be incorporated into the EFS endpoint • Updated metastasis-free survival and disease-specific survival per Investigator assessments to include "or Investigator biopsy review if a biopsy is required for a suspected new lesion" to ensure that biopsy results can be incorporated into the EFS endpoint • Added "PFS2 (time from the date of randomization to the earliest date of progression which occurs on subsequent therapy following an EFS event or death) as defined by local standard clinical practice" endpoint to the following secondary objectives: to assess the efficacy of Arm 1 versus Arm 2 in muscle-invasive bladder cancer (MIBC) patients with adequate renal function and to assess the efficacy of Arm 1 versus Arm 2 in MIBC patients • Clarified the secondary endpoint for European Organization for Research and Treatment of Cancer 30-item Core Quality of Life Questionnaire (EORTC QLQ-C30) scale/item scores as the adjusted mean change from baseline and time to definitive clinically meaningful deterioration in EORTC QLQ-C30 • Clarified the exploratory endpoints for the PRO-CTCAE, PGIC, and patient global impression of severity as descriptive summary of responses	

Section # and Name	Description of Change	Brief Rationale
Section 4.3.2 (Gemcitabine plus cisplatin dose rationale):	Added text summarizing relevant studies confirming the dose and treatment schedule for the 21-day gemcitabine plus cisplatin regimen	
Sections 4.4 (End of study definition) and 6.6 (Treatment after the end of the study):	Added standard text summarizing roll-over and safety extension study options	For clarity and completeness
Section 5.1 (Inclusion criteria):	• Inclusion criterion 4: removed the time limit for prior intravesical chemotherapy for patients entering the study to allow for patients treated with intravesical chemotherapy following the transurethral resection of bladder tumors regardless of time frame • Inclusion criterion 6, changed tumor sample age for PD-L1 from ≤3 years to ≤3 months	
Section 5.2 (Exclusion criteria):	• Changes to Exclusion criterion 2 and 3: added to provide clarity regarding patient eligibility with respect to the extent of surgery allowed on study • Exclusion criterion 6, added autoimmune pneumonitis and autoimmune myocarditis to the list of autoimmune or inflammatory disorders • Exclusion criterion 7, added uncontrolled angina to the list of uncontrolled intercurrent illnesses that are excluded • Exclusion criterion 8, added history of myocardial infarction within the past 6 months prior to randomization due to potential cardiotoxic effects observed with gemcitabine • Exclusion criterion 20, removed the note from this exclusion that patients should not receive live vaccine while receiving investigational product (IP) and up to 30 days after the last dose of IP • Exclusion criterion 22, added a 2-year time limit for prior pelvic radiotherapy	
Section 5.3 (Lifestyle restrictions):	• Clarified that male contraception of condom plus spermicide is applicable only in countries where spermicide is approved, since spermicide is not available in all countries • Clarified to follow the local prescribing information related to contraception for the chemotherapy agents (gemcitabine plus cisplatin)	
Section 5.4 (Screen failures):	Added PD-L1 biopsy/tumor sample (if the sample was sent to the central laboratory during screening) as data collected on screen failures	
Section 6.1.1.1 (Order of administration):	• Added instructions that if anti-emetics are required, then they should be administered 30 minutes prior to chemotherapy, not prior to durvalumab to provide clarity for use of anti-emetics • Added that gemcitabine + cisplatin (G+C) chemotherapy is to be administered per local practice	

Section # and Name	Description of Change	Brief Rationale
Section 6.1.1.2 (Durvalumab [MEDI4736]):	• Updated information and preparation for study treatment • Added language describing acceptable configurations for in-line filter setup for infusion administration	
Section 6.1.1.3 (Gemcitabine and cisplatin):	Clarified that these drugs are to be locally sourced by the sites instead of AstraZeneca	
Section 6.1.2 (Dose and treatment regimens):	• For neoadjuvant therapy, added the creatinine clearance requirements for cisplatin to provide clarity to sites for creatinine clearance verification prior to each cisplatin dose • For adjuvant therapy, added text to provide clarification for the start of Cycle 1 Day 1 for patients in Arm 2 • For adjuvant therapy, changed starting time frame for adjuvant therapy from 28 to 42 days after radical cystectomy to allow patients a longer period to recover from cystectomy prior to the baseline adjuvant scan	
Section 6.1.2.1 (Durvalumab [MEDI4736]):	Updated information and preparation for study treatment	
Section 6.1.3 (Duration of treatment and criteria for treatment through progression):	Moved heading from under Surgical plan and clarified the duration of treatment for Arm 1 and Arm 2	
Section 6.1.4 (Storage):	Added based on updated guidance	
Table 9:	• Updated weeks based on schedules of assessments • Changed starting time frame for adjuvant therapy from 28 to 42 days following radical cystectomy to allow patients a longer period to recover from cystectomy prior to the baseline adjuvant scan	
Section 6.2.2 (Procedures for handling incorrectly enrolled or randomized patients):	Added clarification wording to require that the risk/benefit be part of the conversation between the Investigator and Sponsor when determining if a patient is to continue or discontinue treatment	
Section 6.4 (Concomitant therapy):	Added clarification for Arm 1 and Arm 2	

Section # and Name	Description of Change	Brief Rationale
Table 10 (Prohibited concomitant medications):	• Clarified the timelines for usage of prohibited medications for Arm 1 and Arm 2 • Updated live attenuated vaccines prohibition from 30 to 90 days after the last dose of durvalumab based on the half-life (to approximate 5 times the half-life) • Added time frame information for administration of live attenuated vaccines for G+C chemotherapy to provide clarification for the time frame for acceptable/safe vaccine administration based on current Infectious Diseases Society of America (IDSA) recommendations for patients receiving standard chemotherapy only • Clarified the limited use of steroids with durvalumab • Removed palliative radiotherapy for non-target lesions from supportive medication	
Section 6.5 (Dose modification):	Added clarifications	
Section 7 (Discontinuation of treatment phase of study and patient withdrawal):	Added “phase of study” to the section title to indicate that the section is applicable for both treatment arms	
Section 7.1 (Discontinuation of study treatment):	• Added clarification that a patient should discontinue study treatment if a radical cystectomy procedure is not performed (ie, a partial cystectomy or no cystectomy is performed) • Added clarification for Arm 2 since these patients receive no treatment • Removed discontinuation criterion: “clinical progression/recurrence and Investigator determination that the patient is no longer benefiting from treatment with IP.” Not applicable to this study, as patients would discontinue study treatment for Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST 1.1) progressive disease that precludes a patient from a cystectomy or proven recurrence in the adjuvant setting • Updated proven recurrence wording and added section link to Section 8.1.1.2	
Section 7.1.1 (Procedures for discontinuation of study treatment):	• Clarified the procedures for patients who permanently discontinue drug for reasons other than disease progression/recurrence • Updated tumor assessment schedule to reflect change from “every 24 weeks thereafter” to “every 24 weeks for 36 months, and then every 52 weeks (annually) thereafter”	
Section 8.1 (Efficacy assessments):	• Updated EFS and EFS24 using assessments per BICR to include “or by central pathology review if a biopsy is required for a suspected new lesion”	

Section # and Name	Description of Change	Brief Rationale
Section 8.1.1 (Tumor assessments):	Added section for further details for the subsections below	
Section 8.1.1.1 (Investigator RECIST 1.1 imaging review):	• Changed the timing for second "Adjuvant Baseline" scan from 35 to 42 days to allow patients a longer period to recover from cystectomy prior to the baseline adjuvant scan • Removed biopsy text and added details regarding additional scans if a new lesion is radiologically equivocal • Updated tumor assessment schedule to reflect change from "every 24 weeks thereafter" to "every 24 weeks for 36 months, and then every 52 weeks (annually) thereafter"	
Section 8.1.1.2 (Local biopsy review):	Added section to describe the local biopsy review	
Section 8.1.1.3 (Local pathology review):	Added section to describe the local pathology review	
Section 8.1.1.4 (Central biopsy review):	Added section to describe the biopsy review	
Section 8.1.2 (Survival assessments):	Clarified timepoints for assessments	
Section 8.1.3 (Clinical outcome assessments):	Updated to include more information on compliance and clarify PRO administration best practice instructions	
Table 12 (Clinical chemistry):	Added footnote to clarify creatinine testing and creatinine clearance requirements for cisplatin	
Table 13:	Added clarification for percentages of neutrophils	
Section 8.2.3 (Vital signs and measurements):	Updated to provide clarification on vital signs required for Arm 1 and Arm 2 by neoadjuvant and adjuvant phases	
Section 8.2.6 (Patient follow-up contact [Arm 2 only]):	Added section for follow-up in Arm 2	
Section 8.2.7 (Clavien-Dindo assessment):	Added assessment for grading surgical complications	
Sections 8.3.2 (Time period and frequency for collecting AE and SAE information), 8.3.3 (Follow-up of AEs and SAEs), 8.3.11 (Deaths), and 8.3.13 (Safety data to be collected following the final DCO of the study):	Changed collection time to 90 days after the last dose of treatment (Arm 1) or adjuvant study visits (Arm 2) to provide clarification that patients in Arm 2 will be followed with the same frequency and visit schedule as in Arm 1	
Sections 8.4.5 (Management of IP-related toxicities) and 8.4.5.2 (Specific toxicity management and dose modification information - gemcitabine and cisplatin):	Added clarity for each IP versus durvalumab	

Section # and Name	Description of Change	Brief Rationale
Section 8.4.5.1 (Specific toxicity management and dose modification information - durvalumab):	Added additional text providing language about the use, location, and applicability of the toxicity management guidelines	
Section 8.8.1 (Collection of tissue samples for central pathology review, stratification by PD L1 expression, and biomarker research):	• Updated heading wording for clarity • Changed tumor sample age for PD-L1 from ≤3 years to ≤3 months • Added that sites should refer to the Pathology Manual for detailed instructions and guidelines for the mandatory (treatment stage) tissue sample • Clarified the instructions and guidelines for optional additional tumor biopsies • Removed text that the Ventana PD-L1 (SP263) assay would be used to determine PD-L1 status in all specimens	
Section 8.8.2 (Exploratory biomarkers):	• Clarified tumor markers and added pathological staging analysis • Updated urine cytology wording • Updated serum-based markers wording • Clarified plasma-based markers assessment wording	
Section 9 (Statistical considerations):	Updated EFS using assessments per BICR to include "or by central pathology review if a biopsy is required for a suspected new lesion"	
Section 9.1 (Sample size determination):	Updated alpha and power for Arm 1 versus Arm 2 (EFS in MIBC patients with adequate renal function) and Arm 1 versus Arm 2 (EFS in Intent-to-treat)	
Table 15 (Summary of outcome variables and analysis populations):	Added PFS2	
Section 9.3.1.2 (Co-primary endpoint: event-free survival [EFS]):	• Updated EFS using assessments per BICR to include "or by central pathology review if a biopsy is required for a suspected new lesion" • Added clarification in the event that progression is confirmed via biopsy or subsequent scans • Added clarification regarding censoring of patients who take subsequent therapy prior to their last evaluable RECIST assessment or progression or death	
Section 9.3.1.3 (Secondary endpoints):	• Updated EFS using assessments per BICR to include "or by central pathology review if a biopsy is required for a suspected new lesion" • Clarified definition of metastasis-free survival • Added PFS2	
Section 9.3.2.1 (Adverse events):	Added wording on AE summaries for any AE within 90 days of completion of adjuvant visit and any AE occurring from radical cystectomy	

Section # and Name	Description of Change	Brief Rationale
Section 9.3.3 (Calculation or derivation of patient-reported outcome variables):	Updated the time to definitive/sustained clinically meaningful deterioration in health-related quality of life functioning or symptoms analysis	
Table 16 (Mean change and clinically meaningful change - EORTC QLQ-C30):	Updated change from baseline definitions	
Table 18 (Pre-planned statistical and sensitivity analyses to be conducted):	• Updated EFS using assessments per BICR to include "or by central pathology review if a biopsy is required for a suspected new lesion" • Updated secondary analysis per local Investigator to include "or Investigator biopsy review if a biopsy is required for a suspected new lesion" • Updated endpoint from time to deterioration to time to definitive/sustained clinically meaningful deterioration (EORTC QLQ-C30)	
Section 9.4.1.1 (Multiple testing strategy):	Removed "per BICR" for EFS	
Section 9.4.1.3 (Event-free survival [EFS]):	• Updated description for subgroup analysis of lymph node metastasis • Added PD-L1 status subgroup analysis • Updated attrition bias assessment analysis	
Section 9.4.2.8 (Patient-reported outcomes):	Updated the analysis for EORTC QLQ-C30	
Section 9.5 (Interim analyses):	Added detail on the analysis of the co-primary endpoint pCR	
Section 10 (References):	• Added the following references based on the updates made to the main text: Birgitte et al 2008, Dindo et al 2004, Horn et al 2018, Inman et al 2007, Jan et al 2016, Rizvi et al 2016, Rubin et al 2014, and Von der Maase et al 2000 • Updated National Comprehensive Cancer Network reference from 2017 to 2019	
Appendix C (Handling of human biological samples):	Updated based on new standard AstraZeneca template wording	
Appendix F (Guidelines for evaluation of objective tumor response using RECIST 1.1 criteria [Response Evaluation Criteria in Solid Tumors]):	Updated based on new standard AstraZeneca template wording	
Appendix I (Abbreviations):	Added CSP, CTLA-4, DCO, FDG-PET, IMP, NL, PFS2, REVPRDI, TC, and TMG	
Global/other changes:	Minor corrections and clarifications throughout the protocol to improve readability and correct errors	

Appendix K Changes Related to Mitigation of Study Disruptions Due to Cases of Civil Crisis, Natural Disaster, or Public Health Crisis

Note: Changes below should be implemented only during study disruptions due to any of or a combination of civil crisis, natural disaster, or public health crisis (eg, during quarantines and resulting site closures, regional travel restrictions and considerations if site personnel or study patients become infected with SARS-CoV-2 or similar pandemic infection) during which patients may not wish to or may be unable to visit the study site for study visits. These changes should only be implemented if allowable by local/regional guidelines and following agreement from the Sponsor.

K 1 Reconsent of Study Patients During Study Interruptions

During study interruptions, it may not be possible for the patients to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary, eg, telemedicine visits. Reconsent should be obtained for the alternative means of carrying out visits and assessments as per local and regional regulations and/or guidelines regarding reconsent of study patients should be checked and followed. Reconsent may be verbal if allowed by local and regional guidelines (note, in the case of verbal reconsent the ICF should be signed at the patient's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

Please note reconsent is not required in situations where alternative means of carrying out visits is already indicated as per protocol (irrespective of civil crisis, natural disaster or public health crisis) e.g. in Table 3 Schedule of Assessments for Arm 2 patients in adjuvant phase, where some visits are via virtual contact (not in-clinic).

K 2 Rescreening of Patients to Reconfirm Study Eligibility

Additional rescreening for screen failure due to study disruption can be performed in previously screened patients. The investigator should confirm this with the designated study physician.

In addition, during study disruption there may be a delay between confirming eligibility of a patient and either enrolment into the study or commencing of dosing with IP. If this delay is outside the screening window specified in Table 1 [Schedule of assessments for screening and neoadjuvant treatment (all treatment arms)] the patient will need to be rescreened to reconfirm eligibility before commencing study procedures. This will provide another opportunity to re-screen a patient in addition to that detailed in Table 1. The procedures detailed in Table 1 must be undertaken to confirm eligibility using the same randomization number as for the patient.

K 3 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix, the term telemedicine visit refers to remote contact with the patients using telecommunications technology including phone calls, virtual or video visits, and mobile health devices.

During a civil crisis, natural disaster, or public health crisis, on-site visits may be replaced by a telemedicine visit if allowed by local/regional guidelines. Having a telemedicine contact with the patients will allow adverse events, concomitant medication, and other information including efficacy data where relevant to be collected according to study requirements to be reported and documented.

K 4 Data Capture During Telemedicine or Home/Remote Visits

Data collected during telemedicine visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the patient themselves.

K 5 COVID-19 Risk Assessment

The safety of patients is of primary importance. Any potential risks of participating in the study, particularly with the added challenges due to COVID-19 outbreak, should be weighed against the anticipated benefit (see also principle 2.2 of ICH GCP). Investigators are advised to use clinical judgment in determining infection prevention precautions for study patients.

The emergence of SARS-CoV-2 presents a potential safety risk for cancer patients. Patients enrolling in this study may require more frequent visits to the site for study treatment administration and for study assessments compared to patients receiving standard of care.

Therefore, several risk mitigation factors have been implemented related to study conduct during the COVID-19 outbreak, for patient management in an event of COVID-19, and actions to be taken on study treatment (see Section K 8). With these measures in place, it is considered that the anticipated potential benefits for the patients enrolled in this study outweigh the potential risks. All implemented measures prioritise trial patient safety and data validity; in case these two conflict with each other, trial participant safety should always prevail (see also European Medicines Agency Guidance on the management of clinical trials during the COVID-19 [coronavirus] pandemic [
EMA 2020]).

Notably, patients with active COVID-19 infection confirmed by local laboratory testing will not be eligible for study enrolment (see CSP Section 5.2, Exclusion Criterion 7).

K 6 Potential Risks during COVID-19

Every effort should be made to follow the CSP. Section K 9 provides a dose modification and management plan for patients with confirmed or suspected COVID-19 who are being treated with study intervention durvalumab. The risk-benefit assessment should be carefully considered for each patient enrolling in the study based on the known safety risks related to COVID-19, individual needs, and local guidelines and restrictions. Investigators must continue to use their best clinical judgment in determining the most optimal care for patients and utmost diligence in determining their eligibility for study participation, continued study treatment, and overall assessment of benefit/risk of study treatment or participation.

The sponsor must be promptly notified of a site's inability to perform study activities due to COVID-19 outbreak in order to minimise any potential risks.

K 7 New Patient Enrolment

Study sites may continue to recruit new patients into the study provided the following activities to preserve study integrity can be met:

- Upon discussion with the site monitor, the study site has confirmed the ability to enrol and manage new patients effectively and in compliance with the protocol.
- Data will continue to be entered into the eCRF and queries resolved in a timely manner.

Per CSP Exclusion Criterion 7 (see CSP Section 5.2), patients with uncontrolled intercurrent illness, including but not limited to, ongoing or active infection are not eligible for the study participation and hence such patients (including those who have confirmed COVID 19) should not be included for study participation.

K 8 Study Treatment Administration

If an AE or SAE is associated with COVID-19, the investigator should determine whether the patients' treatment with investigational product should continue, be interrupted, or be discontinued in accordance with the CSP.

AEs, SAEs, cycle delays and/or treatment suspensions associated with COVID-19 along with logistical issues should be reported according to the eCRF Completion Guidelines.

For dosing discontinuations, where applicable, the dosing discontinuation guidelines should be followed, and the End of Treatment Form(s) completed

K 9 Ongoing Patients

Patients receiving study intervention should continue to undergo safety assessments prior to dosing in accordance with the CSP. In case it is not feasible to perform safety assessments, study intervention should be interrupted until such assessments can be completed.

K 9.1 If a Patient has an Event Suspected to be COVID-19

Delay or omit study intervention as appropriate and test for COVID-19 per local health authority or institutional guidance.

- Signs and symptoms of COVID-19 include but are not limited to new onset of fever, new or worsening cough, shortness of breath, difficulty breathing and sometimes abnormal chest imaging and may be similar to those of an imAE.

- In accordance with the CSP and the TMGs for imAEs, thorough evaluation should be performed to accurately identify the underlying pathology in case an AE is encountered for a participant.

- If COVID-19 is ruled out, study intervention may be resumed per the CSP.

- If COVID-19 **is confirmed or diagnosis still suspected after evaluation**, manage COVID-19 per local guidance until full recovery.

K 9.2 Patient with Confirmed COVID-19

Patients with confirmed COVID-19 (by local laboratory testing and/or combination of key symptoms) should have study intervention withheld and COVID-19 managed per local guidance.

In case of confirmed COVID-19 and a simultaneous imAE requiring treatment, investigators are advised to apply clinical judgement regarding the use of corticosteroids as per the durvalumab TMGs. This includes also the consideration of alternate immunosuppressive agents other than corticosteroids for imAE management, depending on the individual patient's presentation (Curigliano et al 2020).

K 9.3 Restarting Study Intervention

Study intervention must not be resumed until recovery from COVID-19 (eg, confirmed by imaging, lab testing and/or absence of symptoms) and COVID-19-specific treatment has been completed per local guidance.

The study clinical lead should be contacted if any additional guidance or clarification is needed.

K 9.4 Vaccination Against COVID-19

Protocol restrictions applying to live attenuated vaccines are relevant for live attenuated COVID-19 vaccines as well. Investigators should apply their discretion assessing the risk-benefit of other types of COVID-19 vaccines for patients in clinical trials. Ideally, administration of the vaccine should be done on a different day other than the day of study drug administration to differentiate any potential AEs seen from the vaccine and study drug. The administration of the vaccine and any potential AEs associated with the vaccine are to be documented on the concomitant medication and AE eCRFs, respectively.

References

Curigliano et al 2020
Curigliano G, Banerjee S, Cervantes A, Garassino M, Garrido P, Girard N. Managing cancer patients during the COVID-19 pandemic: an ESMO multidisciplinary expert consensus. Ann Oncol 2020;31(10):1320-35.

EMA 2020
EMA, Clinical Trials Facilitation and Coordination Group, European Commission. Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic, Version 2, 27 March 2020. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/guidanceclinicaltrials_covid19_en.pdf. Accessed: 17 December 2020.

Appendix L Country-specific Requirements

L 1 Germany

Section # and heading	Description of change with reason
8.8.7 German biomarker sub-study (participating sites only)	In addition to planned biomarker analyses performed for the overall study patient population, a biomarker sub-study will be performed at select sites (approximately 15) in Germany to assess additional immune, mutational and/or molecular subtyping biomarkers from tumor samples collected at baseline and again at the time of cystectomy.

Below is the wording captured in the German Local CSP:

In addition to planned biomarker analyses performed for the overall study patient population, a biomarker sub-study will be performed at select sites (approximately 15) in Germany to assess additional immune, mutational and/or molecular subtyping biomarkers from tumor samples collected at baseline and again at the time of cystectomy. Association and correlation with biomarker results and clinical responses (therapy response, outcomes) will be investigated. The sub-study is intended to collect samples from approximately 50-80 patients recruited as part of the NIAGARA study (total of 1050 patients globally), at sites located in Germany only. Participation in this sub-study for these patients is optional and will require a separate consent process.

Sample Collection for Sub-Study

In addition to the samples described in Section 8.8.1 and 8.8.2, the following samples will be collected from patients that consent to the OPTIONAL sub-study:

- SCREENING: An additional FFPE tissue block (or unstained slides) will be collected from the initial sample confirming MIBC (ie, non-MIBC samples will not be acceptable). Tissue can be collected from newly acquired or archival specimens (≤ 3 months olds).

- CYSTECTOMY: An additional FFPE tissue block (or unstained slides) will be collected from samples taken at the time of cystectomy (including for patients undergoing a partial cystectomy).

Samples will be collected, labeled, stored, and shipped as detailed in the Laboratory Manual.

Tumor Marker Analyses

Samples intended for analysis as part of the German sub-study will initially be received by the central laboratory and will be subsequently processed, in accordance with the instructions in the Laboratory Manual, and sent to testing laboratory for analysis.

If sufficient tissue is available (after prioritization has been given to the biomarker analyses required for the parent NIAGARA study), the following analyses will be performed for tumor tissue samples obtained from patients that consented to the sub-study:

1) Intrinsic MIBC subtyping (screening samples only)
   - Immunohistochemical subtyping via consensus-IHC panel derived by the consensus-working group: CK5, CK14, CK20, GATA3, FOXA1, CD44
   - Gene expression-based subtyping according to the TCGA-II, consensus-working-group approach or other molecular subtyping algorithms using RNA-sequencing or similar technologies (e.g. Nanostring-Technology).
2) Spatial and quantitative characterization of the tumor immune microenvironment (screening and cystectomy samples)
   - Spatial and quantitative immunoscoring of key immune cell populations (CD3, CD4, CD8, FOXP3, CD68, CD163, Granzyme B and MHC1) detected by immunohistochemistry.
   - Gene expression profiling of tumor and immune biomarkers using RNA-sequencing or similar technologies (e.g. Nanostring-Technology).
   - Assessment of PD-L1 status by SP263-CDA (Ventana) in post-treatment tissues and correlation with PD-L1 status analysis of pre-treatment tissues as implemented in NIAGARA-main study based on exploratory digital PD-L1- assessment
   - Stromal tumor infiltrating lymphocyte assessment on HE-slide.
3) Mutational profiling of tumors (screening and cystectomy samples)
   - Mutational next-generation sequencing (NGS)-based profiling of all tumor samples before treatment (TMB, mutational signatures, key genetic alterations e.g. fibroblast growth-factor receptor [FGFR]-alterations).
   - Mutational NGS-based profiling of tumors in patients without pCR (TMB, mutational signatures, key genetic alterations e.g. fibroblast growth-factor receptor [FGFR]-alterations).

Specific biomarker analyses may be adjusted based on biomarker assay availability and/or emerging data.

Once the sub-study analyses are complete, all sub-study samples will be returned to the central laboratory or AZ-assigned biobank for storage. Samples will be stored for a maximum of 15 years from the end of study, after which they will be destroyed or repatriated. Analysis of the exploratory biomarker data within this sub-study will be analyzed and reported independently from the NIAGARA study in cooperation with the BRIDGE-Consortium.

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