Clinical Study Protocol	
Study Intervention	Durvalumab
Study Code	D933RC00002
Version	3.0
Date	03 November 2025
EU CT Number	2024-519246-75

A Phase IIIb, Open-label, Single-arm, Global Study of Perioperative Durvalumab With Neoadjuvant ddMVAC or Gem/Cis in Patients With Muscle-Invasive Bladder Cancer (NIAGARA-2)

Sponsor Name: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifier Number(s):

EU CT Number 2024-519246-75

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

Version Scope: Global

Brief Title: Perioperative Durvalumab With Neoadjuvant ddMVAC or Gem/Cis in Patients With Muscle-Invasive Bladder Cancer

Study Phase: IIIb

Acronym: NIAGARA-2

Study Clinical Lead and Contact Information will be provided separately.

Coordinating Principal Investigators

Stephane Oudard, MD, PhD
Georges Pompidou European Hospital, Oncology Department
20 Rue Leblanc
75015 Paris France

Michiel S. van der Heijden, MD, PhD
The Netherlands Cancer Institute
Plesmanlaan 121
1066 CX Amsterdam The Netherlands

SUMMARY OF CHANGES

DOCUMENT HISTORY	
Document	***Date of Issue***
CSP version 3.0	*03-November-2025*
CSP version 2.0	*21-May-2025*
CSP version 1.0	*30-October-2024*

CSP Version 3.0 03-November-2025

This modification is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the EU Clinical Trial Regulation Article 2, 2 (13) because the modifications either significantly impact the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Modification:

This amendment is developed to delete an inclusion criterion (at least one lesion ≥10mm, not previously irradiated), add the Clavien-Dindo assessment for grading surgical complications, update the duration of ddMVAC dosing to 4 cycles, remove the "two missed visits" rule from event-free survival, and to correct minor typographical errors, administrative changes, and changes for consistency.

Summary of Changes:

List of Modifications

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
Overall CSP	The CSP version number and date is revised at all applicable instances.	Revisions made as CSP is amended	Non-substantial
Multiple sections throughout the CSP	(a.) Throughout the entire protocol, text that references duration of dosing of ddMVAC is updated from "for up to 6 cycles" to "**for 4 cycles.** However, participants may receive up to 6 cycles of ddMVAC if this is consistent with the treating institution's standard practice." (b.) Deleted the text "at the investigator's discretion" or related languages.	(a.) Updated to reflect clinical practice and ensure consistency in number of cycles administered (b.) The phrase "at the investigator's discretion" has been removed throughout the protocol to enhance clarity and standardization of study procedures	(a.) Substantial (b.) Non-substantial
Section 1.1 Synopsis Rationale	Following text has been added: Based on the positive NIAGARA results,	For clarity	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	perioperative durvalumab plus neoadjuvant gem/cis has been listed in NCCN guideline (category 1) (NCCN Guidelines® Insights: Bladder Cancer 3.2024), EAU guideline (level of evidence 1b) (European Association of Urology Guidelines 2024), and has received Score A by ESMO-MCBS (score A) (Powles et al 2024b). In addition, perioperative durvalumab plus neoadjuvant gem/cis has been approved in multiple regions including the US, and EU.		
Section 1.1 Synopsis (Rationale), Section 2 Introduction, and Section 4.2.2 NIAGARA-2 Rationale for Neoadjuvant Chemotherapy	Referencing to NCCN Guidelines® Insights: Bladder Cancer 3.2024 and European Association of Urology Guidelines 2024 has been done.	For clarity	Non-substantial
Section 1.1 Synopsis (Objectives and Endpoints) and Section 3 Objectives and Endpoints (Table 6 Objectives and Endpoints)	Table footnote d is updated as follows: "FAS includes all participants enrolled in the study who have received at least 1 dose of study treatment" and a Note has been added "FAS is the same as the SAF."	Clarifying edit	Non-substantial
Section 1.1 Synopsis Rationale and Section 4.3.1.5 Rationale for Shorter Infusion Time	Updated referencing to durvalumab IB, Edition from "20" to "21."	For consistency	Substantial
Section 1.1 Synopsis Executive Steering Committee and Section 9.6 Executive Steering Committee	Text has been updated to include "An executive steering committee (ESC) **that includes independent experts."**	Clarifying edit	Non-substantial
Section 1.2 Schema (Figure 1 Study Design)	(a.) Schematic diagram is updated for ddMVAC dosing, from 6 cycles to 4 cycles (b.) A footnote is added for ddMVAC "Participants may receive up to 6 cycles of ddMVAC if this is consistent with institutional standard practice and as clinically indicated."	(a.) Updated to reflect reduced dosing duration (b.) Clarifying edit	Non-substantial
Section 1.3 Schedule of Activities – Table 1 Schedule of Activities for Screening and Neoadjuvant Durvalumab in	(a.) Cycle 6 is updated to "optional" (b.) ddMVAC administration (in Cycle 5) on week 9 is updated to optional (c)	Clarifying edit	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
Combination With ddMVAC	A footnote has been added for both the changes (a) and (b) mentioned above "C5 ddMVAC administration is optional as per the institution's standard and as clinically indicated. C6 visit is optional and should only be completed if ddMVAC is being administered at this visit as per the institution's standard and as clinically indicated."		
Section 1.3 Schedule of Activities – Table 3 Schedule of Activities for Adjuvant Durvalumab	Clavien-Dindo Assessment is added to Schedule of Activities.	Updated to accommodate new assessment for grading surgical complications	Substantial
Section 2.1 Study Rationale	Referencing to NCCN Guidelines® Insights Bladder Cancer 5.2018 has been done.	For clarity	Non-substantial
Section 2.1 Study Rationale	Details of estimated overall survival at 24 months from the randomised Phase III NIAGARA study has been added. Information on use of perioperative durvalumab with neoadjuvant chemotherapy as a new treatment option for cisplatin eligible patients with muscle-invasive bladder cancer has been added.	For clarity and consistency	Substantial
Section 2.1 Study Rationale, Section 2.3.2 Benefit Assessment, and Section 4.2.1 Rationale for Study Design	Text has been updated to include efficacy results from NEMIO study 2025.	To align with the updated NEMIO study	Non-substantial
Section 2.2.1 Immunotherapies	Cemiplimab (LIBTAYO™) and tiselizumab (TEVIMBRA™) has been added in the list of therapies.	For clarity	Non-substantial
Section 2.2.2 Durvalumab	Treatment option for MIBC, advanced or metastatic bile duct or gallbladder cancer has been added based on FDA approval.	For clarity and consistency	Substantial
Section 2.3 Benefit/Risk Assessment	Text and numeric values have been updated.	Updated to align with Investigator's Brochure (IB) edition 21	Non-substantial
Section 2.3.1 Risk Assessment	Surgical outcomes and neoadjuvant safety from the randomised Phase III NIAGARA study have been added.	For clarity and consistency	Substantial
Section 2.3.2 Benefit Assessment	Details on improvement in event-free survival, overall	For clarity and consistency	Substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	survival, and a numerical increase in pathologic complete response rate in randomised Phase III NIAGARA study have been added.		
Section 4.3.2.1 Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin Dose Rationale	The following text has been added: Extending ddMVAC beyond 4 cycles partially improves local disease control without any survival benefit (5-year OS 79% 4 cycles versus 75% > 4 cycles, p = 0.27). Given the toxicity of ddMVAC, only 4 cycles should be delivered as neoadjuvant treatment in MIBC (Pfister et al 2021, Pfister et al 2022).	For clarity	Substantial
Section 4.3.2.3 Cisplatin Split-dose Rationale	Details on post-hoc analysis in the subset of patients with borderline renal function have been added.	For clarity	Substantial
Section 5.1 Inclusion Criteria – Inclusion Criterion 2	Text is updated to include the N1 disease definition "N1 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 be resectable, as per the planned lymphadenectomy procedure (see Section 6.1.6 Surgical Plan). Lymph nodes with < 10 mm short axis diameter are considered non-pathological per RECIST1.1."	Clarifying edit	Non-substantial
Section 5.1 Inclusion Criteria – Inclusion Criterion 5	"At least one lesion, not previously irradiated, that qualifies as a RECIST 1.1 Target lesion at baseline and can be accurately measured at baseline as ≥ 10 mm in the longest diameter (except lymph nodes, which must have short axis ≥ 15 mm) with CT or MRI and is suitable for accurate repeated measurements" is deleted. All subsequent inclusion criteria are renumbered.	Not applicable to this study. Primary tumours in bladder may not be measurable on scans and only confirmed via cystoscopic assessment	Substantial
Section 5.1 Inclusion Criteria – Inclusion Criterion 7b	(a.) Definition of post-menopausal is updated from "…amenorrhoeic for 12 months	(a.) Updated for accuracy as there is no randomisation for the	(a.) Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	prior to the planned date of randomisation" to "…amenorrhoeic for 12 months prior to the **first dose of study treatment.**"	study	
	(b.) Pregnancy test Requirement for negative serum pregnancy test result is updated from "…at Visit 1" to "…**at screening.**"	(b.) Updated to align with Schedule of Activities (SoA)	(b.) Non-substantial
	(c.) Numbering is updated to 7b from 8b due to upstream inclusion criterion deletion	(c.) Updated for alignment	(c.) Non-substantial
Section 5.4 Screen Failures	Text is added to clarify that rescreened participants are required to sign a new ICF and will be assigned a new participant number (ie, E-code) from the initial screening.	Updated for clarification	Non-substantial
Section 6.1 Study Treatments Administered – Table 7 Investigational Products	(a.) Text is added to clarify that dose of cisplatin on Day 1 may be reduced from 70 mg/m^2 OR **35 mg/m^2** (dose to be determined based on renal function), with a second dose of **35 mg/m^2 to be administered on Day 8 ONLY if the dose on Day 1 was reduced to 35 mg/m^2 due to renal function.** (b.) footnote a is updated to include the details for SoC cisplatin-based NAC treatment may be supplied centrally through AstraZeneca "which will be labelled and accompanied by prescribing information with local language translated text in accordance with regulatory guidelines. (c.) A footnote is added for ddMVAC "Participants may receive up to 6 cycles of ddMVAC if this is consistent with institutional standard practice and as clinically indicated."	(a.) Updated to clarify that in the event that creatinine clearance drops below 60 mL/min, the cisplatin dose may be divided into 2 administrations, as per institutional practice, for management of renal toxicity; (b.) To maintain consistency within the protocol (c.) Clarifying edit	Non-substantial
Section 6.1.2 Durvalumab Regimen	Text is updated to include "Q3W as appropriate."	Clarifying edit	Non-substantial
Section 6.1.4 (a.) Dose and Treatment Regimens – Table 8 Study schema. (b.) Figure 2 Dosing Schedule	(a.) Footnote c is added to specify that "ddMVAC administration on weeks 9 and 11 is optional as per institutional standard practice and as clinically indicated."	Clarifying edit	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	(b.) Footnote is added to specify that "C5 and C6 ddMVAC administration at weeks 9 and 11 respectively, are optional as per institutional standard practice and as clinically indicated."		
Section 6.1.6 Surgical Plan	Text is added to allow for **robot-assisted, laparoscopic and open** RC surgical methods	Updated for addition and clarification of surgical methods	Non-substantial
	Text is updated to remove Indiana Pouch as an acceptable method for urinary diversion creation, to add **ureterocutaneostomy**, and to change ileal neobladder to **small/large bowel** neobladder.	Updated to clarify permitted surgical methods of urinary diversion following radical cystectomy	Non-substantial
Section 6.2.2.2 Administration and Section 2.3.1 Risk Assessment – Table 5 Risk Assessment of Durvalumab	Durvalumab infusion time is updated from "…60 minutes ± 5 minutes in Cycle 1" to "…60 minutes ± **10** minutes in Cycle 1."	Clarification of requirements	Non-substantial
Section 6.3 Assignment to Study Treatment	Text is updated to "Participants must not receive study medication unless all eligibility criteria have been met."	Clarified for accuracy	Non-substantial
6.3.1 Procedures for Handling Incorrectly Enrolled Participants	Text is updated to "Participants who fail to meet the eligibility criteria should not, under any circumstances, receive study medication" Text is updated to "Where a participant does not meet all the eligibility criteria but incorrectly received study medication, the investigator…"	Clarified for accuracy	Non-substantial
Section 8.1.1.1 Imaging Tumour Assessments	Text is updated to allow additional modalities, including FDG-PET scan, for staging.	Updated to permit additional imaging methods for staging	Non-substantial
Section 8.2.5.3 Clavien-Dindo Assessment	New section has been added. Text of this section has been updated to describe the additional Clavien-Dindo Assessment for grading surgical complications. Details on classification has also been added.	Updated to add assessment for grading surgical complications	Substantial
Section 9.2 Sample Size Determination	Text "are not enrolled" is replaced with "do not meet eligibility criteria."	Clarifying edit	Non-substantial
Section 9.3 Populations for Analyses – Table 12 Populations for Analysis	(a.) FAS description is updated to specify that the FAS consists of enrolled participants who have received at least 1 dose of	Clarifying edit	Non-substantial

Section Number and Name	Description of Change	Brief Rationale	Substantial /Non-substantial
	study treatment" and text is added "Note the FAS is the same as the safety analysis set (SAF)." (b.) RC set and Non-RC set description is updated to specify that participants must have received at least one dose of study treatment to be included.		
Section 9.4.3.1 Safety and Tolerability: Adverse Events	Section is updated to add the following text: "Supporting AE summaries for any AE occurring from radical cystectomy to 90 days post-radical cystectomy, including Clavien-Dindo assessment, will also be provided. Further details will be provided in SAP."	Clarifying edit	Non-Substantial
Section 9.4.3.2 Event-free Survival	Section is updated to delete the following text: "However, if the participant presents an event after 2 or more consecutive missed visits, the participant will be censored at the time of the visits prior to the 2 missed visits."	Text regarding the "2 missed visits rule" is deleted to minimize the loss of clinically relevant events	Substantial
Appendix G 5 Prohibited, and Permitted Concomitant Medications/Therapies (Table 22)	Replaced the wording "other than those under investigation in this study" with "other than durvalumab and the investigator selected cisplatin-based neoadjuvant chemotherapy."	Clarifying edit	Non-substantial
Appendix I Document History	Added Appendix I Document History.	For traceability	Non-substantial
Section 11 References	References were updated based on the additions made in synopsis and body of the CSP.	For consistency	Non-substantial

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or special term	Explanation
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AJCC	American Joint Committee on Cancer
ALK	anaplastic lymphoma kinase
ALP	alkaline phosphatase
ALT	alanine aminotransferase/transaminase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase/transaminase
AUC	area under the curve
AUC_{ss}	area under the curve at steady state
AxMP	auxiliary medicinal product
BP	blood pressure
BTC	biliary tract cancer
C	Cycle
CD	cluster of differentiation
CI	confidence interval
C_{max}	maximum observed concentration
$C_{max,ss}$	maximum observed concentration at steady state
COVID-19	coronavirus disease 2019
CR	complete response
CrCl	calculated creatinine clearance
CRO	contract research organisation
CSP	clinical study protocol
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
CV	cardiovascular

Abbreviation or special term	Explanation
CYP	cytochrome P450
DCO	data cut-off
ddMVAC	dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin
DES	data entry site
DFS	disease-free survival
DoR	duration of response
DUS	disease under study
EAP	extended access programme
EAU	European Association of Urology
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EFS	event-free survival
EGFR	epidermal growth factor receptor
ESC	Executive Steering Committee
EU	European Union
EU CT	European Union Clinical Trial
FAS	Full Analysis Set
FDA	United States Food and Drug Administration
FSH	follicle-stimulating hormone
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
gem/cis	gemcitabine and cisplatin
GI	gastrointestinal
GMP	Good Manufacturing Practice
HBcAb	hepatitis B core antibodies
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCP	healthcare provider
HCV	hepatitis C virus
HDV	hepatitis D virus
HIV	human immunodeficiency virus
HR	hazard ratio
HRT	hormone replacement therapy
IATA	International Airline Transportation Association
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

Abbreviation or special term	Explanation
ILD	interstitial lung disease
imAE	immune-mediated adverse event
IMP	investigational medicinal product
INR	international normalised ratio
IO	immuno-oncology
IP	investigational product
IRB	Institutional Review Board
IRR	infusion-related reaction
IRT	interactive response technology
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
LFT	liver function test
LPI	last participant in
mAb	monoclonal antibody
MIBC	muscle-invasive bladder cancer
MIUC	muscle-invasive urothelial cancer
MRI	magnetic resonance imaging
MVAC	methotrexate, vinblastine, doxorubicin, and cisplatin
NA	not applicable
NAC	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NE	not evaluable
NL	new lesion
NSCLC	non-small cell lung cancer
NTL	non-target lesion
ORR	objective response rate
OS	overall survival
PCR	polymerase chain reaction
pCR	pathologic complete response
PD	progression of disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PD-L2	programmed death-ligand 2
pDS	pathologic down-staging

Abbreviation or special term	Explanation
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PLND	pelvic lymph node dissection
PR	partial response
PRAE	possibly treatment-related adverse event
PTT	partial thromboplastin time
QTcF	QT interval corrected by Fridericia's formula
QTL	quality tolerance limit
Q*X*W	every *X* weeks
RC	radical cystectomy
RECIST 1.1	Response Evaluation Criteria in Solid Tumours, Version 1.1
RTSM	Randomisation and Trial Supply Management
SAE	serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SCLC	small-cell lung cancer
SmPC	Summary of Product Characteristics
SD	stable disease
SoA	Schedule of Activities
SoC	standard of care
sPD-L1	soluble programmed death-ligand 1
SUSAR	suspected unexpected serious adverse reaction
T_3	triiodothyronine
T_4	thyroxine
TBL	total bilirubin
TCC	transitional cell carcinoma
TdP	Torsades de Pointes
TKI	tyrosine kinase inhibitor
TL	target lesion
TMG	Toxicity Management Guidelines
TPV	third-party vendor
TSH	thyroid stimulating hormone
TRAE	treatment-related adverse event
UC	urothelial carcinoma
ULN	upper limit of normal
UN	United Nations

Abbreviation or special term	Explanation
WHO	World Health Organisation
WOCBP	women of child-bearing potential

1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase IIIb, Open-label, Single-arm, Global Study of Perioperative Durvalumab With Neoadjuvant ddMVAC or Gem/Cis in Patients With Muscle-Invasive Bladder Cancer (NIAGARA-2)

Brief Title: Perioperative Durvalumab With Neoadjuvant ddMVAC or Gem/Cis in Patients With Muscle-Invasive Bladder Cancer

Regulatory Agency Identifier Number(s):

EU CT Number 2024-519246-75

Rationale

Bladder cancer is the ninth most commonly diagnosed cancer, with increasing incidence and mortality rates. Worldwide, 1.95 million people live with bladder cancer. In 2022, over 610,000 people were newly diagnosed with bladder cancer, and more than 220,000 people died (Ferlay et al 2024). Approximately 20% of patients with bladder cancer present with non-metastatic muscle-invasive bladder cancer (MIBC) at the initial diagnosis (Hahn 2021, Patel et al 2020).

Standard treatment for cisplatin-eligible patients with MIBC involves neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy (RC) with pelvic lymph node dissection PLND (Holzbeierlein et al 2024, Powles et al 2022, Witjes et al 2024). Neoadjuvant Chemotherapy (NAC) regimens such as gemcitabine and cisplatin (gem/cis) and dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) are recommended (NCCN Guidelines® Insights: Bladder Cancer 3.2024, European Association of Urology Guidelines 2024), with an absolute overall survival (OS) benefit of 5% to 10% (Lotan et al 2022). While gem/cis is a widely used NAC regimen, there is growing evidence to support clinical benefit with ddMVAC in MIBC. Neoadjuvant ddMVAC showed meaningful progression-free survival (PFS) and OS benefit over neoadjuvant gem/cis but with a higher toxicity in the randomised Phase III GETUG-AFU V05 VESPER trial (Pfister et al 2022).

For high-risk MIUC patients assessed after RC, adjuvant nivolumab is recommended based on disease-free survival (DFS) benefit in the Phase III CheckMate 274 trial (Bajorin et al 2021, NCCN Guidelines® Insights: Bladder Cancer 3.2024, European Association of Urology Guidelines 2024).

Despite advancements in treatment, approximately 50% of patients with MIBC have recurrence within 3 years (Lee et al 2021, Pfister et al 2022). Moreover, even with survival benefit, less than half of cisplatin-eligible patients receive NAC aligning with the current guideline-recommended treatment strategy (Alimohamed et al 2024), indicating a significant unmet medical need for additional treatment options to improve clinical outcomes and

survival in this patient population.

Durvalumab is a human mAb of the immunoglobulin G1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca for use in the treatment of multiple tumour types. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumour elimination.

In the randomised Phase III NIAGARA study conducted in participants with cisplatin-eligible MIBC, perioperative durvalumab plus neoadjuvant gem/cis followed by RC demonstrated statistically significant and clinically meaningful improvements in EFS (HR: 0.68, 95% CI: 0.56 – 0.82; $p < 0.0001$) and OS (HR: 0.75, 95% CI: 0.59 – 0.93; $p = 0.0106$) compared with gem/cis and RC alone. The addition of perioperative durvalumab to NAC was tolerable and manageable, with no new safety signals. Neoadjuvant durvalumab did not delay surgery and did not impact the ability of patients to undergo or complete surgery (Powles et al 2024a, Powles et al 2024b). Based on the positive NIAGARA results, perioperative durvalumab plus neoadjuvant gem/cis has been listed in NCCN guideline (category 1) (NCCN Guidelines® Insights: Bladder Cancer 3.2024), EAU guideline (level of evidence 1b) (European Association of Urology Guidelines 2024), and has received Score A by ESMO-MCBS (score A) (Powles et al 2024b). In addition, perioperative durvalumab plus neoadjuvant gem/cis has been approved in multiple regions including the US and EU. Following the NIAGARA study results, this Phase IIIb NIAGARA-2 study aims to expand on the data from the Phase III NIAGARA study by investigating the safety and efficacy of perioperative durvalumab in combination with cisplatin-based NAC (ddMVAC as well as gem/cis) in a real-world clinical practice setting.

In addition, the NIAGARA-2 will explore the feasibility and tolerability of 30-minute infusions of durvalumab following a 60-minute infusion in the first cycle. Shortening IV infusion time may reduce the burden on patients and improve hospital drug delivery-related efficiencies. In multiple pivotal Phase III trials, durvalumab 60-minute infusion as a monotherapy and in combination was tolerable across tumour types. Incidence of Grade 3 IRR was less than 0.2%, and no Grade 4 or 5 IRR was reported (durvalumab IB, Edition 21). Safety of durvalumab 30-minute infusion is currently being investigated in advanced BTC patients who are treated with durvalumab in combination with chemotherapy in the Phase IIIb TOURMALINE study.

NIAGARA-2 results will provide further data on perioperative durvalumab in combination with cisplatin-based NAC that is practice-informing.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety of neoadjuvant durvalumab combined with ddMVAC or gem/cis prior to RC	Incidence of Grade 3 or 4 PRAEs as observed prior to RC. [a] A PRAE [b] is defined as an AE that has been assessed by the investigator to be possibly related to study treatment. The analysis will be performed on the SAF [c] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
Secondary	
To further assess the safety and tolerability of perioperative durvalumab combined with ddMVAC or gem/cis	Incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality of treatment-emergent AEs, including PRAEs, AESIs, imAEs, AEs, and SAEs; AEs resulting in study treatment interruption and discontinuation; laboratory findings. The analysis will be performed on the SAF [c] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
To assess the efficacy of perioperative durvalumab combined with ddMVAC or gem/cis in terms of EFS	EFS is defined as the time from first neoadjuvant durvalumab + chemotherapy treatment until the earliest occurrence of any of the following events: • First recurrence of disease after RC • First documented progression in participants who were medically precluded from RC • Time of expected surgery in participants who refuse to undergo RC or failure to undergo RC in participants with residual disease • Death due to any cause The primary measure of interest is EFS rate at 12 months. The analysis will be performed on the FAS [d] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
To assess the efficacy of perioperative durvalumab combined with ddMVAC or gem/cis in terms of DFS	DFS is defined as the time from the date of RC to the earliest of the first recurrence of disease post RC or death due to any cause. The primary measures of interest are DFS rates at 18 and 24 months. The analysis will be performed in a subset of participants in the FAS [d] who undergo RC and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
To assess the efficacy of perioperative durvalumab combined with ddMVAC or gem/cis in terms of OS	OS is defined as the time from first neoadjuvant durvalumab + chemotherapy until death due to any cause. The primary measure of interest is OS rate at 12 months. The analysis will be performed on the FAS [d] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).

To assess the efficacy of neoadjuvant durvalumab combined with ddMVAC or gem/cis followed by RC in terms of pCR	pCR rate is defined as the proportion of participants whose pathologic staging is T0N0M0 as assessed per local pathology review using specimens obtained via RC. Participants who do not undergo RC will be included as failures (did not achieve T0N0M0). The analysis will be performed in the FAS [d] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
To assess the efficacy of neoadjuvant durvalumab combined with ddMVAC or gem/cis followed by RC in terms of pDS	pDS rate is defined as the proportion of participants whose pathologic staging is < P2 per local pathology review using specimens obtained via RC. The analysis will be performed in the FAS [d] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
Exploratory	
To characterise baseline characteristics and clinical outcomes in participants who did not undergo RC	Descriptive statistics of baseline characteristics, clinical outcomes, and reasons for precluding RC. The analysis will be performed in a subset of participants in the FAS [d] who did not undergo RC (non-RC cohort).
To explore feasibility and tolerability of durvalumab 30-minute infusion	Incidence of IRRs and hypersensitivity/anaphylactic reactions. The analysis will be performed on the SAF. [c]

[a] All participants entering this study plan to undergo RC. For participants who do not undergo RC, their data will be collected in the eCRF along with the reason to not undergo RC. The primary analysis of 'safety prior to RC' will include participants' data until the date of decision not to undergo RC (medically precluded or participant's refusal) or the date of planned RC, whichever occurs first.

[b] An event is considered a PRAE if the investigator has answered yes to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

[c] SAF includes all participants enrolled in the study who have received at least 1 dose of study treatment.

[d] FAS includes all participants enrolled in the study who have received at least 1 dose of study treatment. Note the FAS is the same as the SAF.

Overall Design Synopsis

This is a Phase IIIb, open-label, single-arm, multicentre, global study to assess safety and efficacy of neoadjuvant durvalumab in combination with cisplatin-based chemotherapy followed by RC and adjuvant durvalumab in patients with MIBC.

Participants will receive durvalumab in combination with cisplatin-based NAC for up to 12 weeks prior to RC. Either ddMVAC or gem/cis will be selected based on investigator choice and will be administered per institutional clinical practice: ddMVAC Q2W for 4 cycles or gem/cis Q3W for 4 cycles. However, participants may receive up to 6 cycles of ddMVAC if this is consistent with the treating institution's standard practice. Durvalumab 1500 mg will be administered as a 60-minute IV infusion in the first cycle and as a 30-minute IV infusion in subsequent cycles if the 60-minute IV infusion in the first cycle is well tolerated.

Durvalumab administration will be adjusted based on the chemotherapy regimens: Q4W when combined with ddMVAC or Q3W when combined with gem/cis.

The percentage of participants to be treated with durvalumab in combination with neoadjuvant gem/cis will be limited to approximately 30% of the total number of participants.

After RC and adequate recovery (between 42 and 120 days), participants will receive durvalumab 1500 mg Q4W for up to a maximum of 8 cycles or until progression, unacceptable toxicity, withdrawal of consent, or any treatment discontinuation criterion is met.

Brief Summary

The Phase IIIb NIAGARA-2 study aims to expand on the data from the Phase III NIAGARA study by investigating perioperative durvalumab in combination with investigator-selected NAC (either ddMVAC or gem/cis) in a clinical practice setting. This study will further explore the feasibility and tolerability of 30-minute infusions of durvalumab.

Disclosure Statement

This is a Phase IIIb, open-label, single-arm, multicentre, global study to assess safety and efficacy of perioperative durvalumab in combination with investigator's choice cisplatin-based chemotherapy (ddMVAC or gem/cis) in patients with MIBC.

Participant Population

The target population of interest in this study is individuals with MIBC (clinical stage T2-T4aN0/1M0 or T1N1M0) who are eligible to receive cisplatin-based NAC and RC.

Number of Participants

Approximately 202 participants will be screened to achieve 150 treated with study treatment. The percentage of participants to be treated with durvalumab in combination with neoadjuvant gem/cis will be limited to approximately 30% of the total number of participants.

Note: 'Screened' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but are not assigned in the study, are considered 'screen failures'.

Treatment Groups and Duration

Neoadjuvant treatment

The dosing of ddMVAC or gem/cis regimen will be consistent with prescribing information of respective agents as well as in accordance with institutional clinical practice and guidelines.

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

- Durvalumab + ddMVAC
  - Day 1: durvalumab 1500 mg IV; every 4 weeks for 3 cycles
  - Day 1: methotrexate 30 mg/m^2 IV; Day 2: vinblastine 3 mg/m^2 IV, doxorubicin 30 mg/m^2 IV, cisplatin 70 mg/m^2 IV; G-CSF as per institutional standard; every 2 weeks for 4 cycles. However, participants may receive up to 6 cycles of ddMVAC if this is consistent with the treating institution's standard practice.

OR

- Durvalumab + gem/cis
  - Day 1: durvalumab 1500 mg IV; every 3 weeks for 4 cycles
  - Day 1: cisplatin 70 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2; every 3 weeks for 4 cycles

Participants with borderline renal function (40 ≤ CrCl < 60 mL/min)

Results of serum creatinine and a determination of creatinine clearance must be available and reviewed by the treating physician or investigator prior to dosing for participants on the cisplatin split-dose regimen.

- Durvalumab + gem/cis (split-dose cisplatin)
  - Day 1: durvalumab 1500 mg IV, every 3 weeks for 4 cycles
  - 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 3 weeks for 4 cycles

Adjuvant treatment

After RC and adequate recovery between 42 and 120 days, participants will receive durvalumab 1500 mg Q4W for a maximum of 8 cycles or until progression, unacceptable toxicity, withdrawal of consent, or any of treatment discontinuation criteria is met (for study discontinuation criteria, see Section 7.1)

In scenarios when participants are unable to complete the intended number of cycles of chemotherapy and/or durvalumab throughout the study, participants will be permitted to receive fewer cycles of chemotherapy and/or durvalumab following institutional clinical practice based on judgement by the investigator.

Non-cystectomy extension phase

Participants who fulfil the necessary criteria (see Section 6.1.6) may enter the non-cystectomy extension phase after consultation and approval by AstraZeneca. Participants who enter the non-cystectomy extension phase may be administered durvalumab 1500 mg as monotherapy Q4W for a maximum of 8 doses or until study-specific discontinuation criteria are met. For

participants who enter the non-cystectomy extension phase and subsequently undergo a RC, further treatment should be discussed and agreed upon with AstraZeneca.

Treatment through progression

During neoadjuvant treatment, participants who have progression (refer to Appendix E) may continue to the adjuvant portion of treatment if the progression event did not preclude the participant from having a RC (ie, progression is local and/or limited to regional lymph nodes that will be removed during the RC/bilateral lymph node dissection procedure). In the event that progression (ie, distant metastases) precludes a participant from undergoing RC, the participant will proceed to follow-up per institutional practice and be followed for OS.

During the adjuvant treatment phase, participants with proven recurrence (see Section 8.1.1) will proceed to follow-up for OS per institutional practice.

Follow-up of participants post-completion or post-discontinuation of study treatment

Following the last dose of study treatment, all participants will undergo a safety follow-up visit (90 days after the last dose of durvalumab) and will be followed up per institutional practice (every 3 months ± 14 days are recommended) until recurrence or progression, death, withdrawal of consent, or the end of the study, as per the SoA.

See Sections 8.1.2, 8.3.1, 8.3.11, and 9.4.3.4 for a description of assessments following DCO.

Statistical Methods

All safety analyses will be performed on the SAF, which will consist of all participants who take at least 1 dose of study treatment. In addition, safety analysis will be performed by NAC cohorts (ddMVAC cohort and gem/cis cohort).

The primary analysis will be conducted when the LPI has had the opportunity to complete neoadjuvant durvalumab in combination with cisplatin-based chemotherapy (ddMVAC or gem/cis). The primary endpoint (incidence of Grade 3 or 4 PRAEs in neoadjuvant treatment phase) will be summarised by frequency counts and corresponding percentages including 95% CIs based on binomial exact method (Clopper-Pearson).

Safety data will be summarised descriptively overall, by seriousness, by causality, and by maximum NCI CTCAE (v5.0) grade.

If there is less than 40% EFS maturity at the time of the primary analysis, a final analysis may be conducted when there is approximately 40% EFS maturity or the LPI has had the opportunity to be followed up for a minimum of 12 months, whichever occurs first.

The time-to-event outcomes of EFS at 12 months, DFS at 18 and 24 months, and OS at 12 months landmark timepoints will be assessed using the Kaplan-Meier method together with

associated 95% CIs. Also, 25th percentile rates may be reported with associated 95% CIs. CIs will be based on the Brookmeyer-Crowley method. In addition, the Kaplan-Meier curves of EFS, DFS, and OS will be presented graphically.

The proportion of participants who achieved pCR and pDS in the FAS will be calculated along with exact 95% CIs for the proportions, calculated using the Clopper-Pearson method.

The efficacy analyses will be performed in predefined datasets and by NAC cohorts (ddMVAC cohort and gem/cis cohort).

Executive Steering Committee

An executive steering committee (ESC) that includes independent experts will be established to provide guidance on-study conduct, periodic data review, and interpretation of results. In addition to the ongoing overall safety monitoring by AstraZeneca and/or the CRO, the ESC will also periodically assess study data according to an agreed schedule (as well as on an ad hoc basis, based on the results of the ongoing medical review), ensuring that study participants are not exposed to undue risk.

Further details of the ESC remit, procedures, processes, and meeting frequency will be outlined in an ESC Charter.

Interim Analysis

No formal interim analysis is planned for this study. Planned periodic safety data reviews will be conducted to monitor safety and tolerability, as follows:

- An early safety data review will be triggered when approximately 10 participants have received at least 2 cycles of durvalumab + ddMVAC.
- A further data review will be done after approximately 60 participants who received neoadjuvant durvalumab + ddMVAC or gem/cis have been followed up until RC.

At each planned safety data review, all safety data in the clinical database will be summarised.

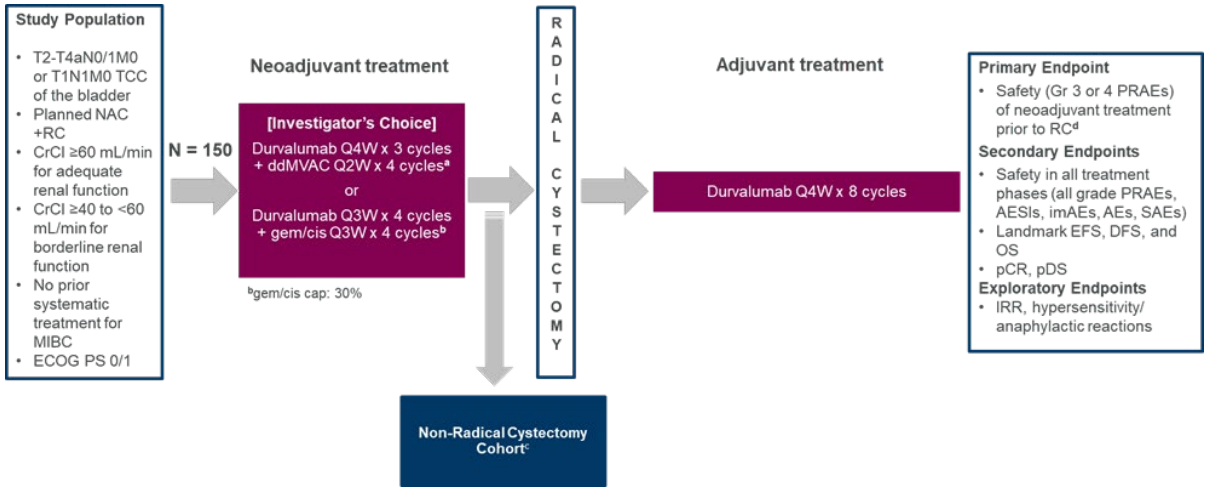
Details of the planned reviews will be provided in the SAP and in the ESC charter.

1.2 Schema

The study treatment phase of this study includes neoadjuvant, surgical, and adjuvant phases (Figure 1):

- Neoadjuvant treatment: participants receive durvalumab + ddMVAC or gem/cis
- Surgery: RC
- Adjuvant treatment: participants receive durvalumab monotherapy

Figure 1 Study Design



[a] Participants may receive up to 6 cycles of ddMVAC if this is consistent with institutional standard practice and as clinically indicated.

[b] The number of participants receiving durvalumab in combination with gem/cis is limited to 30% of the total number of participants.

[c] All participants entering this study plan to undergo RC. For participants who do not undergo RC, their data will be collected in the eCRF along with the reason to not undergo RC. The primary analysis of 'safety prior to RC' will include participants' data until the date of decision not to undergo RC (medically precluded or participant's refusal) or the date of planned RC, whichever occurs first.

[d] For participants who do not undergo RC (medically precluded or participant's refusal), participants' data along with the reason not to undergo RC will be collected in the eCRF. Participants who refuse surgery but are disease-free will be able to receive an additional 8 cycles of durvalumab per decision of investigator. For these participants, safety and efficacy will be described separately.

1.3 Schedule of Activities

The procedures for this study are presented in the SoA for screening and the neoadjuvant treatment phase in Table 1 for participants treated with durvalumab + ddMVAC and Table 2 for participants treated with durvalumab + gem/cis. The procedures for the adjuvant treatment phase are presented in Table 3.

Procedures and/or assessments are required for participants who have discontinued or completed study treatment are presented in Table 4.

Table 1 Schedule of Activities for Screening and Neoadjuvant Durvalumab in Combination With ddMVAC

	Screening	C1 1 cycle = 2 weeks (14 days)	C2 1 cycle = 2 weeks (14 days)	C3 1 cycle = 2 weeks (14 days)	C4 1 cycle = 2 weeks (14 days)	C5 1 cycle = 2 weeks (14 days)	C6 * (optional) 1 cycle = 2 weeks (14 days)	Pre-radical cystectomy	Radical cystectomy (14 days to 56 days after last dose of neoadjuvant therapy)	For details, see Section
Week	**-4 to -1**	**1**	**3**	**5**	**7**	**9**	**11**			
Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**			
Window (± days)	**NA**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Informed consent										
Informed consent [a]	X									5.1
Study procedures										
Inclusion and exclusion criteria	X	X								5.1, 5.2
Demography, including baseline characteristics and tobacco use	X									5.1, 5.2
Medical/surgical history	X									5.1
Full physical examination, including height and weight [b]	X									8.2.1
Targeted physical examination as per institutional standard [c]		X	X	X	X	X	X			8.2.1
Vital signs	X	X	X	X	X	X	X		X	8.2.2
ECG (resting 12-lead) [d]	X	As clinically indicated								8.2.3
Concomitant medications	X	X	X	X	X	X	X	X	X	6.9
Laboratory assessments										
Clinical chemistry [e,f]	X	X [g]	X	X	X	X	X			8.2.4
Haematology [e,f]	X	X [g]	X	X	X	X	X			8.2.4
Coagulation parameters		X [g]								8.2.4
Cortisol [h]	X	X [i]		X		X				8.2.4
TSH (reflex free T_3 or free T_4) [j]	X	X [k]		X		X				8.2.4
Hepatitis B and C and HIV	X									8.2.4

Table 1 Schedule of Activities for Screening and Neoadjuvant Durvalumab in Combination With ddMVAC

	Screening	C1 1 cycle = 2 weeks (14 days)	C2 1 cycle = 2 weeks (14 days)	C3 1 cycle = 2 weeks (14 days)	C4 1 cycle = 2 weeks (14 days)	C5 1 cycle = 2 weeks (14 days)	C6* (optional) 1 cycle = 2 weeks (14 days)	Pre-radical cystectomy	Radical cystectomy (14 days to 56 days after last dose of neoadjuvant therapy)	For details, see Section
Week	**-4 to -1**	**1**	**3**	**5**	**7**	**9**	**11**			
Day	**-28 to -1**	**1**	**1**	**1**	**1**	**1**	**1**			
Window (± days)	**NA**	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**			
Urinalysis	X	As clinically indicated								8.2.4
Pregnancy test [l]	X	X		X		X				8.2.4
Monitoring										
WHO/ECOG performance status	X	X	X	X	X	X	X			8.2.5.2
AE/SAE assessment [m]		<----------							---------->	8.3
IP administration										
Durvalumab [n]		X		X		X				6.1.2, 6.1.4
ddMVAC [n]		X	X	X	X	X* (optional)	X			6.1.3, 6.1.4
Other assessments and assays										
Tumour biopsy (newly acquired or archival per institutional standard)	X									8.1.1
Radical cystectomy									X	6.1.6
Tumour pathology assessment (per institutional standard)									X	8.1.1
Additional tumour biopsies (per institutional standard)		The collection of additional tumour biopsies upon progression of participants as per institutional standard.								8.1.1
Efficacy evaluations										
Neoadjuvant tumour assessments: RECIST 1.1	X [o]							X [p]		8.1 [q], Appendix E

* C5 ddMVAC administration is optional as per the institution's standard and as clinically indicated. C6 visit is optional and should only be completed if ddMVAC is being administered at this visit as per the institution's standard and as clinically indicated.

[a] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

[b] Full physical examinations may include assessments of the general appearance, CV system, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, respiratory, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, haematologic/lymphatic, and neurological systems per institutional clinical practice. Height will be measured at screening only.

[c] A targeted physical examination may include assessments of skin, lungs, CV system, and abdomen (liver and spleen) and is performed by the investigator on the basis of clinical observations and symptomatology as per institutional clinical practice.

[d] Any clinically significant abnormalities detected require additional ECG results to be obtained per institutional clinical practice.

[e] Serum or plasma clinical chemistry (including LFT monitoring) and haematology 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 1 and Day 8 dose of cisplatin (if applicable).

[g] If screening clinical chemistry and haematology 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, aPTT and INR are to be assessed at baseline on Day 1 (unless performed within 3 days prior to Day 1).

[h] Cortisol sample is to be collected as per institutional clinical practice.

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

[j] 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.

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

[l] For WOCBP only. A serum pregnancy test at screening and then urine pregnancy tests after are acceptable. WOCBP are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks within 3 days prior to every dosing visit. 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.

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

[n] Durvalumab will be administered first; methotrexate infusion will start approximately 1 hour after the end of the durvalumab infusion. Durvalumab will be administered as a 60-minute infusion in the first cycle and as a 30-minute infusion in subsequent cycles if the 60-minute IV infusion in the first cycle is well tolerated. **For the first durvalumab infusion (60-minute infusion)**: BP and pulse will be collected/recorded in the eCRF prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes), approximately 30 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 60 minutes ± 5 minutes). A 1-hour observation period is recommended after the first infusion of durvalumab and prior to the initiation of chemotherapy with monitoring of signs and symptoms of IRR and anaphylaxis per institutional standards. **For the first 30-minute durvalumab infusion**: BP and pulse will be collected/recorded in the eCRF prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes), approximately 15 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 30 minutes ± 5 minutes). A 1-hour observation period is recommended after the first infusion of durvalumab 30-minute infusion and prior to the initiation of chemotherapy with monitoring of signs and symptoms of IRR and anaphylaxis per institutional standards. **For subsequent infusions**: BP, pulse, and other vital signs should be measured, collected/recorded in the eCRF prior to the start of the infusion. Participants 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. If there are no clinically significant concerns on previous infusions, the observation period may be reduced for subsequent infusions (suggested duration is 30 minutes).

[o] 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 enrolment, and this scan is designated as the "Neoadjuvant Baseline" scan (ie, lesions are classified as neoadjuvant baseline TLs or NTLs). Lesions in the wall of distensible organs are not reproducibly measurable and should be classified NTLs.

[p] A neoadjuvant follow-up scan must be performed upon completion of NAC prior to surgery; consideration should be given to scheduling this scan as

part of the pre-surgical workup to confirm participant is still eligible for a RC.

[q] For participants who are medically precluded from, refuse, or withdraw from a RC, refer to Section 8.1.1 for tumour assessment schedule

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

Table 2 Schedule of Activities for Screening and Neoadjuvant Durvalumab in Combination With Gem/Cis

	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 neoadjuvant 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
Study procedures												
Inclusion and exclusion criteria	X	X										5.1, 5.2
Demography, including baseline characteristics and tobacco use	X											5.1, 5.2
Medical/surgical history	X											5.1
Full physical examination, including height and weight [b]	X											8.2.1
Targeted physical examination as per institutional standard [c]		X	X	X	X	X	X	X	X			8.2.1
Vital signs	X	X	X	X	X	X	X	X	X		X	8.2.2
ECG (resting 12-lead) [d]	X	As clinically indicated										8.2.3
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	6.9
Laboratory assessments												
Clinical chemistry [e,f]	X	X [g]	X	X	X	X	X	X	X			8.2.4
Haematology [e,f]	X	X [g]	X	X	X	X	X	X	X			8.2.4
Coagulation parameters		X [g]										8.2.4
Cortisol [h]	X	X [i]		X		X		X				8.2.4
TSH (reflex free T_3 or free T_4) [j]	X	X [k]		X		X		X				8.2.4
Hepatitis B and C and HIV	X											8.2.4
Urinalysis	X	As clinically indicated										8.2.4

Table 2 Schedule of Activities for Screening and Neoadjuvant Durvalumab in Combination With Gem/Cis

	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 neoadjuvant 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**			
Pregnancy test [l]	X	X		X		X		X				8.2.4
Monitoring												
WHO/ECOG performance status	X	X	X	X	X	X	X	X	X			8.2.5.2
AE/SAE assessment [m]	<----------										---------->	8.3
IP administration												
Durvalumab [n]		X		X		X		X				6.1.2, 6.1.4
Gemcitabine [n]		X	X	X	X	X	X	X	X			6.1.3, 6.1.4
Cisplatin [n]		X	X [o]	X	X [o]	X	X [o]	X	X [o]			6.1.3, 6.1.4
Other assessments and assays												
Tumour biopsy (newly acquired or archival per institutional standard)	X											8.1.1
Radical cystectomy											X	6.1.6
Tumour pathology assessment (per institutional standard)											X	8.1.1
Additional tumour biopsies (per institutional standard)		The collection of additional tumour biopsies upon progression of participants as per institutional standard.										8.1.1
Efficacy evaluations												
Neoadjuvant tumour assessments: RECIST 1.1	X [p]									X [q]		8.1 [r], Appendix E

[a] Written informed consent and any locally required privacy act document authorisation must be obtained prior to performing any protocol-specific procedures, including screening/baseline evaluations.

[b] Full physical examination may include assessments of the general appearance, CV system, abdomen, skin, head and neck (including ears, eyes, nose,

and throat), lymph nodes, thyroid, respiratory, musculoskeletal (including spine and extremities), urogenital, dermatological, gastrointestinal, endocrine, haematologic/lymphatic, and neurological systems per institutional clinical practice. Height will be measured at screening only.

[c] A targeted physical examination may include assessments of skin, lungs, CV system, and abdomen (liver and spleen) and is performed by the investigator on the basis of clinical observations and symptomatology as per institutional clinical practice.

[d] Any clinically significant abnormalities detected require additional ECG results to be obtained per institutional clinical practice.

[e] Serum or plasma clinical chemistry (including LFT monitoring) and haematology 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 1 and Day 8 dose of cisplatin (if applicable).

[g] If screening clinical chemistry and haematology 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, aPTT and INR are to be assessed at baseline on Day 1 (unless performed within 3 days prior to Day 1).

[h] Cortisol sample is to be collected as per institutional clinical practice.

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

[j] 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.

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

[l] For WOCBP only. A serum pregnancy test at screening and then urine pregnancy tests after are acceptable. WOCBP are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 3 weeks within 3 days prior to every dosing visit. 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.

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

[n] Durvalumab will be administered first; gem/cis infusion will start approximately 1 hour after the end of the durvalumab infusion. Durvalumab will be administered as a 60-minute infusion in the first cycle and as a 30-minute infusion in subsequent cycles if the 60-minute IV infusion in the first cycle is well tolerated. **For the first durvalumab infusion (60-minute infusion)**: BP and pulse will be collected/recorded in the eCRF prior to the beginning of the infusion (measured once from approximately 30 minutes before up to zero minutes), approximately 30 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 60 minutes ± 5 minutes). A 1-hour observation period is recommended after the first infusion of durvalumab and prior to the initiation of chemotherapy with monitoring of signs and symptoms of IRR and anaphylaxis per institutional standards. **For the first 30-minute durvalumab infusion**: BP and pulse will be collected/recorded in the eCRF prior to the beginning of the infusion (measured once from approximately 30 minutes before up to zero minutes), approximately 15 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 30 minutes ± 5 minutes). A 1-hour observation period is recommended after the first infusion of durvalumab 30-minute infusion and prior to the initiation of chemotherapy with monitoring of signs and symptoms of IRR and anaphylaxis per institutional standards. **For subsequent infusions**: BP, pulse, and other vital signs should be measured, collected/recorded in the eCRF prior to the start of the infusion. Participants 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. If there are no clinically significant concerns on previous infusions, the observation period may be reduced for subsequent infusions (suggested duration is 30 minutes).

[o] This is required for participants 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 institutional practice, for management of renal toxicity.

[p] 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 enrolment, and this scan is designated as the "Neoadjuvant Baseline" scan (ie, lesions are classified as neoadjuvant baseline TLs or NTLs). Lesions in the wall of distensible organs are not reproducibly measurable and should be classified NTLs.

[q] A neoadjuvant follow-up scan must be performed upon completion of NAC prior to surgery; consideration should be given to scheduling this scan as part of the pre-surgical workup to confirm participant is still eligible for a RC.

[r] For participants who are medically precluded from, refuse, or withdraw from a RC, refer to Section 8.1.1 for tumour assessment schedule.

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

Table 3 Schedule of Activities for Adjuvant Durvalumab

		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	**42-120 days after radical cystectomy**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Window (days)	**(±14 days)**	**(± 3 days, tumour assessment ± 7 days)**								
Study procedures										
Targeted physical examination as per institutional standard [a]		X		X		X		X		8.2.1
Vital signs		X	X	X	X	X	X	X	X	8.2.2
ECG (resting 12-lead) [b]	As clinically indicated									8.2.3
Concomitant medications	<---------- >									6.9
Laboratory assessments										
Clinical chemistry [c]		X	X	X	X	X	X	X	X	8.2.4
Haematology [c]		X	X	X	X	X	X	X	X	8.2.4
Coagulation parameters		X								8.2.4
Cortisol [d]		X	X	X	X	X	X	X	X	8.2.4
TSH (reflex free T_3 or free T_4) [e]		X	X	X	X	X	X	X	X	8.2.4
Urinalysis	As clinically indicated									8.2.4
Pregnancy test [f]		X[e]	X[e]	X[f]	X	X	X	X	X	8.3.13
Monitoring										
WHO/ECOG performance status		X	X	X	X	X	X	X	X	8.2.5.2
AE/SAE assessment [g]	<---------- >									8.3
IP administration										
Durvalumab [h]		X	X	X	X	X	X	X	X	6.1.2

Table 3 Schedule of Activities for Adjuvant Durvalumab

		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	**42-120 days after radical cystectomy**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	
Window (days)	**(±14 days)**	**(± 3 days, tumour assessment ± 7 days)**								
Other assessments and assays										
Additional tumour biopsies (per institutional standard)		The collection of additional tumour biopsies upon recurrence or progression of participants as per institutional standards.								8.1.1
Clavien-Dindo assessment		90 days post-cystectomy (including a partial cystectomy, if performed)								8.2.5.3
Efficacy evaluations										
Tumour assessments (RECIST 1.1)	X [i]	Tumour assessments occur as per institutional clinical practice (recommended every 12 weeks ±7 days until recurrence/progression, the end of study, death, study discontinuation, or sponsor decision, whichever comes first [j]) For participants who are medically precluded from, refuse, or withdraw from a RC, refer to Section 8.1.1 for tumour assessment schedule.								6.1.5, 8.1, Appendix E

[a] A targeted physical examination may include assessments of skin, lungs, CV system, and abdomen (liver and spleen) and is performed by the investigator on the basis of clinical observations and symptomatology as per institutional clinical practice.

[b] Any clinically significant abnormalities detected should be further investigated following institutional clinical practice.

[c] Serum or plasma clinical chemistry (including LFT monitoring) and haematology are to be collected Q4W prior to the start of infusion 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] Cortisol sample is to be collected as per institutional clinical practice.

[e] 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.

[f] For WOCBP only. A urine or serum pregnancy test is acceptable. WOCBP 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.

[g] For AEs/SAEs reported resulting from the RC, additional information such as concomitant medications must be reported.

[h] Durvalumab will be administered as a 30-minute infusion if patients are well tolerated with the previous 30-minute infusion. BP, pulse, and other vital signs should be measured, collected/recorded in the eCRF prior to the start of the infusion. Participants 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. If there are no clinically significant concerns on previous infusions, the observation period may be reduced for subsequent infusions (suggested duration is 30 minutes).

[i] A CT (preferred) or MRI of the chest, abdomen, and pelvis are recommended to be performed 42 days (± 2 weeks) after RC 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 tumours exist, a fresh selection of TLs and NTLs 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.

Table 4 Schedule of Assessments for Participants Who Have Discontinued or Completed Study Treatment

Evaluation	Safety follow-up visit 90 days (± 5 days) after last durvalumab dose	Regular follow-up visit per institutional standard [a] every 3 to 6 months (± 14 days)	For details, see Section
Physical examination as per institutional standard	X	X	8.2.1
Vital signs	X	X	8.2.2
Weight	X	X	8.2.2
Urinalysis	X	As clinically indicated	Table 10
Pregnancy test as per institutional standard	X	As clinically indicated	8.3.13
AE/SAE assessment	X		8.3
Concomitant medications	X		6.9
WHO/ECOG performance status	X	X [b]	8.2.5.2
Subsequent anti-cancer therapy [c]	X	X	7.1.4
Survival status	X	X	7.1.4, 8.1.2
Clinical chemistry	X		Table 10
Haematology	X		Table 10
Coagulation parameters	As clinically indicated		Table 10
Cortisol [d]	X		Table 10
TSH (reflex free T_3 or free T_4) [e]	X		Table 10
Tumour assessment as per institutional standard [f]	X	X	6.1.5, 8.1, Appendix E

[a] As per institutional standard. Recommended every 3 to 6 months (± 14 days).
[b] WHO/ECOG performance status should also be collected at other site visits that the participant attends, if appropriate site staff are available to collect such information. In addition, WHO/ECOG performance status should be provided when information on subsequent anti-cancer therapy is provided, where possible.
[c] Details of any treatment for bladder cancer (including surgery and radiation) post the last dose of IMP must be recorded in the eCRF. At a minimum, the start date and description of the subsequent anti-cancer therapy should be collected.
[d] Cortisol sample is to be collected as per institutional clinical practice.

[e] 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.

[f] Tumour assessments for participants who discontinued or completed study treatment occur as per institutional clinical practice (recommended every 3 months ± 14 days after the date of RC for the first 24 months, then every 6 months ± 14 days for 36 months, and then every 52 weeks (annually) thereafter until recurrence/progression, the end of study, death, study discontinuation, or sponsor decision, whichever occurs first.

2 INTRODUCTION

Bladder cancer is the ninth most commonly diagnosed cancer, with increasing incidence and mortality rates. Worldwide, 1.95 million people live with bladder cancer. In 2022, over 610,000 people were newly diagnosed with bladder cancer, and more than 220,000 people died (Ferlay et al 2024). Approximately 20% of patients with bladder cancer present with non-metastatic MIBC at the initial diagnosis (Hahn 2021, Patel et al 2020).

Standard treatment for cisplatin-eligible patients with MIBC involves neoadjuvant cisplatin-based chemotherapy followed by RC with PLND (Holzbeierlein et al 2024, Powles et al 2022, Witjes et al 2024). NAC regimens such as gem/cis and ddMVAC are recommended (NCCN Guidelines® Insights: Bladder Cancer 3.2024, European Association of Urology Guidelines 2024), with an absolute OS benefit of 5% to 10%(Lotan et al 2022). While gem/cis is a widely used NAC regimen, there is growing evidence to support clinical benefit with ddMVAC in MIBC. Neoadjuvant ddMVAC showed meaningful PFS and OS benefit over neoadjuvant gem/cis but with a higher toxicity in the randomised Phase III GETUG-AFU V05 VESPER trial (Pfister et al 2022).

For high-risk MIUC patients assessed after RC, adjuvant nivolumab is recommended based on DFS benefit in the Phase III CheckMate 274 trial (Bajorin et al 2021, NCCN Guidelines® Insights: Bladder Cancer 3.2024, European Association of Urology Guidelines 2024).

Despite advancements in treatment, approximately 50% of patients with MIBC have recurrence within 3 years (Lee et al 2021, Pfister et al 2022). Moreover, even with survival benefit, fewer than half of cisplatin-eligible patients receive NAC aligning with current guideline-recommended treatment strategy (Alimohamed et al 2024), indicating a significant unmet medical need for additional treatment options to improve clinical outcomes and survival in this patient population.

2.1 Study Rationale

The unmet need in the treatment of MIBC, aimed at preventing recurrence or progression and improving survival, supports the development of new treatment options with immune-checkpoint inhibitors.

Durvalumab is a human mAb of the immunoglobulin G1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca for use in the treatment of multiple tumour types. Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumour elimination.

Neoadjuvant durvalumab in combination with gem/cis followed by RC and adjuvant durvalumab was assessed in the Swiss Group for Clinical Cancer Research SAKK 06/17

study, an investigator-initiated, open-label, single-arm, Phase II study including 57 cisplatin-fit participants with Stage cT2-T4a cN0-1 operable MIUC (Cathomas et al 2023). In this study, 4 cycles of neoadjuvant gem/cis in combination with 4 cycles of durvalumab (start with gem/cis Cycle 2) were administered, followed by radical surgery. Adjuvant durvalumab was given for 10 cycles. The primary endpoint, EFS at 2 years, was met with 76% (1-sided 90% CI [lower bound], 67%; 2-sided 95% CI, 62% – 85%). EFS at 3 years was 73%, and OS at 2 years and 3 years were 85% and 81%, respectively. Grade 3 and 4 TRAEs during neoadjuvant treatment occurred in 42% and 25% of participants, respectively. TRAEs related to adjuvant durvalumab were Grade 3 in 5 participants (11%) and Grade 4 in 2 participants (4%). No Grade 5 TRAEs occurred. A total of 50 participants received RC and PLND. All participants received neoadjuvant chemo-immunotherapy. The median (interquartile range) number of lymph nodes removed was 29 (range: 23–38). No intraoperative complications were registered. Grade ≥ 3 postoperative complications were reported in 12 patients (24%). Complete nodal dissection (100%) was performed at the level of the obturator fossa (bilaterally) and of the left external iliac region; in 49 patients (98%) at the internal iliac region and at the right external iliac region; in 39 (78%) and 38 (76%) patients at the right and left presacral level, respectively (Afferi et al 2024). This study results suggests a potential benefit of neoadjuvant durvalumab in combination with gem/cis followed by adjuvant durvalumab and supports the surgical safety of RC and PLND following neoadjuvant chemo-immunotherapy in patients with MIUC.

In the randomised Phase III NIAGARA study conducted in participants with cisplatin-eligible MIBC, perioperative durvalumab plus neoadjuvant gem/cis followed by RC demonstrated statistically significant and clinically meaningful improvements in EFS (HR: 0.68, 95% CI: 0.56 – 0.82; $p < 0.0001$) and OS (HR: 0.75, 95% CI: 0.59 – 0.93; $p = 0.0106$) compared with gem/cis and RC alone (Powles et al 2024b). The estimated overall survival at 24 months was 82.2% (95% CI, 78.7 to 85.2) in the durvalumab group and 75.2% (95% CI, 71.3 to 78.8) in the comparison group (hazard ratio for death, 0.75; 95% CI, 0.59 to 0.93; $p = 0.01$ by stratified log-rank test) (Powles et al 2024b). The addition of perioperative durvalumab to NAC was tolerable and manageable, with no new safety signals. Neoadjuvant durvalumab did not delay surgery and did not impact the ability of participants to undergo or complete surgery (Powles et al 2024a, Powles et al 2024b). The results of this trial support the use of perioperative durvalumab with neoadjuvant chemotherapy as a new treatment option for cisplatin-eligible patients with muscle-invasive bladder cancer. Addition of durvalumab to NAC did not impact the rate or timing of radical cystectomy and did not increase the rate of surgical complications. Rates of surgical complications by Clavien–Dindo Classification were similar between study arms. AE profile in the neoadjuvant period was similar between study arms. Immune-mediated AEs in the neoadjuvant period were mostly low grade and consistent with the known safety profile of durvalumab (Catto et al 2025).

Following the NIAGARA study results, the first Phase III trial to show that adding perioperative durvalumab to neoadjuvant gem/cis increases EFS and OS in MIBC, questions

remain on the safety and efficacy of durvalumab in combination with other commonly used chemotherapy regimen such as ddMVAC in the treatment of MIBC. While gem/cis is a widely used NAC regimen, there is growing evidence to support clinical benefit with ddMVAC in MIBC. In the randomised Phase III GETUG-AFU V05 VESPER trial, neoadjuvant ddMVAC showed meaningful PFS and OS benefit over neoadjuvant gem/cis but with a higher toxicity (Pfister et al 2022). Neoadjuvant ddMVAC in combination with durvalumab or durvalumab plus tremelimumab has been investigated in the NEMIO trial, an investigator-initiated randomised Phase I-II trial (GETUG-AFU V09). According to the interim analyses with 113 MIBC participants, both neoadjuvant combination regimens showed tolerable safety profiles without delay in cystectomy and a promising efficacy signal: pCR 49%, 2-year DFS 74.8%, and 2-year OS 77.2% in ddMAVC + durvalumab arm (n = 55); pCR 47%, 2-year DFS 90%, and 2-year OS of 87.9% in ddMVAC + durvalumab + tremelimumab arm (n = 58). However, in the NEMIO trial, adjuvant durvalumab was not assessed (Thibault et al 2025).

Therefore, the Phase IIIb NIAGARA-2 study aims to expand on the data from the Phase III NIAGARA study by investigating the safety and efficacy of perioperative durvalumab with neoadjuvant ddMVAC as well as gem/cis in a clinical practice setting.

In addition, this study will explore feasibility and tolerability of 30-minute infusions of durvalumab following a 60-minute infusion in the first cycle. Durvalumab will be administered as a 60-minute infusion in the first cycle and as a 30-minute infusion in subsequent cycles if the 60-minute IV infusion in the first cycle is well tolerated. Accordingly, safety including IRR and hypersensitivity/anaphylactic reactions will be assessed in this study. IRRs, including urticaria with onset on the day of dosing or 1 day after dosing, are considered ADRs for durvalumab. In the durvalumab monotherapy pooled dataset (N = 3006), IRR (including urticaria) was reported at a frequency of Common (58 patients [1.9%]). Most patients had Grade 1 or 2 events in severity. Six patients (0.2%) had a maximum of Grade 3 IRR. No patients had Grade 4 or Grade 5 events of IRR. Safety data from pivotal Phase III trials with durvalumab in combination with chemotherapy in BTC, NSCLC, and SCLC has not shown an increase in IRRs (durvalumab IB). The safety of durvalumab 30-minute infusion is currently being investigated in advanced BTC patients who are treated with durvalumab in combination with chemotherapy in Phase IIIb TOURMALINE study. Reducing the infusion time of durvalumab to 30 minutes would provide potential benefits to both patients and treatment facilities. Those on immunotherapy infusion typically spend between 2.5 and 6 hours in a hospital-based setting for preparation, infusion, and check-out (Sehn et al 2007, Hartung et al 2020) and also need to travel to and from the hospital/infusion centre. In addition, multiple infusions are required over the course of treatment. Therefore, shorter duration of IV infusion time is to improve patient satisfaction by reducing patient burden of lengthy infusions (Q3W or Q4W) and patient time management and to improve operational and cost efficiencies by reducing hospital drug delivery-related healthcare costs (Rombouts et al 2020).

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). Also in 2018, the NCCN guidelines were revised to reflect the treatment approach of NAC followed by RC plus lymphadenectomy to be offered to all Stage IIIa patients, when feasible. Previously, patients with node-positive disease were not considered cystectomy candidates (NCCN Guidelines Insights Bladder Cancer 5.2018). 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.

2.2 Background

2.2.1 Immunotherapies

Immune responses directed against tumours are one of the body's natural defences against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing, allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T-cells. PD-L1 is one such protein, and is expressed in a broad range of cancers.

PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T cell activation. The 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). The 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 PD-1, an inhibitory signal is transmitted into the T cell, which reduces cytokine production and suppresses T-cell proliferation. Tumour cells exploit this immune-checkpoint pathway as a mechanism to evade detection and inhibit immune response.

PD-L1 is constitutively expressed by B cells, dendritic cells, and macrophages (Rombouts et al 2020, Qin et al 2016). Importantly, PD-L1 is commonly overexpressed on tumour cells or on non-transformed cells in the tumour microenvironment (Pardoll 2012). PD-L1 expressed on the tumour cells 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 tumour microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumour cells in response to endogenous anti-tumour activity. In contrast, CTLA-4 is constitutively expressed by regulatory T cells and upregulated on activated T cells. Binding of CTLA-4 to CD80 or CD86 on immune cells leads to inhibition of T-cell activation (Fife and Bluestone 2008).

The inhibitory mechanism described above is co-opted by tumours 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 anti-tumour 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.

Based on in vitro studies, an antibody that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of anti-tumour T-cells (Blank et al 2006).

In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab was expected to stimulate the patient's anti-tumour immune response by binding to PD-L1 and shifting the balance toward an anti-tumour response.

Stimulating an anti-tumour immune response is a mechanism employed successfully by a number of approved cancer therapies. Blocking the PD-1/PD-L1 pathway is an approach that has been successfully employed with therapies such as pembrolizumab (KEYTRUDA™), nivolumab (OPDIVO™), atezolizumab (TECENTRIQ™), avelumab (BAVENCIO®), cemiplimab (LIBTAYO™), tiselizumab (TEVIMBRA™), and durvalumab (IMFINZI™), which have been approved by a number of various regulatory agencies, including the United States FDA and the EMA, as a treatment for a number of oncology indications.

2.2.2 Durvalumab

Durvalumab is a human mAb of the immunoglobulin G1 kappa subclass that blocks the interaction of PD-L1 (but not PD-L2) with PD-1 on T cells and CD80 (B7.1) on immune cells. It is being developed by AstraZeneca for use in the treatment of multiple tumour types. The proposed mechanism of action 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 tumour elimination. In vitro studies demonstrate that durvalumab antagonises the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of interferon-γ (IFN-γ) (Stewart et al 2015). In vivo studies have shown that durvalumab inhibits tumour growth in xenograft models via a T-cell-dependent mechanism (Stewart et al 2015). Based on these data, durvalumab is expected to stimulate the participant's anti-tumour immune response by binding to PD-L1 and shifting the balance toward an anti-tumour response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

Durvalumab (IMFINZI) in combination with gemcitabine and cisplatin as neoadjuvant treatment, followed by single-agent durvalumab (IMFINZI) as adjuvant treatment following radical cystectomy, is indicated for the treatment of adult patients with MIBC. Durvalumab

(IMFINZI) in combination with chemotherapy (gemcitabine and cisplatin) was the first FDA approval for adults with locally advanced or metastatic bile duct or gallbladder cancer to receive as a first treatment option. Durvalumab is approved in some countries as monotherapy for unresectable Stage III NSCLC (following chemoradiation therapy), and in combination with chemotherapy for extensive-stage SCLC and for locally advanced or metastatic BTC. Durvalumab is also approved when administered in combination with tremelimumab for unresectable hepatocellular carcinoma, and also in combination with tremelimumab plus chemotherapy for participants with metastatic NSCLC without EGFR or ALK mutations. In addition, durvalumab is approved with chemotherapy as neoadjuvant treatment followed by single-agent durvalumab as adjuvant treatment after surgery for adults with resectable NSCLC without EGFR or ALK mutations and also in combination with chemotherapy followed by single-agent durvalumab for adults with primary advanced or recurrent endometrial cancer that is mismatch repair deficient.

A detailed description of the chemistry, pharmacology, efficacy, and safety of durvalumab is provided in the durvalumab IB and in the approved product label(s).

2.3 Benefit/Risk Assessment

As of 30 April 2024, durvalumab is approved in more than 90 countries. An estimated 19,475 patients have received durvalumab in AstraZeneca or MedImmune-sponsored interventional studies in multiple tumour types, stages of disease, and lines of therapy. Of these, 6,325 patients received durvalumab monotherapy, 4,593 patients received durvalumab in combination with tremelimumab, and 8,557 patients received durvalumab or durvalumab plus tremelimumab in combination with an investigational and/or an approved product. An estimated 18,404 patients have been randomised and treated to the various treatment/comparator arms in sponsor-blinded and/or double-blinded studies. In addition,

> 6500 patients have participated in 8 durvalumab EAPs (D4194C00002 [PACIFIC EAP]; D419QR00007 [CASPIAN EAP]; EAP in Australia; D933AR00005 [TOPAZ EAP; ongoing at DCO]; D419CR00019 [HIMALAYA EAP; ongoing at DCO]; D9311C00003 [DUO-E EAP; ongoing at DCO]; D933QR00001 [ADRIATIC EAP; ongoing at DCO]; and D9106R00004 [AEGEAN EAP; ongoing at DCO]). The cumulative worldwide post approval patient exposure since launch is estimated to be approximately 251,348patient-years.

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 ESC.

2.3.1 Risk Assessment

Risk of durvalumab monotherapy is summarised in Table 5.

Table 5 Risk Assessment of Durvalumab

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
Durvalumab		
Risks with durvalumab include, but are not limited to, diarrhoea/colitis, pneumonitis/ILD, endocrinopathies (ie, events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism, type I diabetes mellitus, and diabetes insipidus), hepatitis/increases in transaminases, nephritis/increases in creatinine, rash/dermatitis (including pemphigoid), myocarditis, myositis/polymyositis, encephalitis, immune thrombocytopenia, IRRs, hypersensitivity reactions, pancreatitis, serious infections, and other rare or less frequent inflammatory events including neuromuscular toxicities (eg, Guillain-Barré syndrome, myasthenia gravis).	In monotherapy clinical studies, AEs at an incidence of ≥ 20% include events such as fatigue and decreased appetite. Approximately 10% of participants discontinued the drug due to an AE. Please see the current version of the IB for a detailed summary of the monotherapy data including AEs, SAEs, and CTCAE Grade 3 to 5 events reported across the durvalumab programme.	Refer to "Dosing Modification and TMGs for Durvalumab Monotherapy or in Combination with Other Products" as provided to the investigative site as an Annex document, which is maintained within the Site Master File.
Study Procedures		
Risks with shorter infusion time (30 minutes) of durvalumab are unknown.	The incidence of IRR in the pooled safety data from participants treated with the 60-minute infusion of durvalumab monotherapy is common (1.9%: 58 patients out of 3,006 patients). Most patients had Grade 1 or 2 events in severity. Six patients (0.2%) had a maximum of Grade 3 IRR. No patients had Grade 4 or Grade 5 events of IRR. The safety of durvalumab 30-minute infusion is currently being investigated in advanced BTC patients who are treated with durvalumab in combination with chemotherapy in Phase IIIb TOURMALINE study. PD-1/PD-L1 therapies have shown that faster infusion is	Durvalumab will be administered as a 60-minute IV infusion in the first cycle at Day 1. If tolerated, subsequent infusions will be administered as a 30-minute IV infusion. **For the first durvalumab infusion (60-minute infusion)**: BP and pulse will be collected/recorded in the eCRF prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes), approximately 30 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 60 minutes ±

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
	safely possible (Pembrolizumab, Nivolumab, and Atezolizumab).	10 minutes). A 1-hour observation period is recommended after the first infusion of durvalumab and prior to the initiation of chemotherapy with monitoring of signs and symptoms of IRR and anaphylaxis per institutional standards. standards. **For the first 30-minute durvalumab infusion:** BP and pulse will be collected/recorded in the eCRF prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes), approximately 15 minutes during the infusion (halfway through infusion), and at the end of the infusion (approximately 30 minutes ± 5 minutes). A 1-hour observation period is recommended after the first infusion of durvalumab 30-minute infusion and prior to the initiation of chemotherapy with monitoring of signs and symptoms of IRR and anaphylaxis per institutional standards. **For subsequent infusions:** BP, pulse, and other vital signs should be measured, collected/recorded in the eCRF prior to the start of the infusion. Participants 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. If there are no clinically significant concerns on previous infusions, the observation period may be reduced for subsequent infusions (suggested duration is 30 minutes). In the event of an IRR, infusion time may be increased according to the TMGs. The safety and tolerability of durvalumab with a shorter infusion time will be part of

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation strategy
		the safety data review, including IRRs and hypersensitivity/anaphylactic reactions.

Durvalumab in Combination With Cisplatin-based Neoadjuvant Chemotherapy in Bladder Cancer

The Swiss Group for Clinical Cancer Research SAKK 06/17 study is an investigator-initiated, open-label, single-arm Phase II study including 57 cisplatin-fit participants with Stage cT2-T4a cN0-1 operable MIUC (Cathomas et al 2023). Four cycles of neoadjuvant gem/cis in combination with 4 cycles of durvalumab (starting with gem/cis cycle 2) were administered followed by radical surgery. Adjuvant durvalumab was given for 10 cycles. Grade 3 and 4 TRAEs during neoadjuvant treatment occurred in 42% and 25% of participants, respectively. TRAEs related to adjuvant durvalumab were Grade 3 in 5 participants (11%) and Grade 4 in 2 participants (4%). No Grade 5 TRAEs occurred. A total of 50 participants received RC and PLND. All participants received neoadjuvant chemo-immunotherapy. The median (interquartile range) number of lymph nodes removed was 29 (range: 23 – 38). No intraoperative complications were registered. Grade 3 or higher postoperative complications were reported in 12 participants (24%). Complete nodal dissection (100%) was performed at the level of the obturator fossa (bilaterally) and of the left external iliac region; in 49 participants (98%) at the internal iliac region and at the right external iliac region; in 39 (78%) and 38 (76%) participants at the right and left presacral level, respectively. This study supports the surgical safety of RC and PLND following neoadjuvant chemo-immunotherapy in participants with MIUC (Afferi et al 2024).

The NEMIO study is an investigator-initiated, open-label, randomised Phase I-II trial (GETUG-AFU V09) assessing in the neoadjuvant setting the combination of ddMVAC plus durvalumab alone or with tremelimumab: 4 cycles of ddMVAC/2 weeks + 2 cycles of durvalumab ± tremelimumab every 4 weeks. Preliminary results based on the 60 participants treated with neoadjuvant durvalumab plus ddMVAC showed manageable safety profile. The most common all-grade TRAEs were fatigue (85%), nausea (85%), and anaemia (57%). The most common Grade 3 or 4 TRAEs were anaemia (12%), neutropaenia (8%), and acute kidney injury (5%). The most common immune-related AEs were diarrhoea/colitis (5%), rash/dermatitis (2%), and hypo/hyperthyroid events (2%); no immune-related AEs were Grade 3 or higher. No treatment-related death was reported. Neoadjuvant durvalumab + ddMVAC did not delay cystectomy (Thibault et al 2023).

In the randomised Phase III NIAGARA study conducted in patients with cisplatin-eligible MIBC, the addition of perioperative durvalumab to NAC was tolerable and manageable, with no new safety signals. Any-grade TRAEs were reported in 502 participants (95%) in the durvalumab arm and 487 participants (93%) in the comparator arm. The Grade 3/4 TRAEs (40.6%) and treatment-related deaths (0.6%) were the same between both arms. The most commonly reported Grade 3/4 TEAEs (> 5%) were neutropenia, urinary tract infection, anaemia, and decreased neutrophil count. Immune-mediated AEs occurred in 111 participants (20.9%) in the durvalumab arm and 16 participants (3.0%) in the comparator arm. Neoadjuvant durvalumab did not delay surgery and did not impact the ability of patients to

undergo/complete surgery. Surgery-related AEs with an outcome of death within the first 90 days after RC occurred in 10 participants (2.1%) in the durvalumab arm and 8 participants (1.8%) in the comparator arm (Powles et al 2024a, Powles et al 2024b).

In NIAGARA, durvalumab had no impact on a patient's ability to undergo cystectomy; 88% of patients in the durvalumab arm versus 83% in the comparator arm underwent radical cystectomy. Additionally, neoadjuvant durvalumab did not delay surgery, as there was no difference in time to cystectomy between the study arms. The median time from last dose of neoadjuvant therapy to cystectomy was 5.6 weeks (range: 1.1-16.9) for the durvalumab arm versus 5.4 weeks (range: 1.7-47.6) for the comparator arm. Furthermore, the rates of surgical complication rates in NIAGARA by Clavien-Dindo classification were similar between study arms (Grade I + II: 40% durvalumab arm versus 42% comparator arm; Grade III + IV + V: 16% durvalumab arm versus 16% comparator arm) (Catto et al 2025).

2.3.2 Benefit Assessment

Durvalumab in Bladder Cancer

The potential benefit of durvalumab in bladder cancer was shown in a cohort of 182 participants with locally advanced or metastatic UC who had progressed while on or after a platinum-based chemotherapy. The overall ORR based on BICR was 17%. In participants 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 participants, 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]) (Plimack et al 2014).

The DANUBE study is a Phase III, randomised, open-label, controlled, multicentre, global study of first-line durvalumab monotherapy and durvalumab in combination with tremelimumab versus platinum-based doublet chemotherapy conducted in patients with first-line locally advanced or metastatic UC. In this study, durvalumab + tremelimumab and durvalumab monotherapy (PD-L1 high analysis set) did not result in statistically significant improvement in OS when compared with chemotherapy. In the intent-to-treat population, median OS was 15.1 months (95% CI: 13.1 – 18.0) in the durvalumab plus tremelimumab group and 12.1 months (95% CI: 10.9 – 14.0) in the chemotherapy group (HR: 0.85, 95% CI: 0.72 – 1.02; 2-sided p = 0.075); In the high PD-L1 population, median OS was 14.4 months (95% CI: 10.4 – 17.3) in the durvalumab group and 12.1 months (95% CI: 10.4 – 15.0) in the chemotherapy group (HR: 0.89, 95% CI: 0.71 – 1.11; 2-sided p = 0.30). Although the DANUBE did not meet the coprimary endpoints, it did confirm that durvalumab with or without tremelimumab is an active agent in metastatic UC (Powles et al 2020).

Durvalumab in Combination With Cisplatin-based Neoadjuvant Chemotherapy in Bladder Cancer

The potential benefit of durvalumab in combination with cisplatin-based NAC was demonstrated in multiple clinical trials.

The SAKK 06/17 study is an investigator-initiated, open-label, single-arm, Phase II study including 57 cisplatin-fit participants with Stage cT2-T4a cN0-1 operable MIUC (Cathomas et al 2023). Four cycles of neoadjuvant gem/cis in combination with 4 cycles of durvalumab (starting with gem/cis in Cycle 2) were administered followed by radical surgery. Adjuvant durvalumab was given for 10 cycles. In this study, the primary endpoint was met, with EFS at 2 years of 76% (1-sided 90% CI [lower bound], 67%; 2-sided 95% CI: 62 – 5). EFS at 3 years was 73% and OS at 2 years and 3 years were 85% and 81%, respectively. The EFS and OS results suggested a potential benefit of neoadjuvant durvalumab in combination with gem/cis followed by adjuvant durvalumab.

NEMIO is an investigator-initiated, open-label, randomised phase I-II trial (GETUG-AFU V09) assessing in the neoadjuvant setting the combination of ddMVAC plus durvalumab alone or with tremelimumab: 4 cycles of ddMVAC/2 weeks + 2 cycles of durvalumab ± tremelimumab every 4 weeks. Cystectomy was performed 4 to 8 weeks after the last dose of ddMVAC. In the interim analyses with 113 MIBC participants, both neoadjuvant combination regimens showed a promising efficacy signal: pCR 49%, 2-year DFS 74.8%, and 2-year OS 77.2% in ddMAVC + durvalumab arm (n = 55); pCR 47%, 2-year DFS 90%, and 2-year OS of 87.9% in ddMVAC + durvalumab + tremelimumab arm (n = 58) (Thibault et al 2025).

In the randomised Phase III NIAGARA study conducted in participants with cisplatin-eligible MIBC, perioperative durvalumab plus neoadjuvant gem/cis followed by RC demonstrated statistically significant and clinically meaningful improvements in EFS (HR: 0.68, 95% CI: 0.56 – 0.82; $p < 0.0001$) and OS (HR: 0.75, 95% CI: 0.59 – 0.93; $p = 0.0106$) compared with gem/cis and RC alone. pCR occurred in 37.3% (95% CI: 33.2 – 41.6) of the participants in the durvalumab group and in 27.5% (95% CI: 23.8 – 31.6) of the participants in the comparator group (risk ratio: 1.34, 95% CI: 1.13 – 1.60) based on the reanalysis including the results for the 59 samples omitted from the primary analysis (Powles et al 2024a, Powles et al 2024b). In patients who underwent RC, perioperative durvalumab plus neoadjuvant gem/cis showed a higher pCR rate (42% versus 33%, odds ratio 1.56, 95% CI: 1.18-2.06; nominal $p = 0.0017$) and improvement in DFS (HR: 0.69, 95% CI: 0.51-0.93, nominal $p = 0.0143$) compared with neoadjuvant gem/cis alone. In the subset of patients with borderline renal function defined by CrCl 40-60 mL/min/1.73m^2, perioperative durvalumab plus neoadjuvant gem/cis improved the pCR rate (32% versus 16%, odds ratio 2.43, 95% CI: 1.23-4.80) and EFS (HR: 0.69, 95% CI: 0.46-1.01), compared with neoadjuvant gem/cis alone (Meeks et al 2025).

Durvalumab in Combination With Chemotherapy Agents in Other Tumours

Several pivotal trials support a potential benefit of durvalumab in combination with chemotherapy in multiple tumour types.

In Study D419QC00001 (CASPIAN; SCLC), median OS was 12.9 months (95% CI: 11.3-14.7) for the durvalumab + chemotherapy (etoposide platinum [carboplatin or cisplatin]) arm and 10.5 months (95% CI: 9.3 – 11.2) for the chemotherapy arm; HR: 0.75

(95% CI: 0.63-0.91; nominal p-value = 0.0032). Median PFS was 5.1 months (95% CI: 4.7-6.2) in the durvalumab + chemotherapy arm and 5.4 months (95% CI: 4.8 – 6.2) in the chemotherapy arm; HR: 0.80 (95% CI: 0.67 – 0.96; p = 0.0157). ORR was 79.5% in the durvalumab + chemotherapy arm compared with 70.6% in the chemotherapy arm.

In the POSEIDON study (NSCLC), median OS was 13.3 months (95% CI: 11.4 – 14.7) for the durvalumab + SoC chemotherapy arm and 11.7 months (95% CI: 10.5 – 13.1) for the SoC chemotherapy alone arm; HR: 0.86 (95% CI: 0.724 – 1.016; p = 0.07581). At the time of the 5-year follow-up, median OS was 13.3 months (95% CI: 11.4 – 14.7) for the durvalumab + SoC chemotherapy arm and 11.6 months (95% CI: 10.5 – 13.1) for the SoC chemotherapy alone arm; HR: 0.84 (95% CI: 0.717 – 0.995). Median PFS was 5.5 months (95% CI: 4.7-6.5) for the durvalumab + SoC chemotherapy arm and 4.8 months (95% CI: 4.6 – 5.8) for the SoC chemotherapy alone arm; HR: 0.74 (95% CI: 0.620 – 0.885; p = 0.00093). ORR for the durvalumab + SoC chemotherapy arm was 48.5% (160/330; 95% CI: NR) and median DoR was 6.0 months.

In Study D933AC00001 (TOPAZ-1; BTC), median OS at the planned OS update analysis (DCO 25 February 2022) was 12.9 months (95% CI: 11.6 – 14.1) for the durvalumab + gem/cis group and 11.3 months (95% CI: 10.1 – 12.5) for the placebo + gem/cis group; HR: 0.76 (95% CI: 0.64 – 0.91). Median PFS at the time of interim analysis 2 (DCO 11 August 2021) was 7.2 months (95% CI: 6.7 – 7.4) in the durvalumab + gem/cis group and 5.7 months (95% CI: 5.6 – 6.7) in the placebo + gem/cis group; HR: 0.75 (95% CI: 0.63 – 0.89; p = 0.001). ORR was 26.7% in the durvalumab + gem/cis group compared to 18.7% in the placebo + gem/cis group.

In Study D419KC00001 (DREAM; MPM), median PFS at the primary analysis (DCO 30 September 2019) was 7.0 months (95% CI: 5.7 – 9.0) for patients treated with durvalumab in combination with cisplatin and pemetrexed (Nowak et al 2020). Thirty-one of 54 patients (57.4% [95% CI: 43.2 – 69.3]) were progression-free at 6 months. Median OS was 18.4 months (95% CI: 12.6 – 23.2), and the OS rate at 6 months was 85.2% (95% CI: 72.6 – 92.3). Confirmed ORR was 44.4%; all reported as PR (95% CI: 30.9 – 58.6).

2.3.3 Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimise risk to participants participating in this study, the potential risks identified in association with neoadjuvant durvalumab in combination with cisplatin-based chemotherapy followed by RC and adjuvant durvalumab are justified by the anticipated benefits that may be afforded to participants with MIBC.

3 OBJECTIVES AND ENDPOINTS

Table 6 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the safety of neoadjuvant durvalumab combined with ddMVAC or gem/cis prior to RC	Incidence of Grade 3 or 4 PRAEs as observed prior to RC. [a] A PRAE [b] is defined as an AE that has been assessed by the investigator to be possibly related to study treatment. The analysis will be performed on the SAF [c] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
Secondary	
To further assess the safety and tolerability of perioperative durvalumab combined with ddMVAC or gem/cis	Incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality of treatment-emergent AEs, including PRAEs, AESIs, imAEs, AEs, and SAEs; AEs resulting in study treatment interruption and discontinuation; laboratory findings. The analysis will be performed on the SAF [c] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
To assess the efficacy of perioperative durvalumab combined with ddMVAC or gem/cis in terms of EFS	EFS is defined as the time from first neoadjuvant durvalumab + chemotherapy treatment until the earliest occurrence of any of the following events: • First recurrence of disease after RC • First documented progression in participants who were medically precluded from RC • Time of expected surgery in participants who refuse to undergo RC or failure to undergo RC in participants with residual disease • Death due to any cause The primary measure of interest is EFS rate at 12 months. The analysis will be performed on the FAS [d] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
To assess the efficacy of perioperative durvalumab combined with ddMVAC or gem/cis in terms of DFS	DFS is defined as the time from the date of RC to the earliest of the first recurrence of disease post RC or death due to any cause. The primary measures of interest are DFS rates at 18 and 24 months. The analysis will be performed in a subset of participants in the FAS [d] who undergo RC and by NAC cohorts (ddMVAC cohort and gem/cis cohort).

Table 6 Objectives and Endpoints

Objectives	Endpoints
To assess the efficacy of perioperative durvalumab combined with ddMVAC or gem/cis in terms of OS	OS is defined as the time from first neoadjuvant durvalumab + chemotherapy until death due to any cause. The primary measure of interest is OS rate at 12 months. The analysis will be performed on the FAS [d] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
To assess the efficacy of neoadjuvant durvalumab combined with ddMVAC or gem/cis followed by RC in terms of pCR	pCR rate is defined as the proportion of participants whose pathologic staging is T0N0M0 as assessed per local pathology review using specimens obtained via RC. Participants who do not undergo RC will be included as failures (did not achieve T0N0M0). The analysis will be performed in the FAS [d] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
To assess the efficacy of neoadjuvant durvalumab combined with ddMVAC or gem/cis followed by RC in terms of pDS	pDS rate is defined as the proportion of participants whose pathologic staging is < P2 per local pathology review using specimens obtained via RC. The analysis will be performed in the FAS [d] and by NAC cohorts (ddMVAC cohort and gem/cis cohort).
Exploratory	
To characterise baseline characteristics and clinical outcomes in participants who did not undergo RC	Descriptive statistics of baseline characteristics, clinical outcomes, and reasons for precluding RC. The analysis will be performed in a subset of participants in the FAS [d] who did not undergo RC (non-RC cohort).
To explore feasibility and tolerability of durvalumab 30-minute infusion	Incidence of IRRs and hypersensitivity/anaphylactic reactions. The analysis will be performed on the SAF. [c]

[a] All participants entering this study plan to undergo RC. For participants who do not undergo RC, their data will be collected in the eCRF along with the reason to not undergo RC. The primary analysis of 'safety prior to RC' will include participants' data until the date of decision not to undergo RC (medically precluded or participant's refusal) or the date of planned RC, whichever occurs first.

[b] An event is considered a PRAE if the investigator has answered yes to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

[c] SAF includes all participants enrolled in the study who have received at least 1 dose of study treatment.

[d] FAS includes all participants enrolled in the study who have received at least 1 dose of study treatment. Note that the FAS is the same as the SAF.

4 STUDY DESIGN

4.1 Overall Design

This is a Phase IIIb, open-label, single-arm, multicentre, global study to assess safety and efficacy of neoadjuvant durvalumab in combination with cisplatin-based chemotherapy followed by RC and adjuvant durvalumab in participants with MIBC.

Refer to the study schema (Figure 1) and SoA (Section 1.3) for overall design and required assessments. Day 1 is defined as the first day of study treatment.

Number of participants: Approximately 202 participants will be screened to achieve 150 participants treated with study treatment.

Treatment and Treatment Duration

Neoadjuvant treatment

Participants will receive durvalumab in combination with cisplatin-based NAC for up to 12 weeks prior to RC. Either ddMVAC or gem/cis will be selected based on investigator choice and will be administered per institutional clinical practice: ddMVAC Q2W for 4 cycles or gem/cis Q3W for 4 cycles. However, participants may receive up to 6 cycles of ddMVAC if this is consistent with the treating institution's standard practice. Durvalumab 1500 mg will be administered as a 60-minute IV infusion in the first cycle and as a 30-minute IV infusion in subsequent cycles if the 60-minute IV infusion in the first cycle is well tolerated. In the situation that a participant does not tolerate a 30-minute IV infusion , infusion time may be increased according to the TMGs. Durvalumab administration will be adjusted based on the chemotherapy regimens: Q4W when combined with ddMVAC or Q3W when combined with gem/cis.

Recruitment for participants for durvalumab + neoadjuvant gem/cis will be limited to approximately 30% of the total number of participants.

The dosing of ddMVAC or gem/cis regimen will be consistent with prescribing information of respective agents as well as in accordance with institutional clinical practice and guidelines.

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

- Durvalumab + ddMVAC
  - Day 1: durvalumab 1500 mg IV; every 4 weeks for 3 cycles
  - Day 1: methotrexate 30 mg/m^2 IV; Day 2: vinblastine 3 mg/m^2 IV, doxorubicin 30 mg/m^2 IV, cisplatin 70 mg/m^2 IV; G-CSF as per institutional standard; every 2 weeks for 4 cycles. However, participants may receive up to 6 cycles of ddMVAC if this is consistent with the treating institution's standard practice

OR

- Durvalumab + gem/cis
  - Day 1: durvalumab 1500 mg IV; every 3 weeks for 4 cycles
  - Day 1: cisplatin 70 mg/m^2, gemcitabine 1000 mg/m^2; Day 8: gemcitabine 1000 mg/m^2; every 3 weeks for 4 cycles

Participants with borderline renal function (40 ≤ CrCl < 60 mL/min)

Results of serum creatinine and a determination of creatinine clearance must be available and reviewed by the treating physician or investigator prior to dosing for participants on the cisplatin split-dose regimen.

- Durvalumab + gem/cis (split-dose cisplatin)
  - Day 1: durvalumab 1500 mg IV, every 3 weeks for 4 cycles
  - 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 3 weeks for 4 cycles

Adjuvant treatment

After RC and adequate recovery between 42 and 120 days, participants will receive durvalumab 1500 mg Q4W for up to a maximum of 8 cycles or until progression, unacceptable toxicity, withdrawal of consent, or any of treatment discontinuation criteria is met (for study discontinuation criteria, see Section 7.1).

In scenarios when participants are unable to complete the intended number of cycles of chemotherapy and/or durvalumab throughout the study, participants will be permitted to receive fewer cycles of chemotherapy and/or durvalumab following institutional clinical practice based on judgement by the investigator.

Refer to the study schema (Figure 1) and SoA (Table 1, Table 2, Table 3, and Table 4) for overall design and required assessments. Day 1 is defined as the first day of study treatment.

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

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 participants become infected with SARS-CoV-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 participant'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 participants, maintain compliance with GCP, and minimise risks to study integrity.

Where allowable by local health authorities, ethics committees, health care 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 ICF should be signed at the participant's next contact with the study site).
- Telemedicine visit: Remote contact with the participants using telecommunications technology including phone calls.
- Rescreening: Additional rescreening for screen failure and to confirm eligibility to participate in the clinical study can be performed in previously screened participants. The investigator should confirm this with the designated medical monitor.
- Home or remote visit: Performed by a site qualified HCP or HCP provided by a third-party vendor.

For further details on-study conduct during civil crisis, natural disaster, or public health crisis, refer to Appendix H.

4.2 Scientific Rationale for Study Design

4.2.1 Rationale for Study Design

The unmet need in the treatment of MIBC, aimed at preventing recurrence or progression and improving survival, supports the development of new treatment options with immune-checkpoint inhibitors.

In the randomised Phase III NIAGARA study conducted in participants with cisplatin-eligible MIBC, perioperative durvalumab plus neoadjuvant gem/cis followed by RC demonstrated statistically significant and clinically meaningful improvements in EFS (HR: 0.68, 95% CI: 0.56 – 0.82; $p < 0.0001$) and OS (HR: 0.75, 95% CI: 0.59 – 0.93; $p = 0.0106$) compared with gem/cis and RC alone. The addition of perioperative durvalumab to NAC was tolerable and manageable, with no new safety signals. Neoadjuvant durvalumab did not delay surgery and did not impact the ability of participants to undergo or complete surgery (Powles et al 2024a, Powles et al 2024b).

Following the NIAGARA study results, the first Phase III trial to show that adding perioperative durvalumab to neoadjuvant gem/cis increases EFS and OS in MIBC, questions remain on the safety and efficacy of durvalumab in combination with other commonly used chemotherapy regimen such as ddMVAC in the treatment of MIBC. While gem/cis is a widely used NAC regimen, there is growing evidence to support clinical benefit with ddMVAC in

MIBC. In the randomised Phase III GETUG-AFU V05 VESPER trial, neoadjuvant ddMVAC showed meaningful PFS and OS benefit over neoadjuvant gem/cis but with a higher toxicity (Pfister et al 2022). Neoadjuvant ddMVAC in combination with durvalumab or durvalumab plus tremelimumab has been investigated in the NEMIO trial, an investigator-initiated randomised Phase I-II trial (GETUG-AFU V09). According to the interim analyses with 113 MIBC participants, both neoadjuvant combination regimens showed tolerable safety profile without delay in cystectomy and a promising efficacy signal: pCR 49%, 2-year DFS 74.8%, and 2-year OS 77.2% in ddMAVC + durvalumab arm (n = 55); pCR 47%, 2-year DFS 90%, and 2-year OS of 87.9% in ddMVAC + durvalumab + tremelimumab arm (n = 58). However, in the NEMIO trial, adjuvant durvalumab was not assessed (Thibault et al 2025).

Therefore, the Phase IIIb NIAGARA-2 study aims to expand on the data from the Phase III NIAGARA study by investigating the safety and efficacy of perioperative durvalumab with neoadjuvant ddMVAC as well as gem/cis in a real-world clinical practice setting.

In addition, this study will further explore feasibility and tolerability of durvalumab 30-minute infusion: durvalumab will be administered as a 60-minute infusion in the first cycle and as a 30-minute infusion in subsequent cycles if the 60-minute IV infusion in the first cycle is well tolerated. Accordingly, safety and IRR and hypersensitivity/ anaphylactic reactions will be assessed in this study. Reducing the infusion time of durvalumab to 30 minutes would provide potential benefits to both patients and treatment facilities.

4.2.2 NIAGARA-2 Rationale for Neoadjuvant Chemotherapy

Standard treatment for cisplatin-eligible patients with MIBC involves neoadjuvant cisplatin-based chemotherapy followed by RC with PLND (Holzbeierlein et al 2024, Powles et al 2022, Witjes et al 2024). NAC regimens such as gem/cis and ddMVAC are recommended (NCCN Guidelines® Insights: Bladder Cancer 3.2024, European Association of Urology Guidelines 2024), with an absolute OS benefit of 5% to 10% (Lotan et al 2022). While gem/cis is a widely used NAC regimen, there is growing evidence to support clinical benefit with ddMVAC in MIBC. Neoadjuvant ddMVAC showed meaningful PFS and OS benefit over neoadjuvant gem/cis but with a higher toxicity in the randomised Phase III GETUG-AFU V05 VESPER trial (Pfister et al 2022).

Several studies have demonstrated improved pCR, EFS, and OS with the integration of neoadjuvant, cisplatin-based combination chemotherapy when compared with RC alone. Two large randomised studies have demonstrated improvement in survival with the integration of neoadjuvant, cisplatin-based combination chemotherapy, leading to the utilisation of NAC for participants with MIBC (Galsky et al 2015, Grossman et al 2003, International Collaboration of Trialists 2011).

Gem/cis is the most widely used NAC regimen. gem/cis has shown similar pT0/pT1 rates as methotrexate, vinblastine, adriamycin plus cisplatin in retrospective series and pooled data analyses (Galsky et al 2015, Yuh et al 2013, Lee et al 2013, Dash et al 2008).

However, modified ddMVAC was tested in 2 small single-arm Phase II studies demonstrating high rates of pathologic complete remission (Choueiri et al 2014, Plimack et al 2014). Moreover, a large cross-sectional analysis showed higher rates of down-staging and pathological complete response for ddMVAC (Peyton et al 2018).

In the GETUG/AFU V05 VESPER randomised clinical trial of peri-operative chemotherapy, 500 participants were randomised to either 6 cycles of ddMVAC once every 2 weeks versus 4 cycles of gem/cis once every 3 weeks prior to surgery (neoadjuvant group) or after surgery (adjuvant group) with a primary endpoint of PFS at 3 years. In 493 participants (437 neoadjuvant and 56 adjuvant), a similar pathologic response rate (ypT0N0) in participants treated with ddMVAC 42% and gem/cis 36% (p = 0.2) was seen. The < ypT2N0 rate was 63% and 50% in the ddMVAC and gem/cis participants, respectively. Organ-confined response (< ypT3N0) was observed more frequently in the ddMVAC arm (77% versus 63%, p = 0.001). For all participants in the trial, 3-year PFS was improved in the ddMVAC arm, but the study did not meet its primary endpoint (3-year rate: 64% versus 56%, HR: 0.77 [95% CI:0.57 – 1.02], p = 0.066); nevertheless, the ddMVAC arm was associated with a significantly longer time to progression (3-year rate: 69% versus 58%, HR: 0.68 [95% CI: 0.50 – 0.93], p = 0.014). In the neoadjuvant group, PFS at 3 years was significantly higher in the ddMVAC arm (66% versus 56%, HR: 0.70 [95% CI: 0.51 – 0.96], p = 0.025). However, ddMVAC was associated with more severe asthenia and GI side effects than gem/cis (Pfister et al 2021, Pfister et al 2022).

4.3 Justification for Dose

Durvalumab will be administered at a dose of 1500 mg as an IV infusion, either Q4W in combination with ddMVAC for a total of 3 cycles or Q3W in combination with gem/cis for a total of 4 cycles, followed by durvalumab 1500 mg as monotherapy Q4W up to 8 cycles.

The dosing of ddMVAC or gem/cis regimen will be consistent with prescribing information of respective agents as well as in accordance with institutional clinical practice and guidelines.

A summary of the existing PK, pharmacodynamic, and clinical data has been utilised to guide the regimen selection for this study. Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy, and PK.

4.3.1 Durvalumab Dose Rationale

4.3.1.1 PK/Pharmacodynamic Data

Based on available PK and pharmacodynamic data from ongoing Study CD-ON-MEDI4736-1108 (hereafter referred to as Study 1108) with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited nonlinear (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 showing 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 participants 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, with doses from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W (Fairman et al 2014). Multiple simulations indicated 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 participants; (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 impact; and (d) achieve PK exposure that yields maximal anti-tumour activity in animal models.

Given the similar predicted PK profile (AUC, C_{max}, and C_{trough}), the observation that both weight-based and fixed-dose regimens maintain complete sPD-L1 suppression at the achieved trough concentrations, and available clinical data, the 20 mg/kg, 1500 mg (Q3W, Q4W) and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles.

Currently approved dosing regimens include a weight-based regimen of 10 mg/kg administered Q2W (UC, NSCLC) and a fixed-dose regimen (1500 mg) administered Q3W in combination with chemotherapy followed by Q4W as monotherapy (extensive-stage SCLC and BTC) and as monotherapy Q4W (unresectable stage III NSCLC). Refer to the package insert (or label) for the current approved dosing regimens (schedule and indication) for the specific country, as applicable.

4.3.1.2 Durvalumab Q4W Dose Rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in vitro data, nonclinical activity, clinical PK and pharmacodynamics, biomarkers, and activity data from Study 1108 in participants with advanced solid tumours and from a Phase I trial performed in Japanese participants with advanced solid tumour (D4190C00002). Durvalumab Q4W dose has been tested as a monotherapy or in combination with chemotherapy in multiple Phase III trials including DANUBE (locally advanced or metastatic UC), NIAGARA (MIBC), MYSTIC (metastatic NSCLC), POSEIDON (metastatic NSCLC), CASPIAN (extensive disease SCLC), HIMALAYA (advanced hepatocellular carcinoma), and TOPAZ-1 (advanced BTC).

Refer to the current durvalumab IB for a complete summary of preclinical and clinical information on durvalumab, including safety, efficacy and PK for the 1500 mg Q4W regimens.

4.3.1.3 Durvalumab Combination Dose With Q3W Chemotherapy Rationale

PK modelling and simulation have been conducted to evaluate the switch from Q4W dosing to Q3W dosing for durvalumab. For durvalumab, median C_{max} following the fifth dose of the Q3W regimen and the fourth 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 28,726 and 22,772 µg·day/mL for the Q3W and Q4W schedule, respectively. Therefore, PK modelling suggests that a Q3W schedule does not impose a significant increased safety risk based on expected durvalumab exposures.

PK and simulation have been carried out to compare durvalumab PK profiles using target patient populations from Study D419QC00001 (CASPIAN; durvalumab in combination with chemotherapy) for the 1120 mg Q3W, 1125 mg Q3W, 1500 mg Q3W, and 1500 mg Q4W dosing regimens (Population PK Simulation Report [21 July 2021]). Overall, the distribution of durvalumab exposures at 1120 mg Q3W was predicted to be consistent with the predicted levels at 1500 mg Q4W. 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 did not appear dose-dependent, and PK modelling revealed no meaningful differences in drug levels between Q3W and Q4W dosing.

4.3.1.4 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 ($AUC_{ss,0\text{-}28}$, $C_{max,ss}$, 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 participants 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-participant 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 durvalumab (equivalent to 20 mg/kg) is included in the current study.

4.3.1.5. Rationale for Shorter Infusion Time

Adverse reactions that occur during or shortly after infusion may include fever, chills, hypotension, dyspnoea, tachycardia, cyanosis, respiratory failure, urticaria and pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, rash, headache, flushing, sweating, myalgia, nausea, vomiting, unresponsiveness, and haemodynamic instability. The typical onset can be within 30 minutes to 2 hours after the initiation of drug infusion, although symptoms may be delayed for up to 24 hours. The majority of reactions occur after the first or second exposure to the agent, but between 10% and 30% occur during subsequent treatments (Lenz 2007).

IRR with onset on the day of dosing or 1 day after dosing are considered ADRs for durvalumab monotherapy, the durvalumab + tremelimumab T75 + D combination, and the T300 + D combination. In the durvalumab monotherapy pooled dataset (N = 3006) as a 60-minute IV infusion, IRR (including urticaria) was reported at a frequency of Common (58 participants [1.9%]). Most participants had Grade 1 or 2 events in severity; 6 participants (0.2%) had a maximum of Grade 3 IRR. No participants had Grade 4 or Grade 5 events of IRR. Incidence of IRR of durvalumab + tremelimumab is comparable with durvalumab monotherapy (durvalumab IB, Edition 21).

While a higher rate of infusion is associated with a higher likelihood of an IRR (Vogel 2010), safety data for PD-1/PD-L1 therapies have shown that a shorter infusion is a safe approach (Pembrolizumab, Nivolumab, Atezolizumab). IRRs were commonly observed (≥ 1% to < 10% of patients) with a 30-minute infusion of pembrolizumab, nivolumab, and atezolizumab (first dose of atezolizumab administered over 60 minutes), but mostly Grade 1 or 2. Additionally, nivolumab PK were predicted to be similar in both the 30-minute and 60-minute infusion groups (Waterhouse et al 2018).

Durvalumab 30-minute infusion is currently being tested in the Phase IIIb TOURMALINE study with participants with advanced BTC. In this study, participants received durvalumab 1500 mg as a 60-minute IV infusion in the first cycle and as 30-minute IV infusion in the following cycles if the 60-minute IV infusion in the first cycle is well tolerated in combination with an investigator-selected gemcitabine-based chemotherapy.

Based on the safety data including IRRs observed with durvalumab treatment at the approved 60-minute infusion, increasing the infusion rate and decreasing the infusion duration is anticipated to have an acceptable safety and tolerability profile.

4.3.2 Chemotherapy Dose Rationale

The dosing of ddMVAC or gem/cis regimens used in this study are consistent with prescribing information of respective agents, as well as with current clinical practice and guidelines.

4.3.2.1 Dose-dense Methotrexate, Vinblastine, Doxorubicin, and Cisplatin Dose Rationale

The ddMVAC regimen is recommended to be 30 mg/m2 IV methotrexate on Day 1 Q2W and 30 mg/m2 IV doxorubicin and 3 mg/m2 IV vinblastine on Day 1 Q2W, and 70 mg/m2 IV cisplatin on Day 2 Q2W for participants with adequate renal function (CrCl ≥ 60 mL/min).

The 4-week chemotherapy regimen MVAC was developed in the 1980s. It has since been considered one of the most active chemotherapy regimens, yet this regimen is associated with significant toxicity, which often leads to treatment interruption, delays, and early termination, thus compromising benefits. To improve on the MVAC regimen by attempting to reduce toxicity and improve treatment benefit, dose-dense MVAC (ddMVAC), originally called high-dose MVAC, was developed. The ddMVAC regimen is administered on a shortened week cycle schedule with double the dose-intensity of cisplatin and doxorubicin, while reducing the dose of methotrexate and vinblastine by one-third. Extending ddMVAC beyond 4 cycles partially improves local disease control without any survival benefit (5-year OS 79% 4 cycles versus 75% > 4 cycles, p = 0.27). Given the toxicity of ddMVAC, only 4 cycles should be delivered as neoadjuvant treatment in MIBC (Pfister et al 2021, Pfister et al 2022).

4.3.2.2 Gemcitabine Plus Cisplatin Dose Rationale

The recommended gem/cis dose regimen in this study is cisplatin 70 mg/m^2 IV on Day 1 and gemcitabine 1000 mg/m^2 IV on Days 1 and 8 Q3W for 4 cycles for participants with adequate renal function (CrCl ≥ 60 mL/min) or cisplatin 35 mg/m^2 IV on Day 1 and Day 8 and gemcitabine 1000 mg/m^2 IV on Days 1 and 8 Q3W for 4 cycles for participants with borderline renal function (CrCl ≥ 40 mL/min to < 60 mL/min).

A randomised Phase III study of gem/cis (administered in a 28-day cycle) compared with MVAC in participants 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 (Thibault et al 2023, Von der Maase et al 2000). However, a high incidence of haematologic toxicity was reported, compromising the gemcitabine dose intensity; consequently, gemcitabine doses were modified in 37% of the gem/cis cycles in this Phase III study. A retrospective study comparing a 21-day cycle versus a 28-day cycle of gem/cis in participants 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 haematologic 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 gem/cis regimen, specifically in elderly participants (≥ 65 years old) with urothelial cancer; 57% of participants 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 randomised Phase III has not been conducted to directly compare a 21-day and a 28-day gem/cis regimen in the neoadjuvant setting for UC, published results demonstrating similar efficacy, acceptable tolerability, and also the 21-day regimen is preferred in the current NCCN bladder cancer guidelines (NCCN Guidelines® Insights: Bladder Cancer 3.2024) as a recommended regimen in the neoadjuvant setting, a 21-day gem/cis regimen is recommended in this study.

4.3.2.3 Cisplatin Split-dose Rationale

The dosing of ddMVAC or gem/cis regimens used in this study is consistent with prescribing information of respective agents as well as with current clinical practice and guidelines.

Although cisplatin-based NAC followed by RC is recommended treatment for MIBC patients, some patients are not eligible for cisplatin due to impaired or borderline renal function (Dash et al 2006). For patients with borderline renal function or minimal dysfunction, split-dose modifications regimens with 35 mg/m^2 on Days 1 + 8 or Days 1 + 2 have been used as an alternative to the standard dose of cisplatin-based NAC with 70 mg/m^2 on day. 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 gem/cis dose in participants with adequate renal function (Abdelhafez and Williams 2017, Hussain et al 2012). According to the post-hoc analysis, in the subset of patients with borderline renal function defined by CrCl 40-60 mL/min/1.73m^2, perioperative durvalumab plus neoadjuvant gem/cis improved the pCR rate (32% versus16%, odds ratio 2.43, 95% CI: 1.23-4.80) and EFS (HR: 0.69, 95% CI: 0.46-1.01), compared with neoadjuvant gem/cis alone. Safety profile of these patients was generally consistent with the overall study population (Meeks et al 2025).

4.4 End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study.

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

4.5 Study Stopping Rules

If the study investigators, study medical monitor, or regulatory authorities discover conditions arising during the study that indicate that the participants' safety and/or scientific value of the study and/or quality of the IMP have been compromised, the study should be halted or the

study centre's participation should be terminated.

If the sponsor decides to stop data collection, patients ongoing with study treatment deriving clinical benefit from their assigned treatment may be allowed to continue treatment.

5 STUDY POPULATION

The target population of interest in this study is MIBC participants with clinical stage T2-T4aN0/1M0 or T1N1M0 (participants with T1 stage are allowed only with N1 disease), planning neoadjuvant therapy prior to RC.

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

Participants who do not meet the eligibility criteria requirements are screen failures; refer to Section 5.4.

'Enrolled' participants are defined as those who sign the ICF.

5.1 Inclusion Criteria

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

Age

1 Participant must be at least 18 or the legal age of consent in the jurisdiction in which the study is taking place at the time of signing the ICF.

Type of Participant and Disease Characteristics

2 Histologically or cytologically documented muscle-invasive TCC (also known as UC) of the bladder.

- Participants with transitional cell and mixed transitional/non-transitional cell histologies (eg, adenocarcinoma, squamous cell)/variant transitional (eg, micropapillary, plasmacytoid, sarcomatoid, nested variant, lymphoepitheliod, nested variant) histologies. Participants with pure non-transitional cell variant histologies and any small-cell histology are not eligible.

- Participants with clinical tumour stage T2-T4aN0/1M0 or T1N1M0 (participant with T1 stage are allowed only with N1 disease) according to the American Joint Committee on Cancer Staging Manual (AJCC Cancer Staging Manual, 8th Edition) TCC of the bladder cancer as determined by the investigator. N1 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 be resectable, as per the planned lymphadenectomy procedure (see Section 6.1.6 Surgical Plan). Lymph nodes with

< 10 mm short axis diameter are considered non-pathological per RECIST1.1.

- Participants should also meet the following additional criteria:
  - Must be planning and per the judgement of the investigator be medically fit for treatment with neoadjuvant durvalumab in combination with neoadjuvant cisplatin-based chemotherapy prior to RC
  - Must be planning and per the judgement of the investigator be medically fit to undergo a RC followed by adjuvant durvalumab at time of enrolment
  - Have not received prior systemic chemotherapy or immunotherapy for treatment of MIBC.

3 An ECOG performance status of 0 or 1 at enrolment.

4 Minimum life expectancy of 12 weeks at first dose of study medication.

5 Adequate organ and bone marrow function as follows:

- Haemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count ≥ 1.5×10^9/L
- Platelet count ≥ 100×10^9/L
- TBL ≤ 1.5 × ULN or ≤ 3 × ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinaemia)
- ALT and AST ≤ 2.5 × ULN
- Calculated CrCl as determined by Cockcroft-Gault (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:

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

Females:

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

*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 IVRS/IWRS.

Weight

6 Minimum body weight of 30 kg at enrolment and at first dose of study medication.

Sex and Contraceptive/Barrier Requirements

7 Male and/or female, assigned at birth, inclusive of all gender identities.

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

(a) Male participants:

- Use of a condom plus an additional contraceptive method from the time of screening throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer.

(b) Female participants:

WOCBP: A woman is considered of child-bearing potential if she is capable of conceiving. While this is typically the case following menarche and up until she becomes post-menopausal, adolescents can ovulate prior to first menarche, and women with irregular menses may also be fertile.
Women not of child-bearing potential: Females not of child-bearing potential are defined as females who are either permanently sterilised (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or who are post-menopausal. Females will be considered post-menopausal if they have been amenorrhoeic for 12 months prior to the first dose of study treatment without an alternative medical cause. A high FSH level in post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or HRT. A post-menopausal state is confirmed by 2 consecutive high FSH values (at least 4 weeks apart) in the post-menopausal range.

1. Contraception methods
    - Female participants should be stable on the chosen method of contraception for a minimum of 3 months before entering a trial.

    - WOCBP must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. WOCBP who are sexually active with a non-sterilised male partner must agree to use one highly effective method of birth control, as defined below, throughout the total duration of the drug treatment and the drug washout period (from the time of screening throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment

period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer). Cessation of contraception after this point should be discussed with a responsible physician.

- Highly effective birth control methods include the following:
  - Non-hormonal
    - Total sexual abstinence provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments)
    - A vasectomised partner (confirmed absence of sperm in semen)
    - Bilateral tubal occlusion (caveat: failure rate > 1%)
    - Intrauterine device (copper)
  - Hormonal contraceptives associated with inhibition of ovulation
    - Medroxyprogesterone injections
    - Levonorgestrel intrauterine system
    - Combined oral or transdermal contraceptives (ethinyl estradiol plus progestin)
    - Intravaginal device (eg, ethinyl estradiol and etonogestrel): The following are not acceptable methods of contraception: periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea. Female condom and male condom should not be used together.
- For genotoxic or suspected genotoxic study interventions, the recommended duration of contraception in female participants in clinical studies should be until the end of relevant systemic exposure including potential genotoxic metabolites (ie, 5 half-lives after the last dose) plus 6 months. In the more theoretical case of treatment with a pure aneugenic pharmaceutical the recommended duration of contraception should be until the end of relevant systemic exposure (ie, 5 half-lives after the last dose) plus 1 month.

2. Pregnancy test
   - All WOCBP must have a negative serum pregnancy test result at screening.

Informed Consent

8 Capable of giving signed informed consent, as described in Appendix A 3, which includes compliance with the requirements and restrictions listed in the ICF and in the protocol.

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

Other Inclusion Criteria

10 All races, gender, and ethnic groups are eligible for this study.

5.2 Exclusion Criteria

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

Medical Conditions

1 Evidence of lymph node (N2-3) or metastatic UC (M1), extravesical UC that invades the pelvic and/or abdominal wall for bladder cancer (T4b), or primary non-bladder (ie, ureter, urethral, or renal pelvis) UC of the urothelium.

2 As judged by the investigator, any evidence of diseases (such as severe or uncontrolled systemic diseases, including uncontrolled hypertension, active bleeding diseases, active infection, active ILD/pneumonitis, serious chronic GI conditions associated with diarrhoea, psychiatric illness/social situations), chronic diverticulitis or previous complicated diverticulitis, or history of allogenic organ transplant, which, in the investigator's opinion, makes it undesirable for the participant to participate in the study or that would jeopardise compliance with the protocol.

3 Inoperable tumour(s) with fixation to the pelvic wall on clinical exam.

4 Per the judgement of the investigator, if a nephroureterectomy is required at the time of enrolment for tumour of the mid ureter, renal pelvis, or collecting system.

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

6 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 GI conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs, or compromise the ability of the participant to give written informed consent.

7 History of a myocardial infarction within 6 months prior to first dose of study medication due to potential cardiotoxic effects observed with gemcitabine.

8 History of another primary malignancy except for the following:

- Malignancy treated with curative intent, with no known active disease ≥ 5 years before the first dose of study treatment and of low potential risk for recurrence. Exceptions include adequately resected non-melanoma skin cancer and curatively treated in situ disease.
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated carcinoma in situ without evidence of disease.

- History of active primary immunodeficiency.

9 History of leptomeningeal carcinomatosis.

10 Persistent toxicities (CTCAE Grade ≥ 2) caused by previous anti-cancer therapy; alopecia, vitiligo, and laboratory values defined in the inclusion criteria are excluded toxicities. Participants with irreversible toxicity that is not reasonably expected to be exacerbated by treatment with durvalumab in the opinion of the investigator may be included (eg, hearing loss) only after consultation with AstraZeneca.

11 Known active hepatitis infection, positive HCV antibody, HBsAg, or anti-HBcAb, at screening. Participants who are positive for HCV antibody are eligible only if PCR is negative for HCV RNA. Participants co-infected with HBV and HCV, or co-infected with HBV and HDV, namely: HBV-positive (presence of HBsAg and/or anti-HBcAb with detectable HBV DNA); AND

- HCV-positive (presence of anti-HCV antibodies); OR
- HDV-positive (presence of anti-HDV antibodies).

12 Known to have tested positive for HIV (positive HIV 1 and/or HIV 2 antibodies).

13 Active tuberculosis infection (clinical evaluation that may include clinical history, physical examination and radiographic findings, or tuberculosis testing in line with institutional standard).

14 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], systemic lupus erythematosus, sarcoidosis, granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc), autoimmune pneumonitis, and autoimmune myocarditis. The following are exceptions to this criterion:

- Participants with vitiligo or alopecia
- Participants with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement
- Any chronic skin condition that does not require systemic therapy
- Participants without active disease in the last 5 years may be included but only after consultation with the study clinical lead
- Participants with coeliac disease controlled by diet alone

15 New York Heart Association Class III or IV heart failure (Choueiri et al 2014).

16 Participants with a 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 chemotherapy, including:

- CTCAE Grade ≥ 2 audiometric hearing loss
- CTCAE Grade ≥ 2 peripheral neuropathy

Prior/Concomitant Therapy

18 Any concomitant medication known to be associated with TdP.

19 Any concomitant medication known to be contraindicated to the NAC (ddMVAC or gem/cis).

20 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.

21 Prior exposure to immune-mediated therapy including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1 and anti-PD-L2 antibodies, excluding Bacillus Calmette- Guérin.

22 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 or as an anti-emetic (eg, CT scan premedication)

23 Prior pelvic radiotherapy treatment within 2 years of first dose of study medication.

24 Receipt of live attenuated vaccine within 30 days prior to the first dose of study treatment (see Appendix G 5).

25 Any concurrent anti-cancer treatment without an adequate washout period (eg, 28 days, if sufficient) prior to the first dose of study treatment. Concurrent use of hormonal therapy for noncancer-related conditions (eg, HRT) is allowed.

26 Radiotherapy with a limited field of radiation within 2 weeks, or with wide field of radiation or to more than 30% of the bone marrow within 4 weeks, prior to the first dose of study treatment.

27 Major surgical procedure or significant traumatic injury within 4 weeks of the first dose of study treatment. Note: Local surgery of isolated lesions for palliative intent is acceptable.

Prior/Concurrent Clinical Study Experience

28 Participation in another clinical study with a study treatment or investigational medicinal device administered in the last 3 months (unless the safety profile is known) prior to first dose of durvalumab) or concurrent enrolment in another clinical study (unless it is observational [noninterventional] or the participant is in the follow-up period of an interventional study).

29 Previous enrolment in the present study.

30 Concurrent enrolment in another clinical study, unless it is an observational (non-

interventional) clinical study or during the follow-up period of an interventional study.

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

Other Exclusions

32 Participants with a known hypersensitivity to durvalumab or any excipients of the product(s).

33 Female participants who are pregnant or breastfeeding, or who are planning to become pregnant, or male or female participants of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period).

34 Female participants should refrain from breastfeeding from enrolment to 90 days after the last dose of durvalumab.

35 Judgement by the investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

For procedures for withdrawal of incorrectly enrolled participants, see Section 6.3.1.

5.3 Lifestyle Considerations

The following restrictions apply while the participant is receiving study treatment and for the specified times before and after:

1 Participants must follow the contraception requirements outlined in Appendix F.

2 Participants 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 anti-cancer therapy is started.

There are none of the following:

- Meals and dietary restrictions
- Caffeine or alcohol restrictions

- Activity restrictions
- Other restrictions

Restrictions relating to concomitant therapies are described in Section 6.9 and Appendix G 5.

5.4 Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study but is not subsequently assigned to study treatment/entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened a single time. Rescreened participants are required to sign a new ICF and will be assigned a new participant number (ie, E-code) from the initial screening.

All screen failure participants should have the reason for study withdrawal recorded as 'screen failure' (ie, participant does not meet the required inclusion/exclusion criteria) in the eCRF. This reason for study withdrawal is only valid for screen failures (ie, participants who are not entered in the study).

Participant enrolment is described in Section 6.3.

6 STUDY TREATMENT

Study treatments are all pre-specified medicinal products (classified as IMPs and AxMPs) and other interventions (eg, surgery) intended to be administered to the study participants during the study conduct.

6.1 Study Treatments Administered

AstraZeneca will supply durvalumab.

Neoadjuvant agents ddMVAC or gem/cis will either be locally sourced by the study site or centrally supplied by AstraZeneca.

Details of all study treatments are presented in Table 7. Dose modifications are described in Section 6.6.

Table 7 Investigational Products

Intervention name	Durvalumab (MEDI4736)	ddMVAC [a]	Gemcitabine and Cisplatin [a]
Type	Biologic	Drug	Drug
Dosage form	Concentrate for solution for infusion	As sourced locally	As sourced locally
Unit dose strength(s)	500 mg (50 mg/mL)	NA	NA
Dose level(s) and regimen	Neoadjuvant [b] Q3W for 4 cycles (if with gem/cis) or Q4W for 3 cycles (if with ddMVAC) Day 1: 1500 mg IV Adjuvant Q4W up to 8 cycles Day 1: 1500 mg IV	Neoadjuvant Q2W for 4 [c] cycles Day 1: methotrexate 30 mg/m^2 IV Day 2: doxorubicin 30 mg/m^2 IV and vinblastine 3 mg/m^2 IV Day 2: cisplatin 70 mg/m^2 IV	Neoadjuvant Q3W for 4 cycles Day 1: cisplatin 70 mg/m^2 OR 35 mg/m^2 IV (dose to be determined based on renal function) and gemcitabine 1000 mg/m^2 IV Day 8: gemcitabine 1000 mg/m^2 IV and cisplatin 35 mg/m^2 (to be administered ONLY if the dose on Day 1 was reduced to 35 mg/m^2 due to renal function)
Route of administration	IV infusion	IV infusion	IV infusion
Use	Experimental	Standard of care	Standard of care
IMP and AxMP	IMP	AxMP	AxMP
Sourcing	Provided centrally by the sponsor	Provided locally by the study site	Provided locally by the study site
Packaging and labelling	Study treatment will be provided in 1500-mg vials. Vials will be provided in a carton of 3; 1 carton = 3 vials (1500-mg). Each vial will be labelled as required per country requirement. [c]	Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.	Labels will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language.
Provider	AstraZeneca	Sourced locally by site [a]	Sourced locally by site [a]

[a] Under certain circumstances when local sourcing is not feasible, a SoC cisplatin-based NAC treatment may be supplied centrally through AstraZeneca, which will be labelled and accompanied by prescribing information with local language translated text in accordance with regulatory guidelines.

[b] Dosing of durvalumab will occur prior to the dosing of chemotherapy.

[c] Participants may receive up to 6 cycles of ddMVAC if this is consistent with institutional standard practice and as clinically indicated.

[d] Label text prepared for durvalumab will show the product name as “MEDI4736” or “durvalumab” depending upon the agreed product name used in the approved study master label document. All naming conventions are correct during this transitional period.

6.1.1 Order of Administration

Durvalumab administration will be administered first; ddMVAC or gem/cis chemotherapy via IV infusion will start approximately 1 hour after the end of the durvalumab infusion.

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

Participants will receive durvalumab via IV infusion over 60 minutes. If the 60-minute IV infusion in the first cycle is well tolerated, 30-minute IV infusion may be administered in subsequent cycles . In the case in which a participant does not tolerate a 30-minute IV infusion , infusion time may be increased according to the TMGs.

It is recommended that a 60-minute observation period take place after durvalumab is administered, at least for Cycles 1 and 2. If no issues are observed following durvalumab administration during the first 2 cycles, the observation period may be reduced for subsequent infusions (suggested duration is 30 minutes).

ddMVAC or gem/cis chemotherapy will be administered per institutional practice.

6.1.2 Durvalumab Regimen

Durvalumab will be supplied as a concentrate for solution for infusion. Durvalumab 500 mg will be supplied in a vial containing 50 mg/mL durvalumab, 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate and 0.02% weight/volume (w/v) polysorbate 80; the solution has a pH of 6.0 and density of 1.054 g/mL. The label-claim volume for durvalumab is 10 mL.

All participants will receive durvalumab 1500 mg as a 60-minute IV infusion in the first cycle (Day 1) and as 30-minute IV infusion in subsequent cycles if the 60-minute IV infusion in the first cycle is well tolerated.

Participants who will be treated with durvalumab in combination with gem/cis will receive 1500 mg durvalumab as an IV infusion Q3W during the neoadjuvant treatment phase starting on Cycle 1 Day 1 for up to a maximum of 12 weeks (4 doses/cycles) until RC, unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met (see Figure 2; for study discontinuation criteria, see Section 7.1).

Participants who will be treated with durvalumab in combination with ddMVAC will receive 1500 mg durvalumab as an IV infusion Q4W during the neoadjuvant treatment phase starting on Cycle 1 Day 1 for up to a maximum of 12 weeks (3 doses/cycles) until RC, unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met (see Figure 2; for study discontinuation criteria, see Section 7.1).

In scenarios when participants are unable to complete the intended number of cycles of

chemotherapy prior to RC, participants will be permitted to receive fewer cycles of chemotherapy following institutional clinical practice based on treating physician decision.

Post RC, participants will receive 1500 mg durvalumab as an IV infusion Q4W during the adjuvant treatment phase for up to a maximum of 32 weeks (8 cycles) or unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met (see Figure 2; for study discontinuation criteria, see Section 7.1).

If a participant's weight falls to 30 kg or below (≤ 30 kg) the participant should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q3W in combination with gem/cis and Q4W in combination with ddMVAC or monotherapy as an adjuvant treatment, until the weight improves to > 30 kg, at which point the participant should start receiving the fixed dosing of durvalumab 1500 mg Q4W or Q3W as appropriate.

6.1.3 Chemotherapy Regimen

ddMVAC or gem/cis will be locally sourced by sites and/or AstraZeneca marketing companies 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 labelled with local language translated text in accordance with regulatory guidelines.

6.1.4 Dose and Treatment Regimens

Participants in the neoadjuvant treatment phase will receive chemotherapy based on investigator's decision (Table 8). Chemotherapy will be administered as per institutional practice/prescribing information.

In scenarios when participants are unable to complete the intended number of cycles of chemotherapy prior to RC, participants will be permitted to receive fewer cycles of chemotherapy following institutional clinical practice based on treating physician decision.

Refer to the local prescribing information with regard to warnings, precautions, and contraindications.

Table 8 Study Schema

Treatment arm	Neoadjuvant treatment												RC	Adjuvant treatment
Week	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**56 d (8 wks)**	**1 cycle = 4 wks (28 d) [a]**
Durvalumab (Q4W) + ddMVAC (Q2W)														
Durvalumab	X				X				X					X 8 cycles
ddMVAC	X		X		X		X		X [c]		X [c]			
Durvalumab (Q3W) + gem/cis (Q3W)														
Durvalumab	X			X			X			X				X 8 cycles
Gem/Cis	X	X [b]		X	X [b]		X	X [b]		X	X [b]			

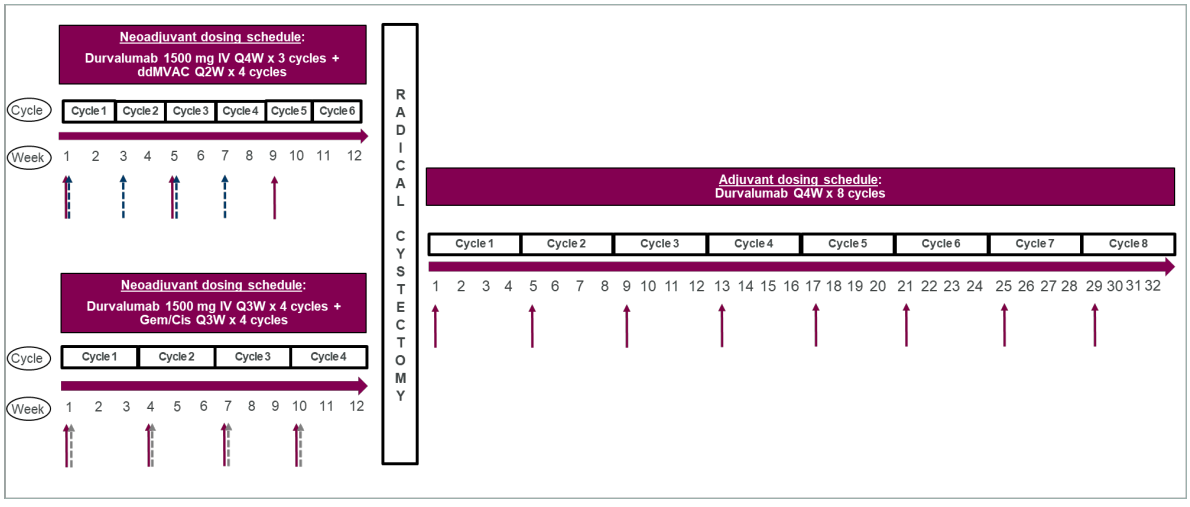
[a] Treatment will start 42-120 days following RC.

[b] This is required for participants 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 institutional practice, for management of renal toxicity.

[c] ddMVAC administration at weeks 9 and 11 is optional as per institutional standard practice and as clinically indicated.

Note: If there is a dosing delay for NAC, durvalumab doses should be held to ensure that dosing is administered on Day 1 of each cycle.

Figure 2 Dosing Schedule



Colour key for arrows: maroon = durvalumab; blue dashed = ddMVAC; grey dashed = gem/cis; black dashed = optional.
Note: If there is a dosing delay for NAC, durvalumab doses should be held to ensure that dosing is administered on Day 1 of each cycle. C5 and C6 ddMVAC administration at weeks 9 and 11 respectively, are optional as per institutional standard practice and as clinically indicated.

6.1.5 Duration of Treatment

Participants will receive durvalumab 1500 mg as an IV infusion in combination with cisplatin-based NAC during the neoadjuvant treatment phase, with administration beginning on Day 1 for a maximum of 12 weeks until RC or progression, unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met (for study discontinuation criteria, see Section 7.1).

In scenarios when participants are unable to complete the intended number of cycles of chemotherapy prior to RC, participants will be permitted to receive fewer cycles of chemotherapy following institutional clinical practice based on treating physician decision.

Participants in the gem/cis investigator's choice chemotherapy treatment arm during the neoadjuvant treatment phase will receive gemcitabine (1000 mg/m^2 IV on Days 1 and 8) and cisplatin (35 mg/m^2 IV on Days 1 and 8 or 70 mg/m^2 IV on Day 1) in 21-day cycles for 4 cycles until RC, unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met (for study discontinuation criteria, see Section 7.1).

Participants in the ddMVAC investigator's choice chemotherapy treatment arm during the neoadjuvant treatment phase will receive methotrexate (30 mg/m^2 IV on Day 1), doxorubicin (30 mg/m^2 IV on Day 2), vinblastine (3 mg/m^2 IV on Day 2), and cisplatin (70 mg/m^2 IV on Day 2) Q2W for 4 cycles until RC, unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met (for study discontinuation criteria, see Section 7.1). However, participants may receive up to 6 cycles of ddMVAC if this is consistent with the treating institution's standard practice.

During the neoadjuvant treatment phase, participants who have RECIST 1.1-defined radiological progression (refer to Appendix E) may continue to the adjuvant portion of treatment if the progression event did not preclude the participant from having a RC (ie, progression is local and/or limited to regional lymph nodes that will be removed during the RC/bilateral lymph node dissection procedure). In the event that progression (ie, distant metastases) precludes a participant from undergoing RC, the participant will proceed to follow-up per institutional practice and be followed for OS.

Post-RC, participants will receive durvalumab monotherapy 1500 mg as an IV infusion during the adjuvant treatment phase for up to 8 cycles (32 weeks) or until recurrence or progression, unacceptable toxicity, withdrawal of consent, or an intervention discontinuation criterion is met (for study discontinuation criteria, see Section 7.1).

Participants who refuse surgery but are disease-free are able to receive the additional 8 cycles of durvalumab monotherapy 1500 mg per decision of investigator.

6.1.6 Surgical Plan

RC 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 NAC. RC is not recommended earlier than 14 days after the last dose of neoadjuvant therapy.

If RC cannot be performed within the 56-day timeframe (8 weeks) from the last dose of NAC due to a medical reason, it may be delayed per institutional clinical practice. If surgery is delayed more than 70 days (10 weeks), AstraZeneca should be consulted.

Robot-assisted, laparoscopic, or open RC will be performed as per institutional practice. Male participants will undergo radical cystoprostatectomy and urinary diversion along with bilateral pelvic lymph node dissection. Female participants will undergo RC. Ahysterectomy and bilateral salpingectomy may be performed by the participant'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, small/large bowel neobladder, ureterocutaneostomy, or as per institutional 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.

RC is a planned study procedure for all participants. If an alternative procedure is performed, it should be documented in eCRF.

In a setting in which a participant refuses an RC at the study-specified time, after having a complete clinical response determined locally by multimodal assessment (see below) and without any additional intervention (eg, transurethral resection of bladder tumour), the participant may be permitted to continue into a non-cystectomy extension phase to continue with study treatment that mirrors that for the adjuvant phase. This allowance is only permitted after consultation and agreement with AstraZeneca. Participants who enter the non-cystectomy extension phase may be administered durvalumab 1500 mg (as monotherapy) for a total of 8 doses (see Section 6.1.2). Multimodal assessment for determining a complete clinical response includes the following:

- Required: cystoscopy (with biopsies, per local practice and if feasible) 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 Preparation, Handling, Storage, and Accountability

The investigator or designee (eg, pharmacist) must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study treatment received at the site and throughout the entire study duration until authorisation is provided for on-site destruction or removal of the IMP, reflecting completion of the study. In the event of a temperature excursion detected at any time during the study, sites will follow the reporting procedures for notifying the sponsor (or designated party); release of study treatment for clinical use can only occur once the event has been reviewed and approval is provided by the sponsor (or designated party).

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

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

Further guidance and information for the final disposition of unused study treatments are provided in the Study Reference Manual.

6.2.1 Storage of Study Treatment: Durvalumab

Durvalumab vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen (Table 9). The investigator, or an approved representative (eg, pharmacist), will ensure that all study treatment is stored in a secured area, in refrigerated temperatures (2°C to 8°C; 36°F to 46°F) 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.

Study treatment must be kept in original packaging until time of preparation to prevent prolonged light exposure.

The dose of durvalumab must be prepared by the investigator's or site's designated study intervention manager using aseptic technique and following institutional practices and site requirements. Total time from needle puncture of the study treatment vial to the start of administration must not exceed the following:

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

If the final product is stored at both refrigerated and ambient temperatures, the total time must not

exceed 24 hours otherwise a new dose must be prepared from new vials. Durvalumab vials do not contain preservatives; any unused portion of the vial must be discarded immediately after use.

Table 9 Investigational Product Storage

Investigational product		Storage temperature	Duration
Durvalumab	Vial (500 mg/vial)	2°C to 8°C (36°F to 46°F)	Within the individually assigned expiry date on the label

6.2.2 Durvalumab Infusion Preparation and Administration

6.2.2.1 Preparation

Durvalumab is a sterile, clear to opalescent, colourless to slightly yellow solution, free from visible particles. Each vial selected for dose preparation should be inspected.

A dose of 1500 mg for participants > 30 kg in weight will be prepared using an IV bag containing 0.9% sodium chloride for injection or 5% dextrose for injection. Add 30 mL (ie, 1500 mg) of durvalumab 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 participant weight falls to ≤ 30 kg, weight-based dosing at 20 mg/kg will be prepared using an IV bag size selected such that the final concentration is within 1 to 15 mg/mL.

6.2.2.2 Administration

Durvalumab infusions are to be administered 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.

The durvalumab infusion time in this study is 60 minutes ± 10 minutes in Cycle 1, followed by 30 minutes ± 5 minutes in subsequent cycles if the 60-minute IV infusion in the first cycle is well tolerated; however, if there are interruptions, the total allowed time must not exceed 8 hours with the infusion bag maintained at room temperature, otherwise a new dose must be prepared from new vials.

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

The IV line will be flushed according to institutional practices to ensure the full dose is administered. Infusion time does not include the final flush time.

6.2.3 Standard of Care Cisplatin-based Neoadjuvant Chemotherapy Treatment

The SoC cisplatin-based NAC agents, ddMVAC or gem/cis, will either be locally sourced by the study site or centrally supplied by AstraZeneca and will be prepared and administered according to prescribing information or treatment guidance in general use by the investigating

site. Under certain circumstances when local sourcing by the study site is not feasible, AstraZeneca will centrally supply the study treatment, which will be labelled and accompanied by prescribing information with local language translated text in accordance with regulatory guidelines. Accountability and storage requirements, as specified in Section 6.2, apply for any study treatment supplied by AstraZeneca.

6.3 Assignment to Study Treatment

Before study initiation, login instructions for the IRT and/or login information and instructions for the RTSM will be provided to each site.

Participant details will be recorded in the IRT/RTSM per country regulations.

At screening/baseline (Days -28 to -1), the investigator 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 participant. However, all screening laboratory and imaging results must have been obtained within 28 days of the first dose of study treatment.
- Obtain a unique 7-digit enrolment code (E-code), through the IRT/RTSM in the following format (ECCNNXXX: CC being the country code, NN being the centre number, and XXX being the participant enrolment code at the centre). This number is the participant's unique identifier and is used to identify the participant on the eCRFs.
- Determine participant eligibility (see Sections 5.1 and 5.2).
- Prior to participant enrolment, the investigator will select the cisplatin-based NAC treatment, either ddMVAC or gem/cis, based on the most appropriate option for the participant per institutional clinical practice guidance. The information will be recorded in the IRT/RTSM system.

Investigators should keep a record (ie, the participant screening log) of all participants who enter screening.

If the participant is ineligible, the IRT/RTSM should be accessed to terminate the participant in the system.

Participants will begin treatment on Cycle 1 Day 1. Participants must not receive study medication unless all eligibility criteria have been met.

If a participant withdraws from the study, then his/her enrolment code cannot be reused. Withdrawn participants will not be replaced.

6.3.1 Procedures for Handling Incorrectly Enrolled Participants

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

Where a participant does not meet all the eligibility criteria but incorrectly receives study medication, the investigator should inform the AstraZeneca study clinical lead immediately, and a discussion should occur between the AstraZeneca study clinical lead and the investigator regarding whether to continue or discontinue the participant from treatment. The AstraZeneca study clinical lead must ensure all decisions are appropriately documented and that the potential benefit/risk profile remains positive for the participant.

6.4 Blinding

Not applicable; this is an open-label study.

6.5 Study Treatment Compliance

When participants are dosed at the site, they will have study treatment(s) prepared, dispensed, and administered by the investigator or designee, under medical supervision. The date, and time if applicable, of the administered study treatment will be recorded in the source documents and recorded in the eCRF. The dose of study treatment and study participant identification will be confirmed at the time of dosing in accordance with institutional treatment verification practices.

6.6 Dose Modification

6.6.1 Durvalumab

Dose delays (interruptions) are permitted for durvalumab therapy; however, dose reduction is **not permitted** (see Dosing Modification and Toxicity Management Guidelines in the Annex document to this CSP).

Participants may delay dosing under certain circumstances.

- Dosing may be delayed per the Dosing Modification and Toxicity Management Guidelines, 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. Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumour efficacy (RECIST 1.1). Subsequent time between 2 consecutive doses cannot be less than 21 days, based on the half-lives of durvalumab (see current IB for durvalumab). If there is a dosing delay

while on the Q3W schedule (neoadjuvant portion especially with gem/cis), 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 tumour efficacy. 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, chemotherapy may still be administered as scheduled.

6.6.2 Standard of Care Chemotherapy Treatment

Dosage adjustments and changes to treatment schedule (delay, interruption, dose reductions) are permitted in accordance with institutional practice and product labelling information. Treatment may be delayed and subsequently resumed per institutional standard clinical practice. Participants may delay and subsequently resume dosing per institutional standard clinical practice. Participants will also be permitted to skip chemotherapy per institutional 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 is delayed, durvalumab should follow the chemotherapy schedule and should be administered on Day 1 of each cycle.
- In the event that chemotherapy is discontinued due to treatment-related toxicity, participants should proceed to RC when clinically feasible, and the remaining durvalumab monotherapy neoadjuvant doses should be skipped. Adjuvant therapy with durvalumab may continue following RC. Note: If the investigator feels that a participant would benefit from administering the 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 institutional clinical practice, for management of renal toxicity.

6.6.3 Management of 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 study treatment 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.

All toxicities will be graded according to NCI CTCAE v5.0.

6.6.3.1 Durvalumab

Comprehensive toxicity management guidelines have been developed to assist investigators with the recognition and management of toxicities associated with the use of the immune-checkpoint inhibitor durvalumab (PD-L1 inhibitor). Given the similar underlying mechanisms of toxicities observed with this compound, these guidelines are applicable to the management of participants receiving drug as monotherapy or in combination. Additionally, these guidelines are applicable when durvalumab is used in combination with other anti-cancer drugs (ie, antineoplastic chemotherapy, targeted agents), administered concurrently or sequentially as part of a protocol-specific treatment regimen. These guidelines apply to AEs considered causally related to durvalumab monotherapy regimen, as assessed by the reporting investigator. The most current version of the toxicity management guidelines entitled "Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy or in Combination with Other Products" is provided to the investigative site as an Annex document and is maintained within the Site Master File.

The toxicity management guidelines provide information for the management of immune-mediated reactions, IRRs, and non-immune-mediated reactions that may be observed with checkpoint inhibitor monotherapy or combination checkpoint inhibitor regimens, with specific instructions for dose modifications (including discontinuations) and treatment interventions. Dose modifications with regards to hold or discontinuation of durvalumab are required actions for the management of potential immune-mediated events or non-immune-mediated adverse reactions, as described in the Dosing Modification and Toxicity Management Guidelines; permanent discontinuation of study treatment for these AEs is considered a study-specific requirement.

Participants should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other aetiologic 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 aetiology, events should be considered potentially immune-related. Following the first dose of study treatment, subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. Investigators are advised to use local practice guidelines and consult local references for the management of toxicities observed with other cancer treatments.

6.6.3.2 Standard of Care Chemotherapy

For management of toxicities due to cisplatin-based NAC (ddMVAC or gem/cis), including dose and treatment modifications, refer to the locally approved prescribing information or manage in accordance with institutional guidelines.

6.7 Continued Access to Study Treatment After the End of the Study

There is no planned treatment after the end of the study but AstraZeneca retains the right to request additional information for any participant with ongoing AEs/SAEs at the end of the

study. Participants should continue appropriate treatment at the discretion of the investigator.

In the event that product development reaches a point where alternative product supply options become available, then these alternative product supply options will be discussed by AstraZeneca with the investigator. AstraZeneca will work with the investigator to transition the participant(s) to alternative supply, where possible. In the event that a roll-over or safety extension study is available at the time of the final data cut-off and database closure, participant(s) currently receiving treatment with the study treatment may then be transitioned to such a study, and the current study may reach its end. The roll-over or extension study would ensure treatment continuation with visit assessments per its protocol, as applicable. Any participant who would be eligible to move to such a study would be given a new informed consent, as applicable.

6.8 Treatment of Overdose

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

For participants receiving chemotherapy (ddMVAC or gem/cis), refer to the local prescribing information for treatment of cases of overdose.

In the event of an overdose, the investigator/treating physician should:

- Evaluate the participant to determine, in consultation with the medical monitor or study clinical lead, if possible, whether study treatment should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate and at least until the next scheduled follow-up. Document the quantity of the excess dose as well as the duration of the overdose. Refer to Section 8.3.15 for details of AE/SAE reporting related to overdose.

6.9 Prior and Concomitant Therapy

Any prior/concomitant treatment, procedure, or other medication considered necessary by the investigator for the participant's safety and wellbeing, (including vaccines, over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) that the participant (except for screen failures) is receiving from the time of screening or receives during the study including the 90-day follow-up period following the last dose of study treatment must be recorded in the eCRF along with:

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

If any concomitant therapy is administered due to new or unresolved AE, it should be recorded.

Participants must be instructed not to take any medications, including over-the-counter products, and/or complimentary alternative medicines/herbal products without first consulting with the investigator.

Restricted, prohibited, and permitted concomitant medications/therapies are described in more detail in Appendix G 5.

Guidance regarding potential interactions with concomitant medications is provided in Appendix G 1.

The study clinical lead or medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

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

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

- Medications administered in the perioperative period that were used to treat an unexpected AE/complication, occurring perioperatively
- Medications administered in the perioperative period that contributed to an unexpected AE/complication, occurring postoperatively
- Medications administered as surgical prophylaxis, including antibiotics administered perioperatively
- Medications administered during the surgery about which the sponsor has requested specific additional information as part of documentation pertaining to a particular participant or as a programme-wide requirement

Medications and Fluids for Chemo-immunotherapy Infusions

Any medication administered as a premedication for ddMVAC or gem/cis 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 sulphate) 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.

Participants 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 Appendix G 5. Refer also to the Dosing Modification and Toxicity Management Guidelines (see Section 8.3.14).

6.9.1 Durvalumab Drug-drug Interactions

There is no information to date on drug-drug interactions with durvalumab either preclinically or in participants.

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. Moreover, it is not expected that durvalumab will induce or inhibit the major drug metabolising cytochrome P450 pathways. As a result, there are no expected PK drug-drug interactions. The mechanism of action of durvalumab involves binding to PD-L1, and therefore significant pharmacodynamic drug interactions with 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.

Guidance regarding potential interactions with concomitant medications is provided in Appendix G 1.

6.10 Rescue Medicine

The study site will supply the required rescue medication that will be obtained locally. The following rescue medications are required to be available at the site:

1 Infliximab/infliximab biosimilar (eg, for colitis).
2 Mycophenolate (eg, for hepatitis).

Under certain circumstances when local sourcing by the study site is not feasible or local regulations prevent the use of infliximab or mycophenolate for this use (as they are considered off-label for management of immunotherapy-related toxicities), AstraZeneca will centrally supply the required rescue medications, which will be labelled and accompanied by prescribing information with local language translated text in accordance with regulatory guidelines. Accountability and storage requirements, as specified in Section 6.2, apply to any study treatment supplied by AstraZeneca. If required to manage an imAE, then the IVRS/IWRS will allocate the specific medication either by a kit or another identification number, to the pharmacist for a specific participant at the time of the event.

As a result of imAEs that could potentially be experienced by participants on durvalumab, appropriate treatment (eg, steroids and specific immunosuppressant rescue medications) must be made readily available to this participant population.

The date of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

7 DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix A.

7.1 Discontinuation of Study Treatment

Note that discontinuation from study treatment is *not* the same thing as a discontinuation or withdrawal from the study (see Section 7.2).

If study treatment is permanently discontinued, the participant should, if at all possible, remain in the study.

The investigator should instruct the participant to contact the site before or at the time if study treatment is stopped. A participant who decides to discontinue study treatment must always be asked about the reason(s) and the presence of any AEs. The reason for discontinuation should be documented in the source document and the appropriate section of the eCRF.

Participants who have permanently discontinued from further receipt of study treatment will need to be discontinued from the IRT/RTSM. All study treatment should be returned by the participant at their next on-site study visit or unscheduled visit.

See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed.

Participants may be discontinued from study treatment in the following situations:

- Progression that precludes curative/complete resection per investigator's assessment: progression that precludes the participant from undergoing an RC either by RECIST 1.1-defined radiological progression or per investigator's assessment; local progression during the neoadjuvant phase might not be a precluding event (refer to Section 8.1.1 and Appendix E).
- Proven recurrence, either by RECIST 1.1-defined radiological progression or positive tumour biopsy from suspected recurrence (see Sections 8.1.1.1 and 8.1.1.2) following RC.
- An RC procedure is not performed (see Section 6.1.6) either due to a medical decision by the investigator or a participant refusal, and entry into the non-cystectomy extension phase is not applicable.

- Investigator determines that the participant is no longer benefiting from study treatment.
- Participant decision: The participant is free to discontinue treatment at any time, without prejudice to further treatment. A participant who discontinues treatment is normally expected to continue to participate in the study (eg, for safety, tumour assessment per institutional standard, and survival follow-up) unless they specifically withdraw their consent to all further participation in any study procedures and assessments (see Section 7.3). Severe noncompliance with the CSP, as judged by the investigator or AstraZeneca.
- Initiation of subsequent anti-cancer therapy, including another investigational agent.
- An AE that, in the opinion of the investigator or AstraZeneca, contraindicates further dosing.
- Any AE that meets criteria for discontinuation defined in the dose modification guidelines for management of study treatment-related toxicities (see the Annex document to this CSP) or as defined in the local prescribing information for the SoC cisplatin-based NAC, ddMVAC or gem/cis.
- Pregnancy or intent to become pregnant.

See the SoA for data to be collected at the time of discontinuation of study treatment and follow-up and for any further evaluations that need to be completed (Table 4).

7.1.1 Procedures for Discontinuation of Study Treatment

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

Participants who are permanently discontinued from further receipt of study treatments regardless of the reason will be identified as having permanently discontinued treatment. Participants who are permanently discontinued will enter follow-up. The recommended schedule of assessment is defined in Table 4.

7.1.2 Procedures for Discontinuation of Study Plan (No Radical Cystectomy)

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

considered resectable, who are therefore precluded from undergoing an RC, and the participant will be entered into the follow-up phase (see Table 4).

Participants who do not have an RC performed for medically excluded reasons will be entered into the follow-up phase. Further disease assessments in these participants are outlined in Section 8.1.1.

Participants who refuse to proceed with an RC will be managed as follows:

- Participants who are determined to be in complete response (see Section 6.1.6) and who enter into a non-cystectomy 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 RC, in case of disease recurrence.
- Participants with residual disease will be entered into follow-up phase.

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

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

7.1.3 Follow-up of Participants Post Discontinuation of Study Treatment

All participants who discontinue the study treatment will be followed up for safety assessments 90 days ± 5 days after their last dose of study treatment. Additional assessments to be performed at the time of the 90-day safety follow-up are detailed in the SoA (Table 4). All AESIs, regardless of severity or seriousness, must be followed until either event resolution, end of study, including any post-treatment follow-up, trial termination, withdrawal of consent, or participant death (see Section 8.3.12).

Participants who have discontinued study treatment will be followed up with tumour assessments using RECIST 1.1 per institutional practice until the end of study, trial termination, withdrawal of consent, or participant death (Table 4).

7.1.4 Follow-up for Survival

Participants will be followed up for survival status as indicated in the SoA until death, withdrawal of consent, or the end of the study. Survival information may be obtained via telephone contact with the participant or the participant's family, or by contact with the participant's current physician. Additional assessments, including subsequent anti-cancer therapy and tumour assessment as per institutional standard, are to be recorded at the time of survival follow-up and are detailed in the SoA (Table 4).

7.2 Participant Discontinuation/Withdrawal from the Study

Discontinuation of the participant from the study by the investigator:

- A participant may be discontinued from the study at any time at the discretion of the

investigator for behavioural or compliance reasons.

- At the time of discontinuing from the study, if the participant has not been discontinued from the study treatment, see Section 7.1.

Voluntary withdrawal from the study by the participant:

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason) without any implication on the participant's rights.
- A participant who wishes to withdraw from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA.
- If the participant withdraws consent for disclosure of future information, AstraZeneca may retain and continue to use any data collected before such a withdrawal of consent.

  If the participant withdraws from the study, AstraZeneca may retain and continue to use any samples collected before such a withdrawal of consent for the purposes the participant originally consented unless the participant withdraws consent for use of samples already collected. If the participant specifically withdraws consent for any use of samples, it must be documented in the site study records by the investigator and the investigator must inform the local and global study team. Destruction of any samples taken and not yet tested should be carried out in line with documented sample withdrawal wishes in conjunction with what was stated in the informed consent and local regulation.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and no contact has been established by the time the study is completed.

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible. The participant should be counselled on the importance of maintaining the assigned visit schedule and ascertain whether the participant should or wishes to and/or continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls, texts, emails, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the

participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study/been lost to follow-up. Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants, including those who did not get study intervention. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA (see Section 1.3). Requirements for data collection following study enrolment until the end of the study are described below. Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with AstraZeneca immediately upon occurrence or awareness to determine if the participant 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 participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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

In the event of a significant study continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by AstraZeneca or the investigator, as per local health authority/ethics requirements.

Data Collection Following Study Analysis Until the End of the Study

After the final DCO and database closure, only SAEs will be reported for the purposes of this study (see Section 8.3.11).

For SAE and AE reporting and laboratory assessment collection after final analysis, see Section 8.3.11.

8.1 Efficacy Assessments

This study will evaluate the secondary endpoints of EFS, DFS, OS, and pathologic response. The efficacy assessments of EFS and DFS (median and landmark) will be derived using investigator's assessments according to RECIST 1.1 or by local pathology review if a biopsy is required for a suspected new lesion. For OS assessments, death dates may be found by checking publicly available death registries, where allowed by local regulations. Pathologic response, pCR and pDS will be derived using local pathology review of the RC sample.

Planned timepoints for all efficacy assessments are provided in the SoA (see Section 1.3).

8.1.1 Tumour Assessments

Pathologic response, pCR and pDS, assessment will be done by local pathology review of RC samples (Sections 8.1.1.2). EFS and DFS efficacy assessment will be assessed by investigator by either RECIST 1.1 on imaging scans (Sections 8.1.1.1) or by pathology on biopsy samples if required (Sections 8.1.1.2 and 8.1.1.3).

8.1.1.1 Imaging Tumour Assessments

Tumour assessments at baseline, during treatment, and at regular (follow-up) intervals are evaluated as described in the SoA (Section 1.3) using images from CT (preferred) or MRI, with IV contrast, assessed according to RECIST 1.1 following institutional clinical practice by investigators. Additional modalities (eg, Fluorodeoxyglucose - Positron Emission Tomography scan, etc.) for staging purposes can be used. The RECIST 1.1 assessments of baseline images identify TLs (defined as measurable) and NTLs. On-study images are evaluated for TLs and NTLs chosen at baseline and for new lesions NLs when they appear. This allows determination of follow-up TL response, NTL lesion response, the presence of unequivocal NLs, and overall timepoint responses (CR, PR, SD, PD, NE).

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

A second "Adjuvant Baseline" scan should be collected 42 days (± 2 weeks) after RC and should be performed as close as possible and importantly prior to the first date of adjuvant treatment (Table 3). 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 tumours are identified, a new selection of target and/or non-target lesions are recorded. A follow-up scan should be performed per institutional clinical practice at least 4 weeks later, as an assessment using RECIST 1.1. The use of an earlier scan is in place to allow early confirmation of a lesion with recurrence or progression. Additionally, a new lesion can be evaluated pathologically at any time, when feasible, to confirm metastatic disease.

On-study adjuvant tumour assessments will occur as per institutional clinical practice. It is recommended every 12 weeks ± 7 days 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 at least 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 may be followed regardless of any delays in dosing.

Tumour Assessment for Participants Not Undergoing a Radical Cystectomy

Participants with confirmed progression during the neoadjuvant phase outside of the pelvis or progression of a lymph node in the true pelvis that is determined to be unresectable, and who are therefore precluded from undergoing an RC, will be entered into the follow-up phase (see Table 4).

Participants who *refuse* to proceed with a RC will have tumour assessments performed as follows:

- Participants who are determined to be in complete clinical response (see Section 6.1.6) and who enter into a non-cystectomy extension phase with a plan for a potential delayed cystectomy are recommend to have a scan obtained 12 weeks after the last scan that was performed in the neoadjuvant phase, and then every 12 weeks ± 7 days 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 participant has not progressed, every attempt should be made to perform the subsequent assessments according to the original imaging schedule. For participants who discontinue treatment due to toxicity or other reasons in the absence of unequivocal recurrence, tumour assessments are recommended to continue according to the schedules of assessments.

  - Participants with local progression during the non-cystectomy extension phase, who are not precluded from undergoing a delayed RC, are recommended to have a post-cystectomy (adjuvant) baseline scan obtained and additional scans performed according to the on-study adjuvant schedule.
  - Participants who are medically precluded from undergoing a delayed RC will be entered into follow-up phase.
  - For participants who refuse a delayed RC procedure in case of recurrence, the participant will be entered into follow-up phase.
- Participants with residual disease (microscopic or macroscopic) and who refuse RC will be followed up for tumour assessment using RECIST 1.1 per institutional standard practice and will be followed for evaluation of OS.

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 tumour, progression will be recorded using the date of biopsy.

8.1.1.3 Local Pathology Review

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

8.1.2 Overall Survival

Assessments for survival will be conducted at every visit during study treatment and follow-up. After completion of study treatment or treatment discontinuation, assessments for survival will be made per institutional clinical practice. The recommended frequency of assessment is every 3 to 6 months (± 14 days). Survival information may be obtained via telephone contact with the participant, participant's family, by contact with the participant's current physician, or local death registries as described in Section 7.3.

Note: Survival calls will be made following the DCO date for the analysis (these contacts should generally occur within 7 days of the DCO date). If participants are confirmed to be alive or if the death date is after the DCO date, then these participants will be censored at the date of DCO.

8.2 Safety Assessments

This study will evaluate the primary endpoint of incidence of Grade 3 or 4 PRAEs as observed prior to cystectomy. Additional safety secondary endpoints will be evaluated as described in Section 3.

Planned timepoints for all safety assessments are provided in the SoA (see Section 1.3).

8.2.1 Physical Examinations

Physical examinations, as well as assessment of height and weight, will be performed at timelines as specified in the SoA (see Section 1.3). Full physical examinations will include assessments of the general appearance, CV system, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, respiratory, musculoskeletal (including spine and extremities), urogenital, dermatological, GI, endocrine, haematologic/lymphatic, and neurological systems. Height will be measured at screening only.

A targeted physical examination may include assessments of skin, lungs, CV system, and abdomen (liver and spleen) as per institutional standard. Additional assessments are performed by the investigator on the basis of clinical observations and symptomatology.

Investigators should pay particular attention to clinical signs related to previous serious illnesses, as new or worsening abnormalities may qualify as AEs (see Section 8.3.4 for details).

8.2.2 Vital Signs

Vital signs (temperature, BP, pulse, and respiration rate) will be assessed at timelines as specified in the SoA (see Section 1.3). 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 signs results should be reported as AEs are described in Section 8.3.4. For any AEs of infusion reactions, the vital signs values should be entered into the eCRF.

8.2.2.1 Vital Signs at First Infusion (60-Minute Durvalumab Infusion)

On the first infusion day, participants will be monitored and vital signs collected/recorded in the eCRF prior to, during, and after infusion of study treatment as presented in the bulleted list below. Participants should be carefully monitored during the initial infusion with each intervention for possible haemodynamic changes, associated with a possible infusion reaction.

BP and pulse will be collected from participants before, during, and after each 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 BP and pulse measurements 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 and prior to the initiation of chemotherapy with monitoring per institutional standards.

8.2.2.2 Vital Signs at First 30 Minutes of Durvalumab Infusion

On the second infusion day, participants will be monitored and vital signs collected/recorded in the eCRF prior to, during, and after infusion of study treatment as presented in the bulleted list below.

BP and pulse will be collected from participants before, during, and after each infusion at the following times (based on a 30-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 15 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 30 minutes ± 5 minutes)

If the infusion takes longer than 30 minutes, then BP and pulse measurements 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 30-minute infusion of durvalumab and prior to the initiation of chemotherapy, with monitoring per institutional standards.

8.2.2.3. Vital Signs at Subsequent Infusions

BP, pulse, and other vital signs should be measured, collected/recorded in eCRF prior to the start of the infusion. Participants 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 eCRF page. If there are no clinically significant concerns after the first 2 cycles (60 minutes for the first cycle, 30 minutes for the second cycle), the observation period may be reduced for subsequent infusions (suggested duration is 30 minutes).

8.2.3 Electrocardiograms

Single 12-lead ECGs will be performed at timepoints as specified in the SoA (see Section 1.3) after the participant has been resting semi-supine for at least 5 minutes and recorded while the participant remains in that position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTcF intervals.

All ECGs should be performed and assessed by the investigator as to whether they are clinically significantly abnormal. Any clinically significant abnormalities detected require additional ECG results to be obtained per institutional clinical practice.

Situations in which ECG results should be reported as AEs are described in Section 8.3.4.

8.2.4 Clinical Safety Laboratory Tests

Blood and urine samples for determination of clinical chemistry, haematology, coagulation, and urinalysis will be taken at the visits indicated in the SoA.

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.

Clinical chemistry, haematology, and urinalysis will be performed at a local laboratory at or near to the investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site. Every effort should be made to obtain and provide the corresponding laboratory reference ranges.

Other safety laboratory tests include assessment for pregnancy (serum at screening and urine at other timepoints), and HBsAg, HCV antibodies, and HIV antibodies. Pregnancy tests may be performed at the site using a licensed test (urine or serum pregnancy test). Women of child-bearing potential are required to have a pregnancy test within 7 days prior to the first dose of study treatment and then within 3 days prior to every dosing visit. 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. Urine or serum pregnancy test will be performed at least monthly throughout the total duration of study treatment and up to 90 days after the last dose of durvalumab or up to end of the period specified in the SmPC or package insert of the cisplatin-based NAC agents (ddMVAC or gem/cis), whichever is longer. Abnormal clinically significant laboratory results should be repeated as soon as possible (preferably within 72 hours).

The laboratory variables to be measured are listed in Table 10.

Table 10 Laboratory Safety Variables

Haematology/Haemostasis (whole blood)	**Clinical chemistry (serum or plasma)**
Leukocyte count (total white cell count)	Albumin
Absolute lymphocyte count [a]	ALP [c]
Absolute neutrophil count [a]	ALT [c]
Haemoglobin	Amylase [d]
Platelet count	AST [c]
Coagulation	Bicarbonate [b]
PTT and INR [b]	Bilirubin, total [c]
	Calcium, total or calcium corrected (for albumin)
	Chloride [b]
Urinalysis	Cortisol [f]
Colour and appearance	Creatinine and creatinine clearance [e]
pH and specific gravity	Gamma-glutamyl transferase [b]
Blood	Glucose (random/fasting)
Bilirubin	Lactate dehydrogenase
Glucose	Lipase [d]

Ketones	Magnesium [b]
Protein	Potassium
	Protein, total
	Sodium
	TSH
	T_3 free (reflex)
	T_4 free (reflex)
	Urea nitrogen/blood urea nitrogen, depending on institutional practice

[a] Can be recorded as absolute counts or as percentages. Total white cell count therefore has to be provided.
[b] Bicarbonate (where available), chloride, creatinine clearance, gamma-glutamyl transferase, INR, magnesium and PTT testing are to be performed at baseline, on Day 1 (unless all screening laboratory clinical chemistry and haematology assessments are performed within 3 days prior to Day 1), and if clinically indicated.
[c] Tests for ALT, AST, ALP, and TBL must be conducted and assessed concurrently. If TBL ≥ 2 × ULN (and no evidence of Gilbert's syndrome), then fractionate into direct and indirect bilirubin.
[d] It is preferable that both amylase and lipase parameters are assessed. For sites where only one of these parameters is routinely measured, either lipase or amylase is acceptable.
[e] CrCl 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.
[f] Sample for cortisol testing is to be collected as per institutional clinical practice.
For further details, please refer to the SoA.
Note: For urinalysis, microscopy is preferred to investigate white blood cells, with use of high-power field; dipstick can be used as well.
Note: For coagulation parameters, aPTT (either as a ratio or as an absolute value, in seconds) and INR are to be assessed at baseline on Neoadjuvant Cycle 1 Day 1 (unless all screening laboratory haematology assessments are performed within 3 days prior to Day 1), Adjuvant Cycle 1 Day 1, and as clinically indicated.

The investigator should assess the available results with regard to clinically relevant abnormalities in documentation. 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 8.3.4.

If a participant develops AST or ALT ≥ 3 × ULN together with TBL ≥ 2 × ULN, please refer to Appendix D, for further instructions.

All participants with CTCAE Grade 3 or 4 laboratory values at the time of completion or discontinuation from study treatment must be followed and 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.

8.2.5 Other Safety Assessments

8.2.5.1 Pneumonitis (ILD) Investigation

If new or worsening pulmonary symptoms (eg, dyspnoea) 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 8.3.16) will be applied. The results of the full diagnostic workup (including high-resolution CT, blood and sputum culture, haematological 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 oedema, or pulmonary haemorrhage. In the presence of confirmatory high-resolution CT 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 (see the Annex document to this CSP) should be followed.

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.

8.2.5.2 WHO/ECOG Performance Status

WHO/ECOG performance status will be assessed at the times specified in the SoA 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.

8.2.5.3 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 SoA (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, such 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[a]) requiring IC/ICU management
Grade IVa	Single organ dysfunction (including dialysis)
Grade IVb	Multiorgan dysfunction
Grade V	Death of a patient

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

8.3 AEs, SAEs, and Other Safety Reporting

The principal 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.

Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorised representative) will notify the investigator or designees of symptoms. These must then be assessed by the investigator and, if considered an AE it will be reported by the investigator.

The investigator and any designees are responsible for detecting, documenting, recording, and reporting events that meet the definition of an AE.

Adverse Event Variables

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Maximum CTCAE grade or changes in CTCAE grade
- Whether the AE is serious or not (see Appendix B)
- Investigator causality rating against the IMP(s)/study treatment(s) (yes or no)
- Action taken with regard to IMP(s)/study treatment(s)
- Administration of treatment for the AE
- Outcome

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

- Date AE met criteria for SAE
- Date investigator became aware of SAE
- AE description
- Seriousness criteria
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

The grading scales found in the revised NCI CTCAE v5.0 will be utilised for all events. This version will be used for the duration of the study. 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 NCI CTCAE can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

AEs and SAEs will be collected from the time of signature of the ICF and throughout the treatment period until the follow-up period is completed (90 days after the last dose of durvalumab). Collection and reporting of AEs and SAEs after the final DCO is described in Section 8.3.11.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a treated participant, the investigator shall, without undue delay, report the SAE to AstraZeneca as described in Section 8.3.12.

8.3.2 Follow-up of AEs and SAEs

Any AEs that are unresolved at the participant's 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 durvalumab), but without further recording in the eCRF. AstraZeneca retains the right to request additional information for any participant with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.3 Causality Collection

The investigator should assess causal relationship between IMP/study intervention (durvalumab, cisplatin-based NAC, surgery) and each AE and 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 IMP/study intervention?'

For SAEs, causal relationship should 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 located in Appendix B.

8.3.4 Adverse Events Based on Examinations and Tests

Deterioration as compared with baseline in protocol-mandated laboratory values, vital signs, physical examinations, and ECGs should only be reported as AEs if they meet any of the following:

- Fulfil any of the SAE criteria
- Are the reason for discontinuation of the IMP/study treatment
- Are clinically relevant as judged by the investigator (which may include but is not limited to consideration as to whether intervention or non-planned visits were required or other action was taken with the IMP/study treatment, eg, dose adjustment or drug interruption)

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 should use the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

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 DUS.

The results from the protocol-mandated laboratory tests and vital signs will be summarised in the CSR.

8.3.5 AEs Based on Signs and Symptoms

All AEs spontaneously reported by the participant or care provider or 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 eCRF. 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.

8.3.6 Hy's Law

Cases where a participant shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq 3 \times$ ULN together with TBL $\geq 2 \times$ ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law.

8.3.7 Disease Recurrence or Progression

Disease recurrence or progression can be considered as a worsening of a participant's condition attributable to the disease for which the IMP/study treatment is being studied. It may be an increase in the severity of the DUS 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 PD, should not be reported as AEs during the study.

8.3.8 New Cancers

The development of a new cancer should be regarded as an AE and will generally meet at least one of the serious criteria (eg, important medical event). New primary cancers are those that are not the primary reason for the administration of study treatment and are identified after the participant's inclusion in this study. They do not include metastases of the original cancer.

8.3.9 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 study treatment, must be reported as follows:

- Death clearly resulting from PD 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 PD under study, the AE causing the death must be reported 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, if appropriate, and should assign the main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE and documented in the Statement of Death page in the eCRF, but every effort should be made to determine a cause of death. 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 follow-up period after the administration of the last dose of study treatment should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined follow-up period and the event is considered to be due to a late-onset toxicity to study treatment, then it should also be reported as an SAE.

8.3.10 Adverse Events of Special Interest

AESIs are events of scientific and medical interest specific to the further understanding of durvalumab safety profile and require close monitoring. An AESI can be serious or non-serious. All AESIs will be recorded in the eCRF. Serious AESIs will be recorded and

reported as per Section 8.3.12. AESIs are detailed in the IB, Section 5.5.

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. An imAE is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology.

If the investigator has any questions in regards to an event being an imAE, the investigator should promptly contact the study clinical lead.

AESIs/imAEs observed with anti-PD-L/PD-1 agents such as durvalumab include pneumonitis, hepatitis, diarrhoea/colitis, intestinal perforation, endocrinopathies (hypo- and hyperthyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and type 1 diabetes mellitus), nephritis, rash/dermatitis, myocarditis, myositis/polymyositis, pancreatitis, and rare/less frequent events (including, but not limited to haematological events, neuromuscular toxicities [such as myasthenia gravis and Guillain-Barré syndrome], non-infectious encephalitis, non-infectious meningitis, pericarditis, rheumatological events, sarcoidosis, skin events, uveitis [and other events involving the eye] and vasculitis).

In addition, IRRs and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

More detailed guidelines for their evaluation and treatment are described in detail in the Dose Modification and Toxicity Management Guidelines (see the Annex document to this CSP). These guidelines have been prepared by the sponsor to assist the investigator in the exercise of his/her clinical judgement in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study treatment/study regimen by the reporting investigator.

8.3.11 Safety Data to be Collected Following the Final Data Cut-off of the Study

For participants continuing to receive durvalumab after the final DCO and database closure, AEs and SAEs will be collected, but only SAEs will be reported. In addition, it is recommended that participants continue the scheduled site visits and investigators monitor the participant's safety laboratory results periodically during treatment with durvalumab in order to manage AEs, consistent with the durvalumab dose modification guidelines for management of study treatment-related toxicities (see the Annex document to this CSP). All data after the final DCO and database closure will be recorded in the participant notes but, with the exception of SAEs, will not otherwise be reported for the purposes of this study.

All SAEs that occur in participants still receiving durvalumab (or within the 90 days following the last dose of durvalumab) after the final DCO must be reported as detailed in Section 8.3.12.

8.3.12 Reporting of SAEs

All SAEs must be reported whether or not considered causally related to the IMP/study treatment. All SAEs will be recorded in the eCRF during study conduct. After study completion, when the EDC is closed and an SAE needs to be reported, a paper SAE form should be used.

If any SAE occurs during of the study, investigators or other site personnel will inform the appropriate AstraZeneca representatives within 1 day ie, immediately but **no later than 24 hours** of when they become aware of it.

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

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately. Investigators or other site personnel will 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.

Once the investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the investigator or other study site staff reports the SAE via secure method to the appropriate AstraZeneca representative.

When the EDC is temporarily not accessible the AstraZeneca study representative should confirm that the investigator/site staff enters the SAE in the AstraZeneca EDC when access resumes.

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

For regulatory reporting requirements for SAEs, see Appendix A 1.

The reference document for definition of expectedness/listedness is the IB for the AstraZeneca IMP.

8.3.13 Pregnancy

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

- If the pregnancy is discovered before the study participant has received any study intervention

8.3.13.1 Maternal Exposure

If a participant becomes pregnant during the study, the IMP/study treatment including durvalumab should be discontinued immediately and the pregnancy reported to AstraZeneca. Please follow the local prescribing information for the chemotherapy agents (ddMVAC or gem/cis).

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatment may have interfered with the effectiveness of a contraceptive medication. All pregnancies should be collected and provided to the AstraZeneca DES via PREGREP module in the eCRF. If an AE/SAE is associated with the pregnancy, AE/SAE eCRF modules should also be completed and sent to AstraZeneca DES. Congenital anomalies/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 anomaly/birth defect) should be followed up and documented even if the participant was discontinued from the study. The paper based PREGOUT form should be used to report the outcome of the pregnancy.

If any pregnancy occurs during the study, the investigator or other site personnel should inform the appropriate AstraZeneca representatives immediately but no later than 24 hours they become 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 one or 5 calendar days** for SAEs (see Section 8.3.12) and **within 30 days** for all other pregnancies.

8.3.13.2 Paternal Exposure

Male participants should refrain from fathering a child or donating sperm from the time of screening throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer. Please follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for the chemotherapy agents (ddMVAC or gem/cis).

Pregnancy of the participant'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 anomaly) occurring from the date of the first dose of study treatment until 90 days after the last dose of durvalumab monotherapy should, if possible, be followed up and documented in the Pregnancy Report Form. Consent from the pregnant partner must be obtained before the Pregnancy Report Form is completed.

8.3.14 Medication Error, Drug Abuse, and Drug Misuse

8.3.14.1 Timelines

Medication error, drug abuse, and drug misuse alone are not AEs/SAEs. All medication errors/drug abuse/drug misuse are to be collected for IMPs and AstraZeneca AxMPs and provided to AstraZeneca DES via the respective Medication Error eCRF module or Drug Abuse/Drug Misuse paper CRF forms. If an AE/SAE is associated with the medication error/drug abuse/drug misuse, the AE/SAE eCRF modules should also be completed and sent to AstraZeneca DES.

If an event of medication error, drug abuse, **or** drug misuse occurs during the study, then the investigator or other site personnel informs the appropriate AstraZeneca representatives within **one calendar day**, ie, immediately but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to AstraZeneca DES within **one** (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 event of medication error, drug abuse, or misuse (see Section 8.3.12) and **within 30 days** for all other events.

8.3.14.2 ddMVAC or Gem/Cis

For participants receiving neoadjuvant ddMVAC or gem/cis, refer to the local prescribing information for treatment of cases of medication error/drug abuse/drug misuse.

8.3.14.3 Medication Error

For the purposes of this clinical study a medication error is an **unintended** failure or mistake in the treatment process for an IMP/study treatment or AstraZeneca AxMP that either causes harm to the participant or has the potential to cause harm to the participant.

The full definition and examples of a medication error can be found in Appendix B 4.

8.3.14.4 Drug Abuse

Drug abuse is the persistent or sporadic **intentional**, non-therapeutic excessive use of IMP/study treatment or AstraZeneca AxMP for a perceived reward or desired non-therapeutic effect.

The full definition and examples of drug abuse can be found in Appendix B 4.

8.3.14.5 Drug Misuse

Drug misuse is the **intentional** and inappropriate use (by a study participant) of IMP/study treatment or AstraZeneca AxMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs/study treatment(s) or AstraZeneca AxMPs, outside the intended use as specified in the protocol and includes deliberate administration of the product

by the wrong route.

The full definition and examples of drug misuse can be found in Appendix B 4.

8.3.15 Reporting of Overdose

Refer to Section 6.8 for definition and treatment of overdose.

Overdose alone is not an AE/SAE. All overdoses are collected for IMPs and AstraZeneca AxMPs and provided to AstraZeneca DES via the Overdose eCRF module.

An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an IMP/study treatment or AstraZeneca AxMP occurs in the course of the study, the investigator or other site personnel inform appropriate AstraZeneca representatives immediately, but **no later than 24 hours** of when they become aware of it.

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to AstraZeneca DES **within one** (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 overdose (see Section 8.3.12) and **within 30 days** for all other overdoses.

For participants receiving SoC cisplatin-based NAC (ddMVAC or gem/cis) 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.

8.3.16 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 (see Section 6.6).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.
- Dose delays (interruptions) are permitted for immune-oncology therapy; however, dose reduction is not permitted.
- Participants should be thoroughly evaluated to rule out any alternative aetiology (eg, disease progression/recurrence, concomitant medications, or infections). This includes ddMVAC- or gem/cis-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 aetiology, all events should be potentially immune-

related and the TMGs should be followed (see Section 8.3.16.1).

- In the event that the AE has clear immune-related aetiology, ddMVAC or gem/cis chemotherapy may still be administered as scheduled while durvalumab administration is delayed per TMGs (see Section 8.3.16.1).
- In the event that ddMVAC or gem/cis chemotherapy is discontinued due to treatment--related toxicity, participants should proceed to RC when clinically feasible, and the remaining durvalumab monotherapy neoadjuvant doses should be skipped. Adjuvant therapy with durvalumab may continue following RC. Note: If the investigator feels that a participant 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, v5.0.

8.3.16.1 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 inhibitor durvalumab (MED4736; PD-L1 inhibitor). These guidelines are applicable when the drug is used alone or used in combination and is administered concurrently or sequentially with other anti-cancer drugs (ie, antineoplastic chemotherapy) as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, IRRs, 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 anti-cancer treatment (see Section 8.3.16.2).

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” and is maintained within the Site Master File.

Participants should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other aetiologic 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 aetiology, 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 judgement 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.

8.3.16.2 Specific Toxicity Management and Dose Modification Information – Chemotherapy (ddMVAC or Gem/Cis)

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 participants receive the planned neoadjuvant therapy as per institution standard and as clinically indicated, if conditions allow. In the event of unfavourable tolerability, participants who are unable to complete the study-specified number of neoadjuvant treatment cycles participants may receive less than the planned cycles.

8.4 Pharmacokinetics

PK parameters are not evaluated in this study.

8.5 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.6 Biomarkers

Biomarkers other than those per institutional standards are not evaluated in this study.

8.7 Immunogenicity Assessments

Immunogenicity is not evaluated in this study.

8.8 Medical Resource Utilisation and Health Economics

Health economics/medical resource utilisation parameters are not evaluated in this study.

8.9 Study Participant Feedback Questionnaire

The study participant feedback questionnaire is not applicable in this study.

9 STATISTICAL CONSIDERATIONS

The primary objective of this study is to assess the safety of neoadjuvant durvalumab with neoadjuvant ddMVAC or gem/cis in individuals with MIBC in terms of incidence of Grade 3 or 4 PRAEs prior to RC. All participants entering this study plan to undergo RC. For participants who do not undergo RC, the primary analysis of 'safety prior to RC' will include participants' data until the date of decision not to undergo RC (medically precluded or participant's refusal) or the date of planned RC, whichever occurs first. The secondary objectives of this study are to further assess safety and tolerability of perioperative durvalumab combined with ddMVAC or gem/cis followed by RC and adjuvant durvalumab in terms of incidence, severity, nature, seriousness, intervention/treatment, outcome, and causality of TRAEs, including PRAEs, AESIs, imAEs, AEs, and SAEs; AEs resulting in study treatment interruption and discontinuation; and to assess efficacy in terms of EFS, DFS, OS, pCR, and pDS.

Statistical analyses will be performed across all participants in the study and by NAC cohorts (ddMVAC and gem/cis). The analyses will be conducted by AstraZeneca or its representatives.

A comprehensive SAP will be prepared and signed by 90 days after enrolment of the first participant, and any subsequent amendments will be documented, with final amendments completed prior to reporting of the data.

The SAP will include a more technical and detailed description of the planned statistical analyses. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 Statistical Hypotheses

No hypotheses testing is planned for this study.

9.2 Sample Size Determination

The study is designed as a single-arm study with incidence of Grade 3 or 4 PRAEs prior to RC as the primary endpoint. All participants entering this study plan to undergo RC. For participants who do not undergo RC, the primary analysis of 'safety prior to RC' will include participants' data until the date of decision not to undergo RC (medically precluded or participant's refusal) or the date of planned RC, whichever occurs first. Therefore, no formal sample size calculation will be done.

The sample size estimation is based on 32% incidence of Grade 3 or 4 TRAEs reported for

durvalumab in combination with ddMVAC in the NEMIO study (Thibault et al 2023), given that durvalumab + gem/cis will be limited to approximately 30% of the total number of participants. It is expected that similar incidence rate will be observed in this NIAGARA-2 study given the similar participant population and treatment.

Under the above assumptions, the precision of point estimates of incidence rates of Grade 3 or 4 PRAEs prior to RC ranging from 20% to 40% are calculated overall (approximately 150 participants) and in the cohort of participants receiving durvalumab in combination with ddMVAC (105 [70%] or more participants), using 95% exact binomial CIs (Table 11).

Based on the precision estimates, a sample size of approximately 150 participants will provide a precision of approximately ± 7% to ± 8% with an exact binomial 95% CI for the overall participants, and approximately ± 9% to ± 10% for the durvalumab in combination with ddMVAC cohort.

With the sample size of 150 participants, the 95% CI for an observed incidence rate of 32% would be (24.6% – 40.1%) for the overall participants, assuming the 32% reported in NEMIO is observed in NIAGARA-2 study. The 95% CI for an observed incidence rate of 32% would be (23.6% – 42.2%) for the durvalumab in combination with ddMVAC cohort.

If the underlying/true incidence rate of Grade 3 or 4 PRAEs prior to RC was 32%, on repeated implementations of this study, there would be approximately 2.5% chance of observing a proportion less than 24.6% or greater than 40.1%.

Table 11 Estimated Precision Around Varying Incidence of Grade 3 or Grade 4 PRAEs, Overall and for ddMVAC Cohort

Participants overall (n=150)	Observed rate (n)	20% (30)	25% (38)	30% (45)	32% (48)	35% (53)	40% (60)
	95% CI	13.9 - 27.3	18.6 - 33.1	22.8 - 38.0	24.6 - 40.1	27.7 - 43.5	32.1 - 48.3
		(± 7.3)	(± 7.7)	(± 8.0)	(± 8.1)	(± 8.2)	(± 8.3)
Durvalumab + ddMVAC (n = ~105)	Observed rate (n)	20% (21)	26% (27)	30% (32)	32% (34)	35% (37)	40% (42)
	95% CI	12.8 - 28.9	17.7 - 35.2	21.9 - 40.2	23.6 - 42.2	26.2 - 45.2	30.6 - 50.0
		(± 8.9)	(± 9.5)	(± 9.7)	(± 9.8)	(± 9.9)	(±10.0)

95% CI based on the binomial (Clopper-Pearson) exact method.
The intervals are not symmetric: the distance (eg ± 7.3) is for guidance and is from the incidence rate to the furthest limit.
Observed number of subjects (n) are rounded up to nearest integer value.

Note: 'Screened' means a participant's, or their legally acceptable representative's, agreement to participate in a clinical study following completion of the informed consent process. Potential participants who are screened for the purpose of determining eligibility for the study, but do not meet the eligibility criteria in the study, are considered 'screen failures'.

9.3 Populations for Analyses

The populations for analysis are defined in Table 12.

Table 12 Populations for Analysis

Population/Analysis set	Description
Full Analysis Set (FAS)	The FAS consists of all participants who are enrolled in the study who have received at least 1 dose of study treatment. The FAS will be used for all efficacy endpoints excluding DFS. Note that the FAS is the same as the SAF.
RC Set	The RC Set consists of all participants who are enrolled in the study, received at least 1 dose of study treatment, and who undergo RC. This subset of the FAS will be used for DFS.
Non-RC Set	The Non-RC Set consists of all participants who are enrolled in the study, received at least 1 dose of study treatment, and who did not undergo RC, due to medical preclusion, participant's refusal, or had residual disease.
Safety Analysis Set (SAF)	The SAF consists of all enrolled participants who have received at least 1 dose of study treatment.
NAC Cohort: ddMVAC	Participants who received at least 1 dose of durvalumab + ddMVAC during neoadjuvant treatment.
NAC Cohort: gem/cis	Participants who received at least 1 dose of durvalumab + gem/cis during neoadjuvant treatment.

9.4 Statistical Analyses

9.4.1 General Considerations

All outputs will be summarised overall and by treatment cohorts (durvalumab in combination with ddMVAC; durvalumab in combination with gem/cis) using the FAS/ SAF as required.

Descriptive statistics will be used for all variables, as appropriate, and will be presented overall and by NAC cohort (durvalumab in combination with ddMVAC; durvalumab in combination with gem/cis). Continuous and count variables will be summarised by the number of observations, mean, standard deviation, median, upper and lower quartiles, minimum, and maximum. Categorical variables will be summarised by frequency counts and percentages for each category.

Unless otherwise stated, percentages will be calculated out of the population total for the

corresponding treatment cohort. Overall totals will be calculated for baseline summaries only.

Safety data will be summarised descriptively overall, by seriousness, by causality, and by maximum NCI CTCAE (v5.0) grade.

In general, for efficacy endpoints the last observed measurement prior to first dose of study intervention will be considered the baseline measurement, unless otherwise stated. However, if an evaluable assessment is only available after enrolment but before the first dose of treatment then this assessment will be used as baseline. For RECIST 1.1 tumour assessments, baseline must be no more than 28 days before the date of enrolment. If a baseline radiological tumour assessment is performed more than 28 days before enrolment, then it will be reported as a protocol deviation, but the scan will still be included as baseline.

If there is less than 40% EFS maturity at the time of the primary analysis, a final analysis may be conducted when there is approximately 40% EFS maturity or the LPI has had the opportunity to be followed up for a minimum of 12 months, whichever occurs first.

All participants entering this study plan to undergo RC. For participants who do not undergo RC, their data will be collected in the eCRF along with the reason to not undergo RC. The primary analysis of ‘safety prior to RC’ will include participants’ data until the date of RC, the date of decision not to undergo RC (medically precluded or participant’s refusal) or the date of partial cystectomy.

A subgroup analysis of efficacy endpoints EFS and OS may be performed using a subset of participants in the FAS who underwent RC (RC Set). Data from the subgroup analysis may be presented by pCR and by pDS response (Success and Failure). Further details on the analysis will be provided in the SAP.

Depending on the extent of any impact, summaries of data relating to civil crisis, natural disaster, or public health crisis may be generated. More details will be provided in the SAP.

9.4.2 Primary Endpoint

The primary endpoint is the incidence of Grade 3 or 4 PRAEs as observed prior to RC. All participants entering this study plan to undergo RC. For participants who do not undergo RC, the primary analysis of ‘safety prior to RC’ will include participants’ data until the date of decision not to undergo RC (medically precluded or participant’s refusal) or the date of planned RC, whichever occurs first.

A PRAE is defined as a possibly related AE, where the investigator answered yes to the question ‘Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?’

A PRAE will be included in the primary endpoint if it has a start date prior to RC for participants that undergo RC, date of decision to not have RC for participants that refuse or

are medically precluded, or the date of planned RC, whichever occurs first, and it has a CTCAE Grade of 3 or 4 recorded within this timeframe. A PRAE of Grade 2 or 1 that starts prior to RC and increases in severity to Grade 3 outside the neoadjuvant period would not be included in the primary endpoint but would be included in the safety summary tables and listings under its maximum severity.

All safety analyses will be performed on the SAF, which will consist of all participants who take at least 1 dose of study treatment. In addition, safety analyses will be performed on ddMVAC and gem/cis cohort.

The primary analysis will be conducted when the LPI has had the opportunity to complete neoadjuvant durvalumab in combination with cisplatin-based chemotherapy (ddMVAC or gem/cis). The primary endpoint (incidence of Grade 3 or 4 PRAEs in neoadjuvant treatment phase prior to RC) will be summarised by frequency counts and corresponding percentages including 95% CIs based on binomial exact method (Clopper-Pearson).

9.4.3 Secondary Endpoint(s)

9.4.3.1 Safety and Tolerability

Safety and tolerability will be assessed in terms of AEs (including SAEs), deaths, laboratory data, vital signs, ECGs, and exposure. Data from all cycles of treatment will be combined in the presentation of safety data. 'On treatment' will be defined as assessments between date of start dose and 90 days following discontinuation of study intervention. For AEs, on-treatment (or treatment-emergent AEs) will be defined as any AEs that started after dosing or prior to dosing and which worsens following exposure to the treatment.

Adverse Events

AEs observed up until 90 days following discontinuation of the last dose of study treatment or until the initiation of the first subsequent therapy following discontinuation of treatment (whichever occurs first) will be used for the reporting of the AE summary tables.

Any events in this period that occur after a participant has received further therapy for cancer (following discontinuation of study intervention) will be flagged in the data listings. A separate data listing of AEs occurring more than 90 days after discontinuation of study intervention will be produced. These events will not be included in AE summaries.

Supporting AE summaries for any AE occurring from radical cystectomy to 90 days post-radical cystectomy, including Clavien-Dindo assessment, will also be provided. Further details will be provided in SAP.

Safety data will be summarised descriptively by MedDRA by system organ class and preferred term, by seriousness, by causality, and by maximum NCI CTCAE (v5.0) grade.

Safety Assessments

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

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

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

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

$$\text{Corrected calcium (mmol/L)} = \text{Total calcium (mmol/L)} + ([40 - \text{Albumin (G/L)}] \times 0.02)$$

The denominator used in laboratory summaries will only include evaluable participants, 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 participants 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 participant need only have 1 post-dose value recorded.

The denominator in vital signs data should include only those participants with recorded data.

Exposure

Exposure to study intervention, time on study, and dose delays will be summarised.

Further details of presentation of exposure to study intervention will be detailed in the SAP.

9.4.3.2 Event-free Survival

EFS is defined as the time from first neoadjuvant durvalumab + chemotherapy treatment until the earliest occurrence of any of the following events:

- First recurrence of disease after RC
- First documented progression in participants who were medically precluded from RC
- Time of expected surgery in participants who refuse to undergo RC or failure to undergo RC in participants with residual disease
- Death due to any cause

Progression and recurrence will be by RECIST 1.1 as assessed by the investigator.

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.

Participants who have not presented any of the above events (recurrence, progression, death) at the time of analysis will be censored at the time of the latest date of follow-up. If the participant has no evaluable visits or does not have baseline data, they will be censored at Day 1, unless they die within 2 visits of baseline, then they will be treated as an event with date of death as the event date.

The analysis will be performed in the FAS and by NAC cohorts (ddMVAC cohort and gem/cis cohort).

Analysis Methods

Summaries of the number and percentage of participants experiencing an EFS event and the type of event will be provided.

The EFS rates at 12-month landmark will be assessed using the Kaplan-Meier method together with associated 95% CIs. Also, 25th percentile rate may be reported with associated 95% CIs. CIs will be based on the Brookmeyer-Crowley method. In addition, the Kaplan-Meier curves of EFS will be presented graphically.

9.4.3.3 Disease-free Survival

DFS is defined as the time from the date of RC to the earliest of the first recurrence of disease post RC or death due to any cause.

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

The analysis will be performed in a subset of participants in the FAS who undergo RC and by NAC cohorts (ddMVAC cohort and gem/cis cohort).

Analysis Methods

Summaries of the number and percentage of participants experiencing a DFS event, and the type of event will be provided.

The DFS rates at landmark timepoints (ie, 18 and 24 months) will be assessed using the Kaplan-Meier method together with associated 95% CIs. Also, 25th percentile rate may be reported with associated 95% CIs. CIs will be based on the Brookmeyer-Crowley method. In addition, the Kaplan-Meier curves of DFS will be presented graphically.

9.4.3.4 Overall Survival

Overall survival is defined as the time from the date of first neoadjuvant durvalumab in combination with chemotherapy treatment until death due to any cause. All deaths will be included, regardless of whether the participant withdraws from therapy or receives another anti-cancer therapy.

Any participant not known to have died at the time of analysis will be censored based on the last recorded date on which the participant was known to be alive. Note: Survival calls will be made following the date of DCO for the analysis (these contacts should generally occur within 7 days of the DCO). If participants are confirmed to be alive or if the death date is after the DCO date, then these participants will be censored at the date of DCO. Death dates may be found by checking publicly available death registries.

The analysis will include all participants in the FAS and by NAC cohorts (ddMVAC cohort and gem/cis cohort).

Analysis Methods

The OS rates at 12-month landmark timepoints will be assessed using the Kaplan-Meier method together with associated 95% CIs. Also, 25th percentile rate may be reported with associated 95% CIs. CIs will be based on the Brookmeyer-Crowley method. In addition, the Kaplan-Meier curves of OS will be presented graphically.

9.4.3.5 Pathologic Response Assessment

pCR rate is defined as the proportion of participants whose pathological staging was T0N0M0 as assessed using specimens obtained via RC following the neoadjuvant treatment. pDS rate is defined as the proportion of participants whose pathologic staging is <P2.

pCR and pDS will be assessed per local pathology review.

Analysis Methods

The proportion of participants who achieved pCR and pDS among participants in the FAS and in NAC cohorts (ddMVAC cohort and gem/cis cohort) will be calculated along with exact 95% CIs for the proportions, using the Clopper-Pearson method. Participants who do not undergo RC due to medical preclusion or participant refusal will be included as failures (did not achieve T0N0M0).

9.4.3.6 Subgroup Analyses

A subgroup analysis of EFS and OS may be performed using the same methodology as described for each endpoint in Sections 9.4.3.2 and 9.4.3.4, respectively. The subgroup analysis will be performed using a subset of participants in the FAS who underwent RC (RC Set). The data from the analysis may be presented by pCR and pDS response (ie, success [pathological staging of T0N0M0] and failure).

9.4.4 Exploratory Endpoint(s)

Non-RC Cohort

All participants entering this study plan to undergo RC. However, data from any participant(s) who do not undergo RC (Non-RC Cohort) will be collected in the eCRF along with the reason for not undergoing RC.

The data collected from the Non-RC Cohort will be analysed in descriptive manner to understand patient characteristics and clinical outcomes in this cohort.

30-Minute Infusion

Incidence, severity, and discontinuation of durvalumab due to IRRs and hypersensitivity/ anaphylactic reactions will be summarised for participants who have received durvalumab as a 60-minute infusion and 30-minute infusion.

9.5 Interim Analyses

No formal interim analysis is planned for this study. Planned periodic safety data reviews will be conducted to monitor safety and tolerability, as follows:

- An early safety data review will be triggered when approximately 10 participants have received at least 2 cycles of durvalumab + ddMVAC.
- A further data review will be done after approximately 60 participants who received neoadjuvant durvalumab + ddMVAC or durvalumab + gem/cis have been followed up until RC.

At each planned safety data review, all safety data in the clinical database will be summarised.

Details of the planned reviews will be provided in the SAP and in the ESC charter.

9.6 Executive Steering Committee

An ESC that includes independent experts will be established to provide guidance on-study conduct, periodic data review, and final results interpretation. In addition to ongoing overall safety monitoring by AstraZeneca and/or the CRO, the ESC will also periodically assess study data according to an agreed schedule (as well as on an ad hoc basis, based on the results of the ongoing medical review), ensuring that study participants are not exposed to undue risk.

Further details of the ESC remit, procedures, processes, and meeting frequency will be outlined in an ESC Charter.

For details on the ESC, refer to Appendix A 6.

10 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 as amended at 64th WMA General Assembly, Fortaleza, Brazil, October 2013 and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
  - Applicable ICH GCP Guidelines.
  - Applicable laws and regulations.
- The protocol, revised protocol, 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 revised protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- AstraZeneca will be responsible for obtaining the required authorisations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR) 312.120, ICH guidelines, the IRB/IEC, European Regulation 536/2014 for clinical studies (if applicable), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to AstraZeneca of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- AstraZeneca has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. AstraZeneca will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- In the EU, the sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to IMP will be reported to the EudraVigilance database within the required regulatory timelines.
- For all studies except those utilising medical devices investigator safety reports must be prepared for SUSAR according to local regulatory requirements and sponsor policy and

forwarded to investigators as necessary.

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

Regulatory Reporting Requirements for Serious Breaches of Protocol or GCP

A 'serious breach' means any deviation of the approved version of the protocol or GCP that is likely to affect the safety, rights of trial participants, and/or data reliability and robustness to a significant degree in a clinical trial.

All parties (sponsor, service provider, investigator site staff) involved in the conduct of the clinical trial:

- Are responsible for promptly identifying and documenting any actual or potential serious breach.
- Should have a process in place to ensure that they are able to identify the occurrence of a (actual/potential) serious breach.
- Should report to AstraZeneca (or delegated party) without delay, through the contacts (email address or telephone number) provided by AstraZeneca.

A 2 Financial Disclosure

Investigators and sub-investigators will provide AstraZeneca with sufficient, accurate financial information as requested to allow AstraZeneca 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 study and for 1 year after completion of the study.

A 3 Informed Consent Process

- The investigator or the investigator's representative will explain the nature of the study including the risks and benefits to the participant or their legally authorised representative and answer all questions regarding the study.
- Potential participants must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Participants or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy and data protection Act requirements, where applicable, and the IRB/IEC or study centre.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.
- If new information requires changes to the ICF, consider if participants must be

reconsented and if so, this must be 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 participant or the participant's legally authorised representative.

The ICF will contain a separate section that addresses and documents the collection and use of any mandatory and/or optional human biological sample. The investigator or authorised designee will explain to each participant the objectives of the analysis to be done on the samples and any potential future use. Participants will be told that they are free to refuse to participate in any optional samples or the future use, and may withdraw their consent at any time and for any reason during the retention period.

A 4 Recruitment Strategy

Participants are expected to be recruited through clinical chart review, existing patient lists, referrals, advertisement, etc. Details of recruitment strategy and tools will be provided in a separate document.

A 5 Data Protection

- Participants will be assigned a unique identifier by a trusted third party contracted by the sponsor or by a principal investigator. Any participant records or datasets that are transferred to AstraZeneca will contain the identifier only; participant names or any information, which would make the participant identifiable, will not be transferred.
- The participant must be informed that their personal study-related and coded (pseudonymised) data will be used by AstraZeneca in accordance with local data protection law. The purposes of use and the level of disclosure and use of their data (including the legal basis AstraZeneca relies upon processing their data, where required) must also be explained to the participant in the informed consent.
- The participants must be informed that their medical records may be examined by Quality Assurance auditors or other authorised personnel appointed by AstraZeneca, who are independent of the staff involved in the study in accordance with current Quality Assurance Standard Operating Procedures and Quality Assurance Audit Schedule; by appropriate IRB/IEC members; and by inspectors from regulatory authorities.
- The participant must be informed that data will be collected and used to develop the drug/investigational product, get permission to introduce and keep it on the market, monitor its safety and get it reimbursed eg, by governments eg, throughout the drug development programme, which includes related research activities necessary for this drug development programme, including to understand how the study drug(s) and similar drugs work in the body (eg, evaluate the study drug mode of action, alone or in combination with other study drugs); better understand the studied disease and associated

health problems; develop diagnostic tests for the disease; learn from past studies to plan new studies or improve scientific analysis methods; publish research results in scientific journals or use them for educational purposes. AstraZeneca will only collect and use the minimum amount of personal data to support the research and safety monitoring activities within the drug development programme and will not make personal data available to anyone (including internal staff) who is not authorised or does not have a business need to know the information.

- The participant must be informed that in some cases their data may be further pseudonymised and/or anonymised.
- Appropriate safeguards will be implemented to protect coded data during and after the study that include:
  - Access to the coded data will be restricted and monitored and limited to specific individuals subject to confidentiality obligations (including the obligation to not attempt to re-identify individuals/decode the clinical data).
  - The coded data will be protected with security measures to avoid data alteration, loss, and unauthorised accesses and further de-identification techniques may be applied; as well as other high-standard technical security means such as encryption.
  - A data protection impact assessment, where required, will apply to identify and mitigate privacy risks, if any, associated with each scientific research.
  - The coded data will not be shared for direct marketing purposes or other purposes that are not legal duties or are not related to scientific research purposes of the study. In particular, it will not be used to make decisions about future services available to the participant, such as insurance.
- Participants are also protected legally by the following means, if the coded data will be shared with third parties – other companies within the sponsor group; service providers; research partners, who may be located in countries which do not offer the same level of protection as the participants country for which the participant will be informed in the ICF:
  - Within the sponsor group, the participants' coded data are protected by binding corporate rules. More information about the sponsor's binding corporate rules are provided here: www.astrazenecabindingcorporaterules.com, or by other contractual arrangements as may be required under local law.
  - In all other cases, the participants' coded data are protected by contractual arrangements, codes of conduct, or certifications that set the rules for personal data protection to those available in the participant's country or other alternatives set forth in the law, as well as any supplementary technical and organizational measures that may result out of conducted transfer impact assessments, where required.

Personal Data Breaches

A 'personal data breach' means a breach of security leading to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access to, personal data transmitted, stored or otherwise processed.

- In compliance with applicable laws, the data controller[1] for the processing activity where the personal data breach occurred (AstraZeneca or respectively the site), will notify the data protection authorities without undue delay within the legal terms provided for such notification and within the prescribed form and content.
- Whilst AstraZeneca has processes in place to deal with personal data breaches, it is important that investigators that work with AstraZeneca have controls in place to protect participant data privacy.

The investigator should have a process in place to ensure that:

- Allow site staff or service providers delegated by the investigator/institution to identify the occurrence of a (potential) personal data breach.
- Any (potential) personal data breach is promptly reported to AstraZeneca or delegated party, through the contacts (email address or telephone number) provided by AstraZeneca.

AstraZeneca and the site must demonstrate that they:

- Have taken all necessary steps to avoid personal data breaches and
- Have undertaken measures to prevent such breaches from occurring in the first place and to mitigate the impact of occurred data breaches (eg, applying encryption, maintaining and keeping systems and IT security measures up-to-date, regular reviews and testing, regular training of employees, and developed security policies and standards).
- Where possible, have developed an internal data breach reporting and investigation process and internal protocols with guidance on how to respond swiftly and diligently to the occurrence of a personal data breach.
- Where it has not been possible to develop an internal data breach reporting and investigation process, the site follows AstraZeneca's instructions.

Notification of personal data breach to participants:

- Notification to participants is done by the site for the data breaches that occurred within

---

The **data controller** determines the **purposes** for which and the **means** by which personal data is processed, as defined by the European Commission.

The processing activities for which the site is the data controller and for data breaches occurred within the processing activities of AstraZeneca as the data controller, the notification is done in collaboration with the site and is performed by the site and/or

principal investigator, acting on behalf of AstraZeneca, so that AstraZeneca has no access to the identifying personal information of the participants. The site and/or principal investigator shall conduct the notification by contacting the participants using the information that they gave for communication purposes in clinical research.

- If a personal data breach occurs in a processor's systems, engaged by AstraZeneca, the processor under contractual obligations with AstraZeneca promptly and in due course after discovering the breach notifies AstraZeneca and provides full cooperation with the investigation. In these cases, to the extent AstraZeneca is the data controller for the processing activity where the breach occurred, it will be responsible for the notification to data protection authorities and, if applicable, to participants. If the personal data breach needs to be notified to the participants, the notification to participants is done in collaboration with the site and is performed by the site and/or principal investigator, acting on behalf of the sponsor, so that AstraZeneca has no access to the identifying personal information of the participants.
- If a personal data breach involving an AstraZeneca representative's device (ie, study monitor laptop) occurs, the AstraZeneca representative will provide AstraZeneca with all of the information needed for notification of the breach, without disclosing data that allows AstraZeneca directly or indirectly to identify the participants. The notification will be done by AstraZeneca solely with the information provided by the study monitor and in no event with access to information that could entail a risk of re-identification of the participants. If the data breach must be notified to the data subjects, the notification will be done directly by the study monitor in collaboration with the site and/or principal investigator, acting on behalf of the sponsor, so that AstraZeneca has no access to the identifying personal information of the participants. The contract between AstraZeneca and the study monitor shall expressly specify these conditions.
- The contract between the site and AstraZeneca for performing the clinical research includes the provisions and rules regarding who is responsible for coordinating and directing the actions in relation to the breach(es) and performing the mandatory notifications to authorities and participants, where applicable.

A 6 Committees Structure

A Trial Steering Committee that includes principal investigators for this study and that may include principal investigators from the other pivotal studies will provide:

- Advice on any aspect of the study design or conduct based on requests from AstraZeneca.
- Review relevant research (completed, ongoing, and pending) which may impact upon the study, assure consistency across the entire durvalumab pivotal programme, and to support the study team with interpretation of study outcomes.

A Steering Committee Charter will define the primary responsibilities of the steering committee, its members, and the purpose and timing of meetings.

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 CSP and letters to investigators.

A 7 Dissemination of Clinical Study Data

Study overall results, both technical and written in lay language (Trial Results Summary, also known as Lay Language Summary of overall study results), will be submitted to EU CTIS within a year from global End of Trial Date in all participating countries to ensure scientific integrity, completeness, robustness, and reliability of data published results.

A description of this clinical study will be available on http://www.clinicaltrials.gov as will the summary of the main study results when they are available. The clinical study 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 8 Data Quality Assurance

- All participant data relating to the study will be recorded on eCRF unless transmitted to AstraZeneca or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined in the Risk-Based Quality Plan (or equivalent) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the CSR.
- Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are included in the Monitoring Plan.
- AstraZeneca or designee is responsible for medical oversight throughout the conduct of the study which includes clinical reviews of study data in accordance with the currently approved protocol. Monitoring details describing clinical reviews of study data from a medical perspective are included in more detail in the Medical Oversight Plan.
- AstraZeneca or designee is responsible for the data management of this study including quality checking of the data.
- AstraZeneca assumes accountability for actions delegated to other individuals (eg, CROs).

- Study monitors will perform source data verification for sample of sites, participants, and data, which will be selected in a risk-based fashion as per the Monitoring Plan(s) to confirm that data entered into the eCRF by authorised site personnel are verifiable from source documents.
- Study monitors will perform ongoing source data review as per the Monitoring Plan(s) to confirm that data in source are accurate and complete; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including 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 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 9 Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data and its origin can be found in source data acknowledgement or monitoring guidelines. 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 10 Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants (first site activated).

Start of recruitment is the first participant consented.

Study/Site Termination

AstraZeneca designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of AstraZeneca. 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 AstraZeneca or the investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, AstraZeneca's procedures, or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected

If the study is prematurely terminated or suspended, AstraZeneca shall promptly inform the investigators, the IRBs/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Participants from terminated sites will have the opportunity to be transferred to another site to continue the study.

A 11 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 AstraZeneca before submission. This allows AstraZeneca to protect proprietary information and to provide comments.
- AstraZeneca will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, AstraZeneca will generally support publication of multicentre 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 AEs: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

B 1 Definition of AEs

An AE is the development of any untoward medical occurrence (other than progression of the malignancy under evaluation) in a participant or clinical study participant 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 it is 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 SAEs

An 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-participant hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event that may jeopardise the participant or may require medical treatment to prevent one of the outcomes listed above

Adverse events of **malignant tumours** reported during a study should generally be assessed as **SAEs**. If no other seriousness criteria apply, the ‘Important Medical Event’ criterion should be used. In certain situations, however, medical judgement on an individual event basis should be applied to clarify that the malignant tumour event should be assessed and reported as a **non-SAE**. For example, if the tumour is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumour, the AE may not fulfil the attributes for being assessed as serious, although reporting of the progression of the malignant tumour as an AE is valid and should occur. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as non-serious; examples in adults include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour event in question is a new malignant tumour (ie, it is not the tumour for which entry into the study is a criterion and that

is being treated by the study treatment and is not the development of new or progression of existing metastasis to the tumour under study). Malignant tumours that – as part of normal, if rare, progression – undergo transformation (eg, Richter's transformation of B-cell chronic lymphocytic leukaemia into diffuse large B-cell lymphoma) should not be considered a new malignant tumour.

Life-threatening

'Life-threatening' means that the participant was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the medicinal product would result in the participant'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).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a SAE, 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 participant was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

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 jeopardise the participant 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.

Important medical events:

- 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 anaemia requiring blood transfusion, etc) or convulsions that do not result in hospitalisation.
- Development of drug dependency or drug abuse.

Intensity Rating Scale

The grading scales found in the revised NCI CTCAE version 5 will be utilised for all events.

This version will be used for the duration of the study. 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 NCI 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 an 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 an SAE when it satisfies the criteria shown in Appendix B 2.

B 3 A Guide to Interpreting the Causality Question

When assessing causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the medicinal product:

- Time course. Exposure to suspect drug. Has the participant 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 aetiology 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 recognised 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 judgement. With no available facts or arguments to suggest a causal relationship, the event(s) will be assessed as 'not related'.

Causal relationship in cases where the DUS has deteriorated due to lack of effect should be classified as no reasonable possibility.

B 4 Medication Error, Drug Abuse, and Drug Misuse

Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an IMP or AstraZeneca AxMP 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 recognised 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, eg, wrong route, dose (error greater than ± 10%), 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 refrigerator when it should be at room temperature
- Wrong participant received the medication (excluding IRT/RTSM errors)
- Wrong drug administered to participant (excluding IRT/RTSM errors)

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Errors related to or resulting from IRT/RTSM - 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.

Drug Abuse

For the purpose of this study, drug abuse is defined as the persistent or sporadic intentional, non-therapeutic excessive use of IMP/study treatment or AstraZeneca AxMP for a perceived reward or desired non-therapeutic effect.

Any events of drug abuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Abuse Report Form. This form should be used both if the drug abuse happened in a study participant or if the drug abuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug abuse include but are not limited to:

- The drug is used with the intent of getting a perceived reward (by the study participant or a person not enrolled in the study)
- The drug in the form of a tablet is crushed and injected or snorted with the intent of getting high.

Drug Misuse

Drug misuse is the intentional and inappropriate use (by a study participant) of IMP/study treatment or AstraZeneca AxMP for medicinal purposes outside of the authorised product information, or for unauthorised IMPs/study treatments or AstraZeneca AxMPs, outside the intended use as specified in the protocol, and includes deliberate administration of the product by the wrong route.

Events of drug misuse, with or without associated AEs, are to be captured and forwarded to the DES using the Drug Misuse Report Form. This form should be used both if the drug misuse happened in a study participant or if the drug misuse regards a person not enrolled in the study (such as a relative of the study participant).

Examples of drug misuse include but are not limited to:

- The drug is used with the intention to cause an effect in another person
- The drug is sold to other people for recreational purposes
- The drug is used to facilitate assault in another person
- The drug is deliberately administered by the wrong route
- The drug is split in half because it is easier to swallow, when it is stated in the protocol that it must be swallowed whole
- Only half the dose is taken because the study participant feels that they were feeling better when not taking the whole dose
- Someone who is not enrolled in the study intentionally takes the drug

Appendix C Handling of Human Biological Samples

C 1 Chain of Custody

A full chain of custody is maintained for all samples throughout their lifecycle.

The investigator at each centre keeps full traceability of collected human biological samples from the participants while in storage at the centre until shipment or disposal (where appropriate) and records relevant processing and tracking information related to the samples whilst at the site.

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 record of receipt of arrival and onward shipment or disposal.

AstraZeneca or delegated representatives will keep oversight of the entire life cycle through 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 or other sample archive facilities and will be tracked by the appropriate AstraZeneca Team for the remainder of the sample life cycle.

All appropriately consented samples will be retained for up to a maximum 15 years from last subject last visit.

Samples collected from participants in China will be destroyed or repatriated within 1 year of CSR.

If required, AstraZeneca will ensure that remaining human biological tissue 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

If a participant withdraws consent specifically to the subsequent use of donated human biological samples, applicable samples will be disposed of/destroyed/repatriated, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research. The participant will be presented with the option to opt out of the subsequent use of the donated samples during the withdrawal process. If the participant decides to opt out, then the donated samples will be disposed of. If the participant withdraws consent without opting out for the subsequent use of the donated samples, then the samples will be used per protocol.

Following withdrawal of consent for biological samples, further study participation should be

considered in relation to the withdrawal processes outlined in the ICF.

The investigator:

- Ensures the participant's withdrawal of informed consent to the use of donated samples is highlighted immediately to AstraZeneca or delegate.
- Ensures that relevant human biological samples from that participant, if stored at the study site, are immediately identified, disposed of as appropriate, and the action documented.
- Ensures that the participant and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organisation(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of or repatriated as appropriate, and the action is documented and study site notified.

C 3 International Air Transport Association Guidance Document (62nd Edition)

Labelling and Shipment of Biohazard Samples

The IATA (https://www.iata.org/whatwedo/cargo/dgr/Pages/download.aspx) classifies infectious substances into 3 categories: Category A, Category B, or Exempt:

- **Category A Infectious Substances** are infectious substances in a form that, when exposure occurs, is capable of causing permanent disability, life-threatening, or fatal disease in otherwise healthy humans or animals. **Category A Pathogens** (eg, Ebola, Lassa fever virus) are infectious substances meeting these criteria which cause disease in humans or both in humans and animals, and must be assigned to UN 2814. Infectious substances which cause disease only in animals must be assigned to UN 2900.
- **Category B Infectious Substances** are infectious substances that do not meet the criteria for inclusion in Category A. Category B pathogens (eg, Hepatitis A, C, D, and E viruses) are:
  - Assigned the following UN number and correct shipping name: UN 3373 – Biological Substance, Category B
  - To be packed in accordance with UN 3373 and IATA 650.
- **Exempt Substances** are substances which do not contain infectious substances, or substances which are unlikely to cause disease in humans or animals. These are not subject to these regulations unless they meet the criteria for inclusion in another class.

Clinical study samples will fall into Category B or Exempt under IATA regulations.

Clinical study samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging (https://www.iata.org/whatwedo/cargo/dgr/Documents/DGR-60-EN-PI650.pdf).

Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

D 1 Introduction

This appendix describes the process to be followed in order to identify and appropriately report potential Hy's Law cases and Hy's Law cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the study, the investigator should remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a participant meets potential Hy's Law criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of potential Hy's Law and Hy's Law events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; eg, potential Hy's Law criteria could be met by an elevated ALT from a central laboratory **and/or** elevated TBL from a local laboratory.

The investigator will also review AE data (eg, for AEs that may indicate elevations in liver biochemistry) for possible potential Hy's Law events.

The investigator should participate, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting potential Hy's Law criteria to agree whether Hy's Law criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than drug-induced liver injury caused by the IMP/study treatment.

The investigator is responsible for recording data pertaining to potential Hy's Law/Hy's Law cases and for reporting SAEs and AEs according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study treatment irrespective of an increase in ALP.

Hy's Law

AST or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP/study treatment, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For potential Hy's Law and Hy's Law the elevation in transaminases must precede or be

coincident with (ie, on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

D 3 Identification of Potential Hy's Law Cases

In order to identify cases of potential Hy's Law it is important to perform a comprehensive review of laboratory data for any participant who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN.
- AST ≥ 3 × ULN.
- TBL ≥ 2 × ULN.

Local Laboratories Being Used

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 participant meets potential Hy's Law criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory eCRF.

D 4 Follow-up

D 4.1 Potential Hy's Law Criteria Not Met

If the participant does not meet potential Hy's Law criteria, the investigator will:

- Inform the AstraZeneca representative that the participant has not met potential Hy's Law criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the protocol.

D 4.2 Potential Hy's Law Criteria Met

If the participant does meet potential Hy's Law criteria the investigator will:

- Determine whether potential Hy's Law criteria were met at any study visit prior to starting study treatment.
- Notify the AstraZeneca representative who will then inform the central Study Team.

  Within one day of potential Hy's Law criteria being met, the investigator will report the case as an SAE of potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For participants who met potential Hy's Law criteria prior to starting IMP/study treatment, the investigator is not required to submit a potential Hy's Law SAE unless there is a significant change[2] in the in the participant's condition.
- The Clinical Lead will contact the investigator, to provide guidance, discuss and agree an approach for the study participants' follow-up (including any further laboratory testing) and the continuous review of data.
- Subsequent to this contact, the investigator will:
  - Monitor the participant until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Complete follow-up SAE Form as required.
  - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the study Clinical Lead.
  - Complete the 3 Liver eCRF Modules as information becomes available.

D 5 Review and Assessment of Potential Hy's Law Cases

The instructions in this appendix should be followed for all cases where potential Hy's Law criteria are met.

As soon as possible after the biochemistry abnormality is initially detected, the study clinical lead will contact the investigator in order to review available data and agree on whether there is an alternative explanation for meeting potential Hy's Law criteria other than drug-induced liver injury caused by the IMP/study treatment, to ensure timely analysis and reporting to health authorities within 15 calendar days from date potential Hy's Law criteria was met. 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.

Where 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 an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate eCRF.

[2] **A 'significant' change** in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST, or TBL) 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 clinical lead if there is any uncertainty.

- If the alternative explanation is an AE/SAE: update the previously submitted potential Hy's Law SAE and AE eCRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AstraZeneca 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/study treatment:

- Send updated 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 Hy's Law case, a causality assessment of 'related' should be assigned.

If there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether the case meets the criteria for Hy's Law, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP/study treatment and seriousness criteria is medically important, according to protocol process for SAE reporting.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether Hy's Law criteria are still met. Update the previously submitted potential Hy's Law SAE report following protocol process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 References

Aithal et al 2011
Aithal GP, Watkins PB, Andrade RJ, Larrey D, Molokhia M, Takikawa H, et al. Case definition and phenotype standardization in drug-induced liver injury. Clin Pharmacol Ther 2011;89(6):806-15.

FDA Guidance 2009
Food and Drug Administration. Guidance for industry: Drug-induced liver injury: premarketing clinical evaluation. July 2009. Available from: URL: https://www.fda.gov/downloads/guidances/UCM174090.pdf. Accessed 17 December 2020.

Appendix E Guidelines for Evaluation of Objective Tumour Response Using RECIST 1.1 Criteria (Response Evaluation Criteria in Solid Tumours)

E 1 Introduction

This appendix details the implementation of RECIST 1.1 guidelines (Eisenhauer et al 2009). Investigator assessments will use the RECIST 1.1 guidelines described in this appendix.

E 2 Imaging Modalities and Acquisition Specifications for RECIST 1.1

A summary of the imaging modalities that can be used for tumour assessment of TLs, NTLs and NLs is provided in Table 13.

Table 13 Summary of Imaging Modalities for Tumour Assessment

Target lesions	Non-target lesions	New lesions
CT MRI	CT MRI Plain X-ray Chest X-ray	CT MRI Plain X-ray Chest X-ray Bone scan (Scintigraphy) ^{18}F-fluoro-deoxyglucose-PET/CT

Abbreviations: CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography.

E 2.1 Computed Tomography and Magnetic Resonance Imaging

Computed tomography with IV contrast is the preferred imaging modality (although MRI with IV contrast is acceptable if CT is contraindicated) to generate reproducible anatomical images for tumour 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, tumour assessor (eg, radiologist), and method of tumour assessment (eg, RECIST 1.1) are used consistently for each participant throughout the study. The use of the same scanner for serial scans is recommended, if possible. It is important to follow the image collection/tumour assessment schedule as closely as possible (refer to the SoA), 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 participant 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 artefacts (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 tumour evaluation are anatomic coverage, contrast administration, slice thickness, and reconstruction interval.

a. Anatomic coverage: Optimal anatomic coverage for most solid tumours 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 participants. Because a lesion later identified in a body part not scanned at baseline would be considered as a NL representing PD, 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 tumour measurements but also identification of new disease.

Required anatomical regions to be imaged for assessment of tumour burden (TLs and/or NTLs) at baseline and follow-up visits vary according to the study, and these timepoints are specified in the SoA. Examples include the following:

- Intravenous 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)
- Intravenous contrast-enhanced CT or MRI of the head and neck
- Intravenous 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 participants 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 participant has compromised renal function.

4 Chest-abdomen (-pelvis) MRI with IV MRI contrast, if CT cannot be performed at any time during the study.

b. Intravenous contrast administration: Optimal visualisation and measurement of metastases in solid tumours require 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 tumour lesions are demonstrated to best effect and a consistent method is used on subsequent examinations for any given participant. Oral contrast is recommended to help visualise 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) slices with ≤ 5 mm thickness throughout the entire anatomic region of interest for optimal lesion measurements. However, a slice thickness of ≤ 3 mm is preferred. 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.

E 2.2 Chest X-ray

Chest X-ray assessment will not be used for the assessment of TLs. Chest X-ray can, however, be used to assess NTLs 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.

E 2.3 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.

E 2.4 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. New lesions 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 PD assessment at that timepoint.

E 2.5 18F-Fluoro-deoxyglucose-PET/CT

18F-fluoro-deoxyglucose-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: New lesions will be recorded where there is positive 18F-Fluoro-deoxyglucose uptake [3] not present on baseline or prior 18F-Fluoro-deoxyglucose-PET scan or in a location corresponding to a NL on a companion CT/MRI collected close in time to the 18F-fluoro-deoxyglucose-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 18F-fluoro-deoxyglucose-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

18F-fluoro-deoxyglucose-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 tumour 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 tumour 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.

E 2.6 Ultrasound

Ultrasound examination will not be used for RECIST 1.1 assessment of tumours as it is not a reproducible acquisition method (operator dependent), is subjective in interpretation, and may not provide an accurate assessment of the true tumour size. Tumours identified by ultrasound will need to be assessed by correlative CT or MRI anatomical scan.

E 2.7 Other Tumour Assessments

E 2.7.1 Clinical Examination

Clinical examination of skin/surface lesions (by visual inspection or manual palpation) will not be used for RECIST 1.1 assessments. Tumours identified by clinical examination will need to be assessed by correlative CT or MRI anatomical scans.

3 A positive 18F-fluoro-deoxyglucose-PET scan lesion should be reported only when an uptake (eg, standard uptake value) greater than twice that of the surrounding tissue or liver is observed.

E 2.7.2 Endoscopy and Laparoscopy

Endoscopy and laparoscopy will not be used for tumour assessments as they are not validated in the context of tumour assessment.

E 2.7.3 Histology and Cytology

Histology or tumour markers on tumour biopsy samples will not be used as part of the tumour response assessment as per RECIST 1.1.

Results of cytological examination for the neoplastic origin of any effusion (eg, ascites, pericardial effusion, and pleural effusion) that appears or worsens during the study will not be used as part of the tumour response assessment as per RECIST 1.1.

Furthermore, an overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if an effusion remains present radiologically.

E 3 Measurability of Tumour Lesions at Baseline

E 3.1 RECIST 1.1 Measurable Lesions at Baseline

A tumour 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 [4] diameter for lymph node lesions with intravenous 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 hepatis lymph nodes.

E 3.2 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 effusion, 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). [5]
- Previously irradiated lesions. [6] Brain metastasis.

---

[4] The short axis is defined as the longest in-plane axis perpendicular to the long axis.

[5] Lymph nodes with < 10 mm short axis diameter are considered non-pathological and should not be recorded or followed as NTLs.

[6] Localised post-radiation changes that affect lesion size 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.

E 3.3 Special Considerations Regarding Lesion Measurability at Baseline

- Bone lesions:
  - 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 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 participant, these should be selected over cystic lesions as TLs.

E 3.4 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 TLs at baseline. Target lesions 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 that 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 axis diameter for non-nodal lesions (or short axis diameter for lymph nodes). All measurements should be recorded in millimetres. 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.

E 3.4.1 Special Cases for TL Assessment at Baseline

- For TLs 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.
- Tumour lesions selected for newly acquired 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 a NL.

E 3.5 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.

E 4 Evaluation of Tumour Response and Progression

E 4.1 RECIST 1.1 TL Assessment at Follow-up

This section defines the criteria used to determine objective tumour 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 millimetres. The sum of the diameters for all TLs at each follow-up visit will be compared with the baseline sum of diameters (for response or SD) or to the smallest prior (nadir) sum of diameters (for progression).

E 4.1.1 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 2 or more parts, the sum of the diameters of those parts should be recorded.
- If 2 or more TLs merge, then the sum of the diameters of the combined lesion should be recorded for 1 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 eCRF will trigger an overall visit response of PD.
- When a TL has had any intervention (eg, definitive radiotherapy, embolisation, surgery, transarterial chemoembolisation, etc) during the study, the size of the TL should still be provided where possible and the intervention recorded in the RECIST 1.1 eCRF for the current imaging visit and all subsequent visits. If a TL has been completely removed (surgery) or disappears, the longest diameter should be recorded as 0 mm.

Table 14 RECIST 1.1 Evaluation of Target Lesions

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.
PR	At least a 30% decrease in the sum of the diameters of TL, taking as reference the baseline sum of diameters.
SD	Neither sufficient decrease in the sum of diameters to qualify for PR nor sufficient increase to qualify for PD.
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 demonstrate an absolute increase of at least 5 mm from nadir.
NE	Only relevant if any of the TLs at follow-up were not assessed or NE (eg, missing anatomy) or had a lesion intervention at this visit. Note: If the sum of diameters meets the PD criteria, PD overrides NE as a TL response.
Not applicable	Only relevant if no TLs present at baseline.

Abbreviations: CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease; TL = target lesion.

E 4.2 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 tumour 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 15 RECIST 1.1 Evaluation of Non-Target Lesions

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.
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.
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 participants 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	Only relevant if no NTLs present at baseline.

CR = complete response; NE = not evaluable; NTL = non-target lesion; PD = progressive disease; TL = target lesion.

E 4.3 RECIST 1.1 NL Identification at Follow-up

Details, including the imaging modality, the date of scan, and the location of any NLs will also be recorded in the eCRF. The presence of 1 or more NLs is assessed as progression. The finding of a NL should be unequivocal, ie, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumour. If a NL is equivocal, for example because of its small size, the treatment and tumour assessments should be continued until the previously (pre-existing) NL has been assessed as unequivocal at a follow-up visit, and 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 a NL and will indicate PD.

E 4.4 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 uses the algorithm shown in Table 16.

Table 16 RECIST 1.1 Overall Visit Response

Target lesions	Non-target lesions	New lesions	Overall visit response
CR	CR	No	CR
CR	NA	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
NE	Non-PD or NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Non-CR/non-PD for overall response if only NTL (no TLs) are present at baseline.
Note: An overall assessment of CR (all other disease disappears/reverts to normal) would be changed to PR if ascites remains present radiologically.
Abbreviations: NA = not applicable (only relevant if there were no TLs or NTLs at baseline).

The following overall visit responses are possible depending on the extent of tumour disease at baseline:

- For participants with TLs (at baseline): CR, PR, SD, PD, or NE.
- For participants with NTLs only (at baseline): CR, Non-CR/Non-PD, PD, or NE.
- For participants with no disease at baseline: no evidence of disease (available as an option in the eCRF), PD, or NE.

E 5 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 tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228-47.

Appendix F Contraception Requirements

Contraception requirements for this study are as follows.

F 1 Female Participants

Females not of child-bearing potential are defined as females who are either permanently sterilised (ie, hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or who are post-menopausal.

Females will be considered post-menopausal if they have been amenorrhoeic for 12 months prior to planned enrolment without an alternative medical cause. The following age-specific requirements apply:

- Females < 50 years old are considered post-menopausal if they have been amenorrhoeic for 12 months or more prior to enrolment following cessation of exogenous hormonal treatment and FSH levels in the post-menopausal range.
- Females ≥ 50 years old are considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatment, or had radiation-induced menopause with last menses > 1 year ago, or had chemotherapy-induced menopause with last menses > 1 year ago.

Females of child-bearing potential who are not totally sexually abstinent (ie, refraining from heterosexual intercourse during the entire period of risk associated with study treatments) and intend to be sexually active with a non-sterilised male partner must use at least one highly effective method of contraception from enrolment throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer (Table 17). A highly effective method of contraception is defined as one that has a failure rate of < 1% per year when used consistently and correctly. Cessation of contraception after this time should be discussed with a responsible physician. They should have been stable on their chosen method of birth control for a minimum of 3 months before entering the study and continue to use it throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer.

Females on HRT and whose menopausal status is in doubt will be required to use one of the contraception methods outlined for females of child-bearing potential if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the

type and dosage of HRT. Following confirmation of their post-menopausal status, they can resume use of HRT during the study without use of a contraceptive method.

Non-sterilised male partners of WOCBP participants enrolled in this study must use a male condom plus spermicide (condom alone in countries where spermicides are not approved) from the time of screening of their female partner, throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, (calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.
Total sexual abstinence is an acceptable method provided it is the usual lifestyle of the participant (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments).

F 2 Male Participants with a Female Partner of Child-bearing Potential

Non-sterilised male participants (including males sterilised by a method other than bilateral orchidectomy, eg, vasectomy) who intend to be sexually active with a WOCBP must be using an acceptable method of contraception, such as male condom plus spermicide (condom alone in countries where spermicides are not approved), from the time of screening throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer.

Periodic abstinence (eg, calendar, ovulation symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP/study treatment, and withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together. Male participants should refrain from sperm donation or banking throughout this period.

Vasectomised males are considered fertile if there was no medical assessment of the surgical success and should still use a male condom plus spermicide as indicated above during the clinical study.

Even if the female partner is pregnant, male participants should still use a condom plus spermicide (where approved), as indicated above during the clinical study, if there is a concern about damaging the developing foetus from drug in ejaculate.

Female partners (of child-bearing potential) of male participants enrolled in this study must also use a highly effective method of contraception throughout this period (Table 17) from the

time of screening of their male partner, throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer.

F 3 Highly Effective Methods of Contraception

A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly, see Table 17. 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 participants: Follow the local prescribing information relating to contraception, the time limits for such precautions, and any additional restrictions for the chemotherapy agents (ddMVAC or gem/cis).

Table 17 Highly Effective Methods of Contraception (< 1% Failure Rate)

Non-hormonal methods	Hormonal methods
• Total sexual abstinence (evaluate in relation to the duration of the clinical study and the preferred and usual lifestyle choice of the participant) • Vasectomised sexual partner (with participant assurance that partner received post-vasectomy confirmation of azoospermia) • Bilateral tubal occlusion • Intrauterine device (provided coils are copper-banded)	• Injection: Medroxyprogesterone injection (eg, Depo-Provera®) [a] • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a] • Implants: Etonogestrel-releasing implants (eg, Implanon® or Nexplanon®) • Intravaginal devices: Ethinylestradiol/etonogestrel-releasing intravaginal devices (eg, NuvaRing®) • Combined pill: Normal and low-dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system (eg, Xulane®, Ortho Evra®) • Mini pill: Progesterone-based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based pill

[a] Hormonal methods not prone to drug-drug interactions.

Appendix G Concomitant Medications

G 1 Guidance Regarding Potential Interactions with Concomitant Medications

The use of any natural/herbal products or other "folk remedies" should be discouraged, but use of these products, as well as use of all vitamins, nutritional supplements, and all other concomitant medications must be recorded in the eCRF.

G 2 Drugs Inducing or Inhibiting CYP3A4/5 Metabolism That AstraZeneca Strongly Recommends Are Not Combined With Study Treatment

Moderate inhibitors and inducers of CYP3A4/5 are permitted, but caution should be exercised and participants monitored closely for possible drug interactions.

The following are drugs known to be inducers of CYP3A (Table 18).

The following lists are representative of inducers and inhibitors of CYP 3A enzymes and may lead to important drug-drug interactions with drugs that depend on the CYP 3A subfamily, including CYP3A4/5, for elimination or activation. These lists are not intended to be exhaustive.

If the investigator feels that concomitant administration of medications or herbal supplements will lead to important drug-drug interactions is essential, the study treatment may be discontinued. Please contact AstraZeneca with any queries.

Table 18 Drugs Known to be Inducers of CYP3A

Strong CYP3A inducers (should not be combined)	**Moderate CYP3A inducers (permitted with caution)**
apalutamide	bosentan
carbamazepine	cenobamate
enzalutamide	efavirenz
fosphenytoin	etravirine
lumacaftor	lorlatinib
mitotane	modafinil
phenytoin	nafcillin
rifampin	phenobarbital
St John's Wort	primidone
	rifabutin

CYP = cytochrome P450.
Source: IBM MicroMedex: Drug Interactions: CYP3A Inhibitors, Inducers, and Substrates.

The following are drugs known to be inhibitors of CYP3A (Table 19).

Table 19 Drugs Known to be Inhibitors of CYP3A

Strong CYP3A inhibitors (should not be combined)	Moderate CYP3A inhibitors (permitted with caution)
boceprevir	aprepitant
clarithromycin	atazanavir
cobicistat	ciprofloxacin
conivaptan	crizotinib
grapefruit juice [a, b]	cyclosporine
idelalisib	diltiazem
indinavir	dronedarone
itraconazole	erythromycin
ketoconazole	fluconazole
lopinavir/ritonavir	fluvoxamine
nefazodone	fosamprenavir
nelfinavir	fosnetupitant
posaconazole	grapefruit juice [b] (single strength or low dose)
ritonavir	imatinib
saquinavir	letermovir
telaprevir	netupitant
telithromycin	nilotinib
voriconazole	verapamil

[a] Double-strength grapefruit juice
[b] Participants should abstain from eating large amounts of grapefruit and Seville oranges (and other products containing these fruits eg, grapefruit juice or marmalade) during the study (eg, no more than a small glass of grapefruit juice [120 mL] or half a grapefruit or 1 to 2 teaspoons [15 g] of Seville orange marmalade daily)

Note: Amprenavir, darunavir/ ritonavir, delavirdine, fosamprenavir, mibefradil, mifepristone are known inhibitors but there is not enough information to classify them into a category.
CYP = cytochrome P450.
Source: IBM MicroMedex: Drug Interactions: CYP3A Inhibitors, Inducers, and Substrates.

G 3 Medicines Whose Exposures May Be Affected by Study Treatment That AstraZeneca Considers May Be Allowed With Caution

Medicines that may increase the concentration of chemotherapy drugs are listed in Table 20. Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions. Please refer to the full prescribing information for all drugs prior to co-administration with study treatment.

Table 20 Chemotherapy Exposure, Pharmacological Action, and Toxicity May Be Increased by Concomitant Medicine Treatment

Drug with warning of possible interaction	Rationale	Advice
NSAIDs	May decrease the clearance of methotrexate	Drugs are permitted but caution should be exercised and participants monitored closely for possible drug interactions. Please refer to the full prescribing information for all drugs prior to co-administration with study treatment.
Sulphonamides and penicillins	Displaces bound methotrexate from plasma protein increasing serum methotrexate levels	
Drugs that cause folate deficiency	May lead to increased methotrexate toxicity	
Ciprofloxacin	May inhibit renal tubular transport of methotrexate, increasing serum methotrexate levels	
Probenecid	May inhibit renal excretion of methotrexate, increasing serum methotrexate levels	
Cisplatin	Co-administration reported to cause higher plasma concentrations of vinblastine	
Erythromycin	May increase the toxicity of vinblastine	
Calcium channel blockers	Concurrent administration with doxorubicin should be avoided as they may decrease the clearance of doxorubicin	
Loop diuretics and aminoglycosides	Cisplatin may potentiate the nephrotoxic and ototoxic effects	
Aprepitant	Increased risk of vinca alkaloid-induced adverse effects due to inhibition of CYP3A4	

G 4 Drugs That Prolong QT Interval

G 4.1 Drugs With a Known Risk of TdP

The following drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended (IBM MicroMedex: Drug Interactions: CYP3A Inhibitors, Inducers, and Substrates).

Before study treatment

These drugs **must** have been discontinued prior to the start of administration of study treatment. The interval between discontinuing the drug and the start of study treatment should be investigated to ensure that the drug is adequately eliminated and cleared before starting the study treatment. This interval may be determined by an understanding of the drug's pharmacokinetic properties (ie, elimination half-life), drug compendia, or the medical literature.

During study treatment

It is recommended that these drugs are not co-administered with study treatment and for a period of 2 weeks after discontinuing study treatment; however, if it is considered essential for participant management to co-administer these drugs with study treatment durvalumab therapy close monitoring with ECGs and electrolytes is recommended.

The list of drugs is not exhaustive and is subject to change as new information becomes available and with the approval of new drugs. As such, investigators are recommended to research the drug in question if it causes QT prolongation or if a risk for TdP is present. Consider alternate therapies in management of toxicities.

Table 21 Drugs With a Known Risk of TdP

Drug names			
abiraterone acetate acetylcholine aliskiren amiodarone anagrelide aripiprazole arsenic trioxide atazanavir azithromycin celecoxib chloroquine cilostazol ciprofloxacin citalopram clindamycin clofazimine clozapine desflurane disopyramide dofetilide	efavirenz/emtricitabine/ tenofovir disoproxil fumarate erythromycin escitalopram flecainide fluconazole fluoxetine foscarnet ganciclovir haloperidol hydroxychloroquine hydroxyzine ibutilide ivabradine* ketoconazole lansoprazole/ amoxicillin/ clarithromycin lapatinib levofloxacin	mirtazapine mobocertinib moxifloxacin nelfinavir norfloxacin ofloxacin olanzapine/ fluoxetine omeprazole/ clarithromycin/ amoxicillin ondansetron oxaliplatin pazopanib pentamidine perphenazine pimozide posaconazole propafenone quinidine quinine	sotalol sparfloxacin sulfamethoxazole/ trimethoprim sumatriptan sunitinib tacrolimus technetium Tc 99m tetrofosmin telithromycin terfenadine thioridazine thiothixene toremifene tramadol tramadol/acetaminophen trazodone trifluoperazine vasopressin

Table 21 Drugs With a Known Risk of TdP

dolasetron donepezil droperidol efavirenz	lomefloxacin lopinavir/ritonavir mesoridazine methadone milrinone	saquinavir sertraline sevoflurane solifenacin	vonoprazan/ amoxicillin/ clarithromycin voriconazole ziprasidone

Source: IBM MicroMedex: Drugs that cause Torsade de pointes

G 4.2 Other TdP Risk Categories

Participants receiving drugs that prolong QT interval or may increase the risk of TdP from other TdP risk categories can be enrolled, notwithstanding other exclusions and restrictions, if these drugs are considered essential for participant management, and the participant has been stable on therapy. Close monitoring with ECGs and electrolytes is recommended.

Participants with mean resting corrected QT interval > 470 ms obtained from triplicate ECGs performed at screening, history of QT prolongation associated with other medications that required discontinuation of that medication, any current concomitant medication known to prolong the QT interval and cause TdP, congenital long QT syndrome, family history of long QT syndrome, or unexplained sudden death under 40 years of age in first-degree relatives are excluded from this study.

G 4.3 Guidance Regardless of TdP Risk Category

During study treatment and for a period of 2 weeks after discontinuing study treatment, if it is considered essential for participant management to co-administer drugs known to prolong corrected QT interval, **regardless of TdP risk category**, close monitoring with ECGs and electrolytes is recommended.

Add any additional categories as necessary.

G 5 Prohibited, and Permitted Concomitant Medications/Therapies

Prohibited, and permitted concomitant medications/therapies are described in Table 22 and Table 23. Refer also to the dose modification guidelines for management of study treatment-related toxicities in the Annex document to this CSP.

Table 22 Prohibited Medications/Therapies

Prohibited medication/class of drug/therapy	**Usage**
For all treatment phases	
Any investigational anti-cancer therapy other than those under investigation in this study (including curative radiotherapy)	Must not be given concomitantly while the participant is on study treatment.

Prohibited medication/class of drug/therapy	Usage
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Must not be given concomitantly while the participant is on study treatment.
Any concurrent treatment, including chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than durvalumab and the investigator-selected cisplatin-based neoadjuvant chemotherapy, except for those medications identified as "restricted," as listed above	Must not be given concomitantly whilst the participant is on study treatment. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [eg, by local surgery or radiotherapy]).
Live attenuated vaccines	Must not be given while receiving study treatment and up to 90 days after the last dose of durvalumab. Local guidance should be consulted to determine the acceptable timeframe for vaccine administration following chemotherapy study treatment.
Herbal and natural remedies that may have immune-modulating effects and interfere with activity of the study results	Must not be given concomitantly unless agreed by AstraZeneca.
For durvalumab treatment only	
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers	Must not be given concomitantly, or used for premedication prior to the IO infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of study treatment-related AEs. • Use in participants with contrast allergies. • 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 participant (eg, chronic obstructive pulmonary disease, radiation, nausea, etc). Consult with study clinical lead for prolonged therapy or need for a slow taper. 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.

Prohibited medication/class of drug/therapy	Usage
EGFR TKIs	Must not be given concomitantly. Must 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 first generation EGFR TKIs) has been reported when durvalumab has been given concomitantly.
	Should not be given concomitantly unless agreed by the sponsor

Abbreviations: AE = adverse event; CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4; CYP3A4/5 = cytochrome P450 3A4/5; EGFR = epidermal growth factor receptor; IO = immune-oncology; PD-1 = programmed cell death protein-1; PD-L1 = programmed death-ligand 1; TKI = tyrosine kinase inhibitor.

Table 23 Supportive Medications/Therapies

Supportive medication/class of drug/therapy	Usage
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary to provide adequate AE management, except for those medications identified as "prohibited," as listed above	To be administered as prescribed by the investigator except for those medications identified as "prohibited," as listed in Table 22.
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc]) except for those medications identified as "prohibited," as listed above	Should be used, when necessary, for all participants except for those medications identified as "prohibited," as listed in Table 22.
Bone-modifying agents (bisphosphonates, RANKL inhibitors) used to prevent skeletal-related events and for management of osteoporosis	Permitted
Inactivated viruses, such as those in the influenza vaccine or authorised inactivated COVID-19 vaccines, based on local prescribing information	Permitted.
Required for management of other medical conditions	As required except for those identified as "prohibited," as listed in Table 22.

Abbreviations: AE = adverse event; COVID-19 = Coronavirus disease 2019; RANKL = receptor activator of nuclear factor-κB ligand.

Appendix H 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 participants become infected with SARS-CoV-2 or similar pandemic infection) during which participants 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 notification from the sponsor and instructions on how to perform these procedures will be provided at the time of implementation.

Please note that during civil crisis, natural disaster, or public health crisis, some study assessments and procedures may not be conducted due to international or local policies or guidelines, hospital or clinic restrictions and other measures implemented to ensure the participant's safety. If in doubt, please contact the AstraZeneca study physician.

H 1 Reconsent of Study Participants During Study Interruptions

During study interruptions, it may not be possible for the participants to complete study visits and assessments on site and alternative means for carrying out the visits and assessments may be necessary. Reconsent should be obtained for the alternative means of carrying out visits and assessments and should be obtained prior to performing the procedures described in Appendix H 2 to Appendix H 5. Local and regional regulations and/or guidelines regarding reconsent of study participants 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 participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

Local and regional regulations and/or guidelines regarding reconsent of study participants 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 participant's next contact with the study site). Visiting the study sites for the sole purpose of obtaining reconsent should be avoided.

H 2 Home or Remote Visit to Replace On-site Visit (Where Applicable)

A qualified HCP from the study site or TPV service may visit the participant's home/or other remote location as per local standard operating procedures, as applicable. Supplies will be provided for a safe and efficient visit. The qualified HCP will be expected to collect information per the CSP. Assessments will be performed according to a revised SoA.

H 3 Telemedicine Visit to Replace On-site Visit (Where Applicable)

In this appendix the term telemedicine visit refers to remote contact with the participants 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 participants will allow AEs, concomitant medication, and other information including efficacy data where relevant to be collected according to study requirements to be reported and documented.

H 4 At-home or Remote Location IP Administration Instructions

A qualified HCP from the study site or TPV service should administer the IP at the participant's home or other remote location according to the CSP; only in the case of civil crisis, natural disaster, or public health crisis; and after approval from sponsor. All necessary supplies and instructions for administration and documentation of IP administration will be provided. Additional information related to the visit can be obtained via a telemedicine or home visit.

H 4.1 At-home or Remote Location IP Administration by a Qualified HCP or TPV Service

This is applicable only in the case of civil crisis, natural disaster, or public health crisis; and after approval from sponsor. Prior to at-home or remote location IP administration the investigator must assess the participant or his/her caregiver to determine whether they are appropriate for at-home or remote location administration of IP. Once the participant or his/her caregiver is deemed appropriate for at-home or remote location administration, they must receive appropriate training. All necessary supplies and instructions for administration and documentation of IP administration will be provided. More information related to the visit can be obtained via a telemedicine or home / remote visit.

H 5 Data Capture During Telemedicine or Home / Remote Visits

Data collected during telemedicine or home/remote visits will be captured by the qualified HCP from the study site or TPV service in the source documents, or by the participant themselves.

Appendix I Document History

CSP Version 2.0 21-May-2025
This modification was considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union and in the European Union (EU) Clinical Trial Regulation Article 2, 2 (13) because the modifications either significantly impacted the safety or physical/mental integrity of participants or the scientific value of the study.

Overall Rationale for the Modification:
This amendment was developed to add clarity to the clinical study protocol (CSP) in response to queries raised by regulatory authorities in the EU/ European Economic Area.

Summary of Changes:

List of Modifications

Section Number and Name	Description of Change	Brief Rationale
Overall CSP	The CSP version number and date is revised at all applicable instances.	Revisions made as CSP is amended
Section 1.3 Schedule of Activities – Table 1, Table 2, Table 3, and Table 4	Tables were updated to add cortisol testing to list of laboratory assessments. New footnotes h and i (for Tables 1 and 2) and new footnote d (for Tables 3 and 4) are added to support addition of cortisol testing, and subsequent footnotes have been adjusted.	Addition of relevant laboratory assay
Section 5.1 Inclusion Criteria – Inclusion Criterion #8a and 8b	Text is added to clarify that duration of birth control requirements for male and female participants is from the time of screening throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the Summary of Product Characteristics (SmPC) or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer.	Clarification of contraception requirements
Section 5.2 Exclusion Criteria – Exclusion Criterion #33	Text is added to clarify that duration of birth control requirements for male and female	Clarification of contraception requirements

	participants is from the time of screening throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer.	
Section 8.2.4 Clinical Safety Laboratory Tests – Table 10	Table 10 is updated to add cortisol testing to the list of laboratory safety variables. A new footnote (f) is added specifying that sample for cortisol testing is to be collected as per institutional clinical practice.	Addition of relevant laboratory assay
Section 8.3.13.2 Paternal Exposure	Text is updated to state that male participants should refrain from fathering a child or donating sperm from the time of screening throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer.	Updated for consistency
Appendix F Contraception Requirements – F1 Female Participants and F2 Male Participants with a Female Partner of Child-bearing Potential	Text is added to clarify that duration of birth control requirements for male and female participants and their partners is from the time of screening throughout the total duration of the study and up to 90 days after the last dose of durvalumab (neoadjuvant or adjuvant treatment period) or up to end of the period specified in the SmPC or package insert of the chemotherapy agents (neoadjuvant treatment period), whichever is longer	Clarification of contraception requirements

11 REFERENCES

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.

Afferi et al 2024
Afferi L, Spahn M, Hayoz S, Strebel RT, Rothschild SI, Seifert H, et al. Safety and quality of cystectomy and pelvic lymph node dissection after neoadjuvant durvalumab and cisplatin/gemcitabine. BJU International 2024. https://doi.org/10.1111/bju.16318.

Alimohamed et al 2024
Alimohamed NS, Gotto GT, Kulkarni GS, Black PC, Kassouf W, Sridhar SS, et al. Real-world treatment practices in patients with muscle-invasive bladder cancer (MIBC) treated in Alberta, Canada. *J Clin Oncol* 2024;42:e16596. doi: 10.1200/JCO.2024.42.16_suppl.e16596.

Atezolizumab
Tecentriq. Prescribing information. Roche; 2016. Accessed 31 May 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761034s042lbl.pdf.

Bajorin et al 2021
Bajorin DF, Witjes JA, Gschwend JE, Schenker M, Valderrama BP, Tomita Y, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Eng J Med* 2021;384:2102-2114.

Birgitte et al 2008
Birgitte A, Sengelov L, Von der Maase H. Gemcitabine and cisplatin in locally advanced and metastatic bladder cancer; 3 or 4 week schedule? *Acta Oncologica* 2008;47:110-9.

Blank et al 2006
Blank C, Kuball J, Voelkl S, Wiendl H, Becker B, Walter B, et al. Blockade of PD-L1 (B7-H1) augments human tumor-specific T-cell responses in vitro. *Int J Cancer*. 2006;119(2):317-27.

Cathomas et al 2023
Cathomas R, Rothschild SI, Hayoz S, Bubendorf L, Özdemir BC, Kiss B, et al. Perioperative chemoimmunotherapy with durvalumab for muscle-invasive urothelial carcinoma: primary analysis of the single-arm Phase II trial SAKK 06/17. *J Clin Oncol* 2023;41(33).

Catto et al 2025
Catto JWF, Al-Ahmadie H, Van der Heijden MS, Powels T, Galsky MD, Nishiyama H, et al. Surgical Outcomes and Neoadjuvant Safety with Perioperative Durvalumab for Muscle-Invasive Bladder Cancer. European Association of Urology Congress (EAU) 2025 Annual Meeting;Bladder Cancer Game changer session.

Choueiri et al 2014
Choueiri TK, Jacobus S, Bellmunt J, Qu A, Appleman LJ, Tretter C, et al. Neoadjuvant dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin with pegfilgrastim support in muscle-invasive urothelial cancer: pathologic, radiologic, and biomarker correlates. *J Clin Oncol* 2014;32(18):1889-1894.

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):506-513.

Dash et al 2008
Dash A, Pettus JA 4th, 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):2471-2477.

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.

European Association of Urology Guidelines 2024
Witjes JA, Bruins HM, Carrión A, Cathomas R, Compérat EM, Efstathiou JA, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer: Summary of the 2023 Guidelines. Eur Urol. 2024 Jan;85(1):17-31.

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).

Ferlay et al 2024
Ferlay J, Ervik M, Lam F, Laversanne M, Colombet M, Mery L, et al. (2024). Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available from: https://gco.iarc.who.int/today, accessed [April 2024].

Fife and Bluestone 2008
Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. Immunol Rev 2008;224:166-182.

Galsky et al 2015
Galsky MD, Pal SK, Chowdury 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. doi:10.1002/cncr.29387.

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;349:859-866.

Hahn 2021
Hahn NM. Harrison's principles of internal medicine. Chapter 82: Cancer of the bladder and urinary tract. McGraw-Hill; 2021.

Hartung et al 2020
Hartung JP, Berger T, Bermel RA, Brochet B, Carroll WM, Holmøy T, et al. Shorter infusion time of ocrelizumab: Results from the randomized, double-blind ENSEMBLE PLUS substudy in patients with relapsing-remitting multiple sclerosis. Mult Scler Relat Disord 2020;46:102492.

Holzbeierlein et al 2024
Holzbeierlein J, Bixler BR, Buckley DI, Chang SS, Holmes RS, James AC, et al. Treatment of non-metastatic muscle-invasive bladder cancer: AUA/ASCO/SUO guideline (2017; amended 2020, 2024). J Urol 2024;212:3-10.

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;3:855-859.

IBM MicroMedex: Drug Interactions: CYP3A Inhibitors, Inducers, and Substrates
IBM MicroMedex: Drug Interactions: CYP3A Inhibitors, Inducers, and Substrates. In: Drug Consults [database on the Internet]. Greenwood Village (CO): IBM Corporation; 2022 [cited 27 June 2022]. Available from: www.micromedexsolutions.com.

IBM MicroMedex: Drugs that cause Torsade de pointes
IBM MicroMedex: Drugs that cause Torsade de pointes. In: Drug Consults [database on the Internet]. Greenwood Village (CO): IBM Corporation; 2022 [cited 2022 July 15]. Available from: www.micromedexsolutions.com.

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):2171-2177.

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.

Lee et al 2013
Lee FC, Harris W, Cheng HH, Shenoi J, Zhao S, Wang J, et al. Pathologic response rates of gemcitabine/cisplatin versus methotrexate/vinblastine/adriamycin/cisplatin neoadjuvant chemotherapy for muscle-invasive urothelial bladder cancer. *Adv Urol* 2013;2013:317190.

Lee et al 2021
Lee Y, Kim YS, Hong B, Cho YM, Lee J-L. Comparison of clinical outcomes in patients with localized or locally advanced urothelial carcinoma treated with neoadjuvant chemotherapy involving gemcitabine-cisplatin and high dose-intensity MVAC. *J Cancer Res Clin Oncol* 2021;147:3421-3429.

Lenz 2007
Lenz H-J. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 2007;12:601-609.

Lotan et al 2022
Lotan Y, de Jong JJ, Liu VYT, Bismar TA, Boorjian SA, Huang HC, et al. Patients with muscle-invasive bladder cancer with nonluminal subtype derive greatest benefit from platinum-based neoadjuvant chemotherapy. *J Urol*. 2022 Mar;207(3):541-550.

Meeks et al 2025
Meeks JJ, Van der Heijden MS, Powles T, Galsky MD, Al-Ahmadie M, Nishiyama H, et al. The first report of disease-free survival analyses from the niagara trial of perioperative durvalumab plus neoadjuvant chemotherapy in muscle-invasive bladder cancer. J Urol. 2025; Bladder Cancer: Invasive III (PD37).

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;52:1017-1027.

NCCN Guidelines Insights Bladder Cancer 5.2018
Flaig J, Spiess PE, Abern M, Agarwal N, Bangs R, Buyyounouski MK, et al. J Natl Compr Canc Netw. 2018 Sep;16(9):1041-1053.

NCCN Guidelines® Insights: Bladder Cancer 3.2024
Flaig J, Spiess PE, Abern M, Agarwal N, Bangs R, Buyyounouski MK, et al. J Natl Compr Canc Netw. 2024 May;22(4):216-225.

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):1275-1284.

Nivolumab
Opdivo. Prescribing information. Bristol-Myers Squibb; 2014. Accessed 31 May 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s090lbl.pdf.

Nowak et al 2020
Nowak AK, Lesterhuis WJ, Kok PS, Brown C, Hughes BG, Karikios DJ, et al. Durvalumab with first-line chemotherapy in previously untreated malignant pleural mesothelioma (DREAM): a multicentre, single-arm, phase 2 trial with a safety run-in. *Lancet Oncol* 2020;21(9):1213-1223.

Okazaki and Honjo 2007
Okazaki T, Honjo T. PD-1 and PD-1 ligands: from discovery to clinical application. Int *Immunol* 2007;19(7):813-824.

Pardoll 2012
Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012;12:252-264.

Patel et al 2020
Patel VG, Oh WK, Galsky MD. Treatment of muscle-invasive and advanced bladder cancer in 2020. *CA Cancer J Clin* 2020;70:404-423.

Pembrolizumab
Keytruda. Prescribing information. Merck; 2014. Accessed 31 May 2022. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf.

Peyton et al 2018
Peyton CC, Tang D, Reich RR, Azizi M, Chipollini J, Pow-Sang JM, et al. Down-staging and survival outcomes associated with neoadjuvant chemotherapy regimens among patients treated with cystectomy for muscle-invasive bladder cancer. *JAMA Oncol* 2018;4(11):1535-1542.

Pfister et al 2021
Pfister C, Gravis G, Fléchon A, Soulié M, Guy L, Laguerre B, et al. Randomized Phase III trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin, or gemcitabine and cisplatin as perioperative chemotherapy for patients with muscle-invasive bladder cancer. Analysis of the GETUG/AFU V05 VESPER trial secondary endpoints: chemotherapy toxicity and pathological responses. *Eur Urol.* 2021;79(2):214-221.

Pfister et al 2022
Pfister C, Gravis G, Fléchon A, Chevreau C, Mahammedi H, Laguerre B, et al. Dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin or gemcitabine and cisplatin as perioperative chemotherapy for patients with nonmetastatic muscle-invasive bladder cancer: results of the GETUG-AFU V05 VESPER trial. *J Clin Oncol* 2022;40:2013-2022.

Plimack et al 2014
Plimack ER, Hoffman-Censits JH, Viterbo R, Trabulsi EJ, Ross EA, Greenberg RE, et al. Accelerated methotrexate, vinblastine, doxorubicin, and cisplatin is safe, effective, and efficient neoadjuvant treatment for muscle-invasive bladder cancer: results of a multicenter phase II study with molecular correlates of response and toxicity. *J Clin Oncol* 2014;32(18):1895-1901.

Powles et al 2020
Powles T, van der Heijden MS, Castellano D, Galsky MD, Loriot Y, Petrylak DP, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol* 2020;21;P1574-1588. doi: https://doi.org/10.1016/S1470-2045(20)30541-6.

Powles et al 2022
Powles T, Bellmunt J, Compérat E, De Santis M, Huddart R, Loriot Y, et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol* 2022;33:244-258.

Powles et al 2024a
Powles T, van der Heijden MS, Galsky MD, Al-Ahmadie H, Meeks JJ, Nishiyama H, et al. A randomised Phase 3 trial of neoadjuvant durvalumab plus chemotherapy followed by radical cystectomy and adjuvant durvalumab in muscle-invasive bladder cancer (NIAGARA). Presented at the ESMO Annual Congress Barcelona 2024.

Powles et al 2024b
Powles T, Catto JWF, Galsky MD, Al-Ahmadie H, Meeks JJ, Nishiyama H, et al. Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. *New Engl J Med* 2024; 391:1773-1786.

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; 9:2169–2170.

Rombouts et al 2020
Rombouts MD, Swart EL, Van Den Eertwegh AJM, Crul M. Systematic review on infusion reactions to and infusion rate of monoclonal antibodies used in cancer treatment. *Anticancer Res* 2020;40:1201-1218.

Sehn et al 2007
Sehn LH, Donaldson J, Filewich A, Fitzgerald C, Gill KK, Runzer N, et al. Rapid infusion rituximab in combination with corticosteroid-containing chemotherapy or as maintenance therapy is well tolerated and can safety be delivered in the community setting. Blood 2007; 109:4171-4173.

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):1052-1062.

Thibault et al 2023
Thibault C, Bennamoun M, Fléchon A, Gravis G, Pouessel D, Combe P, et al. Durvalumab (D) +/- tremelimumab (T) in combination with dose-dense MVAC (ddMVAC) as neoadjuvant treatment in patients with muscle-invasive bladder carcinoma (MIBC): results of NEMIO, a randomized phase I-II trial. *Ann Oncol* 2023;34(suppl_2):S1202-S1228. 10.1016/S0923-7534(23)01271-1.

Thibault et al 2025
Thibault C, Bennamoun M, Fléchon A, Gravis G, Pouessel D, Combe P, et al. Durvalumab (D) +/- tremelimumab (T) in combination with dose-dense MVAC (ddMVAC) as neoadjuvant treatment in patients with muscle-invasive bladder carcinoma (MIBC): Updated results (EFS and OS) of NEMIO, a phase I/II trial. Poster presented at *European Society for Medical Oncology (ESMO) 2025 Congress;* 2025; October 17-21, 2025: Berlin, Germany.

Vogel 2010
Vogel WH. Infusion reactions: diagnosis, assessment, and management. *Clin J Oncol Nurs* 2010;14:E10-21.

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;18:3068-3077.

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.

Waterhouse et al 2018
Waterhouse D, Horn L, Reynolds C, Spigel D, Chandler J, Mekhail T, et al. Safety profile of nivolumab administered as 30-min infusion: analysis of data from CheckMate 153. *Cancer Chemother Pharmacol* 2018;81:679-686.

Witjes et al 2024
Witjes JA, Bruins HM, Carrión A, Cathomas R, Compérat EM, Efstathiou JA, et al. EAU guidelines on muscle-invasive and metastatic bladder cancer – limited update. European Association of Urology. April 2024 (http://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer).

Yuh et al 2013
Yuh BE, Ruel N, Wilson TG, Vogelzang N, Pal SK. Pooled analysis of clinical outcomes with neoadjuvant cisplatin and gemcitabine chemotherapy for muscle-invasive bladder cancer. *J Urol* 2013;189:(5):1682-1686.

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.

Signature Page for VV-RIM-05785567 System v4.4
D933RC00002 Clinical Study Protocol version 3

Approve: Document Level Task Verdict: Approved	Ugochinyere Emeribe Content Approval 10-Nov-2025 14:41:36 GMT+0000

Approve: Document Level Task Verdict: Approved	Neelima Denduluri Content Approval 10-Nov-2025 15:21:30 GMT+0000

Signature Page for VV-RIM-05785567 System v4.4
D933RC00002 Clinical Study Protocol version 3