Rad-io

A multi-stage trial of durvalumab (Medi4736) with chemoradiotherapy with 5- fluorouracil and mitomycin C in patients with muscle-invasive bladder cancer

PROTOCOL

Sponsor:	University of Birmingham
Sponsor Protocol Number:	RG_18-220
CRCTU Number:	BL2103
EudraCT Number:	2018-003520-37
ISRCTN:	43698103
IRAS ID No.:	251669

Version Number: 7.0

Date: 30th May 2023

CANCER RESEARCH UK | BIRMINGHAM CANCER RESEARCH UK CLINICAL TRIALS UNIT | UNIVERSITY OF BIRMINGHAM

SIGNATURE PAGE

Rad-IO trial protocol, version 7.0, dated 30th May 2023

This protocol has been approved by:

Name:	Prof. Nicholas James	Trial Role:	Chief Investigator
Signature:	_____	Date:	DD / MON / YYYY

This protocol describes the Rad-IO trial and provides information about procedures for patients taking part in the Rad-IO trial. The protocol should not be used as a guide for treatment of patients not taking part in the Rad-IO trial.

SPONSOR STATEMENT:

Where the University of Birmingham takes on the sponsor role for protocol development oversight, the signing of the IRAS form by the sponsor will serve as confirmation of approval of this protocol.

This protocol has been developed using CRCTU-PRO-SOP-001, version 1.0b, 26-Jul-2010.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	21-Jul-2020	4.0	Substantial	Updated Durvalumab Dosing Modification and Toxicity Management Guidelines (Appendix 2), updated trial endpoint measures, DMC meeting frequency clarified, addition of ISRCTN number, updated trial contact details, clarification of exclusion criteria, detailing use of email for SAE reporting, clarification of trial design, change in Durvalumab preparation guidelines and AE data, clarification of follow up for patients with disease progression, clarification of schedule of events, clarification of follow up, updated method of QoL booklet and LENT SOMA questionnaire distribution and therefore collection of patient postal addresses, clarification of statistical considerations, clarification of SAE definition, updated translational sub-study details, clarification of radiotherapy quality assurance process, correction of typographical errors.
2	18-Jan-2021	5.0	Substantial	Updated Durvalumab Dosing Modification and Toxicity Management Guidelines (Appendix 2), updated eligibility criteria, updated durvalumab administration, cystoscopy, scanning and treatment assessment windows. Correction of final durvalumab concentration. Minor administration changes.
3	18-Oct-2021	5.0a	Non-Substantial	Clarification of baseline assessments required if receiving neo-adjuvant chemotherapy treatment.
4	24-Nov-2021	6.0	Substantial	Exclusion criteria updated. Time from neo-adjuvant treatment completion to start of durvalumab clarified. Location of translational sub-study sample processing clarified. SAE reporting information updated. Durvalumab risks updated. Appendix 2 updated.
5	30-May-2023	7.0	Substantial	Change in sample size, change the trial design from randomised trial to single-arm trial, inclusion of node positive patients, addition of radiotherapy regimen for node positive patients, statistical considerations section update, overall risks with durvalumab updated, durvalumab storage shelf-life updated, changes to follow-up duration, changes to end of trial definition, translational sub-studies section update, administrative changes

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Serious Adverse Event Reporting

Email SAE forms to: reg@trials.bham.ac.uk

TRIAL SYNOPSIS

Title	**RadIO:** A multi-stage trial of durvalumab (Medi4736) with chemoradiotherapy with 5-Fluorouracil and mitomycin C in patients with muscle-invasive bladder cancer
Trial Design	A phase II trial with an integral pilot **Stage 1 (Pilot):** To evaluate feasibility and safety at 3 months of: • First 6 patients randomised to the research arm • First 6 patients in the research arm who received neo-adjuvant chemotherapy • First 6 patients in the research arm who didn't receive neo-adjuvant chemotherapy • First 6 patients in the research with node positive disease **Stage 2 (Efficacy):** This stage is designed as a phase II trial using disease free survival rate at 12 months as a surrogate for overall survival rate. Patients who are assessed for stage 1 will also be included in the analysis for stage 2. **Stage 3 (Efficacy):** Subject to favourable outcome data from stage 2 and additional funding, the trial will roll seamlessly to a phase III trial using a multi-arm multi-stage (MAMS) design with overall survival time as the primary outcome.
Hypothesis	We hypothesise that the known synergistic effects of chemotherapy and radiotherapy are augmented by the addition of further therapies and specifically that checkpoint inhibitors like durvalumab can augment the effect of radiotherapy and chemotherapy in muscle invasive bladder cancer and thus can improve local control and reduce systemic spread.
Aim	To assess the safety, feasibility and efficacy of a combination of radiotherapy with durvalumab and chemotherapy in muscle invasive bladder cancer using a multi-stage design.
Patient Population	Patients with muscle invasive bladder cancer with no metastatic spread, fit for radical chemoradiotherapy and systemic immunotherapy.
Sample Size	Recruitment into the randomised stage 1 portion of the trial will include less than 20 control arm patients. The randomised component of the trial will be closed once all approvals for protocol version 6.0 are superseded 52 research arm patients will be recruited from both Stage 1 and Stage 2 patients

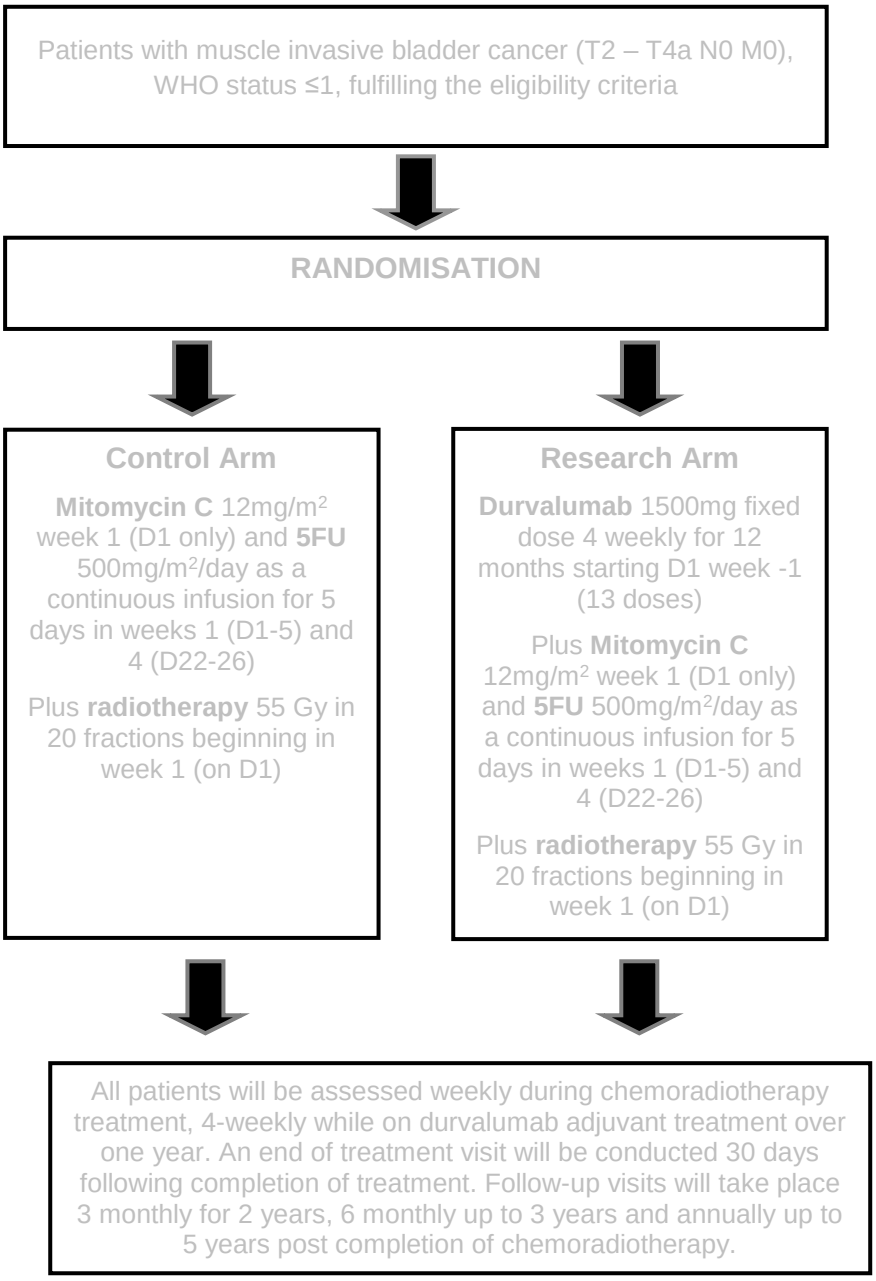
Comparison stage	**Primary Outcome Measures**	**Secondary Outcome Measures**
Stage 1: Pilot	• Evaluation of feasibility and safety after the first 6 patients on the research arm have completed 3 months of follow up post chemoradiotherapy	• Evaluation of feasibility and safety following completion of 3 months of follow up post chemoradiotherapy for: ○ First 6 research arm patients who received neo-adjuvant chemotherapy ○ First 6 research arm patients who did not receive neo-adjuvant chemotherapy ○ First 6 patients in the research arm with node positive disease
Stage 2: Efficacy	• Disease free survival rate at 12 months post chemoradiotherapy	• Toxicity • Delivery of core target therapy (chemoradiotherapy) • Time to local muscle invasive progression • Time to local non-muscle invasive progression • Time to regional nodal progression • Time to local progression • Time to distant progression • Cystectomy within one year • Quality of Life (QoL) • Overall survival time • Disease free survival time

		• Percentage of target drug delivery
Stage 3: Efficacy	• Overall survival time	• Acute and late toxicity • Percentage of target drug delivery • Time to local progression • Time to distant progression • Cystectomy rate • Disease-free survival time • QoL
Inclusion Criteria (see protocol section 4 for full details)	• Aged >18 • Body weight >30Kg • Histologically proven invasive bladder carcinoma (adenocarcinoma, transitional cell carcinoma or squamous cell carcinoma). • Localised muscle invasive carcinoma either surgically or by imaging (T2-T4a N0 M0 or T2-T4a N1-2 M0World Health Organisation (WHO) performance status grade 0 to 1 • Adequate organ and marrow function • Fit for a radical course of radiotherapy • Must have a life expectancy of at least 12 weeks • Evidence of post-menopausal status or negative pregnancy test • Male and female patients of childbearing age willing to use effective contraception • Willing to comply with the protocol • Given written informed consent	

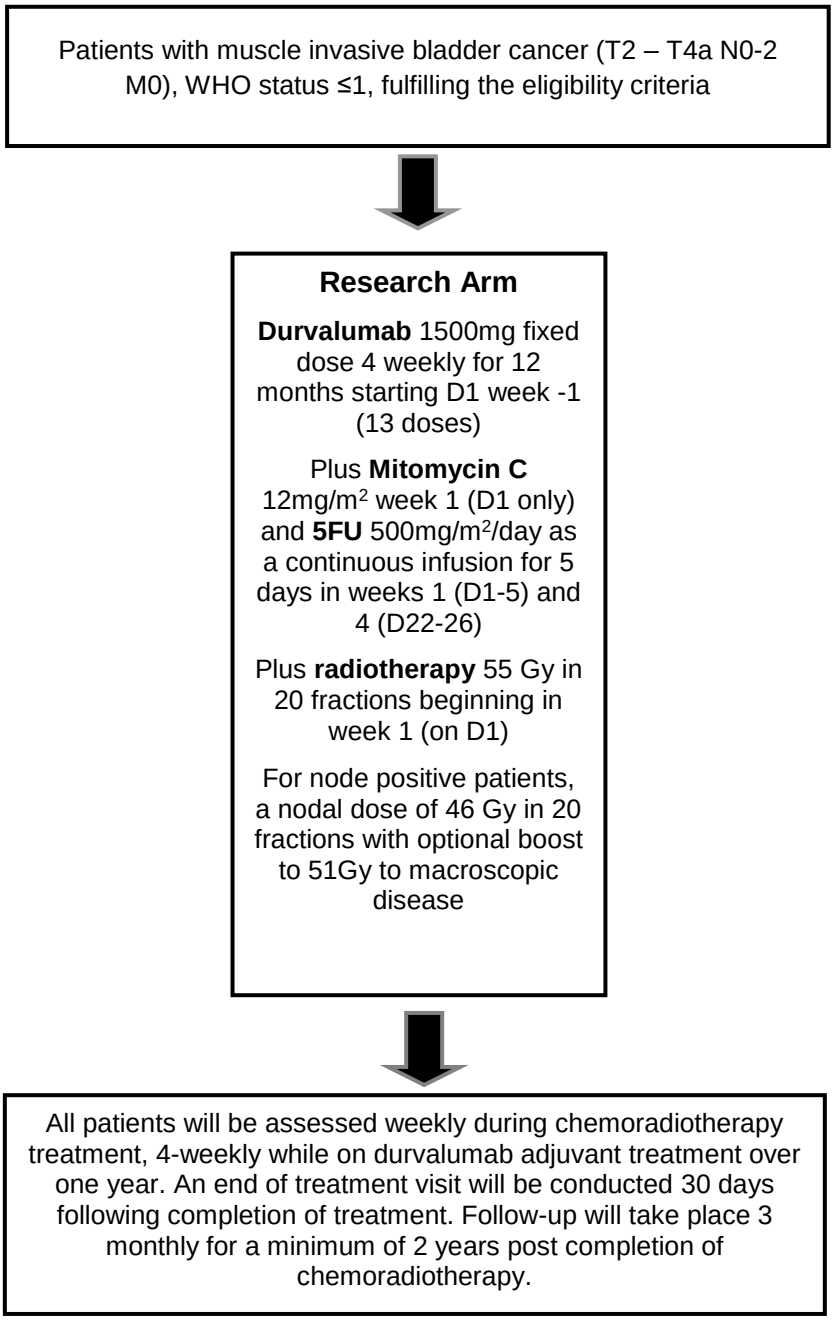
Exclusion Criteria (see protocol section 4 for full details)	• Uncontrolled systemic disease which would preclude the patient from participating in the trial including severe or uncontrolled cardiovascular disease
	• Previous pelvic radiotherapy
	• Bilateral hip replacements compromising accurate radiotherapy planning (with appropriate technical compensation such as MRI based planning, these patients may be included)
	• Evidence of significant clinical disorder, or laboratory finding which makes it undesirable for the patient to participate in the trial
	• Untreated hydronephrosis with complete blockage of drainage from the affected kidney
	• Previous (within last 30 days) or current participation in another trial
	• Any unresolved toxicity CTCAE ≥Grade 2 from previous anticancer therapy
	• Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab
	• Current or prior use of immunosuppressive medication within 14 days prior to registrationrandomisation
	• Current use of brivudin, sorivudin, and analogues
	• Patients with an active non-infective pneumonitis
	• History of active primary immunodeficiency
	• Any concurrent chemotherapy, Investigational Medicinal Product (IMP), biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions is acceptable
	• Major surgical procedure other than transurethral resection of the bladder tumour within 30 days prior to registrationrandomisation
	• History of allogenic organ transplantation
	• Active autoimmune or inflammatory disorders requiring systemic treatment within 3 months prior to registrationrandomisation or documented history of clinically severe autoimmune or inflammatory disorder
	• Uncontrolled intercurrent illness
	• History of another primary malignancy except for:
	  ○ Malignancy treated with curative intent and with no known active disease ≥2years
	  ○ Non-muscle invasive bladder tumours
	  ○ NCCN low risk prostate cancer (T1/T2a, Gleason 6 PSA <10)
	  ○ Treated non-melanoma skin cancer or lentigo maligna
	• Metastatic disease	

	• Acute, serious (e.g. Herpes zoster, chickenpox) or active infection including tuberculosis, hepatitis B, hepatitis C, or human immunodeficiency virus • Bone marrow depression after radiotherapy or treatment with other antineoplastic agents • Pancytopenia or isolated leucopoenia/thrombopenia or haemorrhagic diathesis • Receipt of live attenuated vaccine within 30 days prior to registrationrandomisation • Serious liver impairment • Known homozygotic for dihydropyrimidine or known complete absence of dihydropyrimidine dehydrogenase (DPD) activity • Patients undergoing management for non-malignant disease which may interact with any of the trial treatments • Female patients who are breastfeeding • Known allergy or hypersensitivity to any of the trial drugs or any of the trial drug excipients • Known clinical contra-indications to any of the trial IMPs • Patient unsuitable to participate in the trial or unlikely to comply with protocol
Trial Duration	**Recruitment:** estimated as 4 years **Follow-up:** Minimum of 2 years from completion of chemoradiotherapy
Trial Office	Cancer Research UK Clinical Trials Unit (CRCTU), Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, B15 2TT. ☎ 0121 414 3793 or 0121 415 8544 🖷: 0121 414 2230 ✉ RadIO@trials.bham.ac.uk www.birmingham.ac.uk/Radio

INITIAL TRIAL SCHEMA



NEW TRIAL SCHEMA



SCHEDULE OF EVENTS – Standard Chemoradiotherapy

	Screening		Treatment	Follow-up - * from completion of chemoradiotherapy								
	Baseline (within 28 days of rand, except for cystoscopy/scans)	RANDOMISATION	Day 1 of each week of chemo-radiotherapy Treatment (or within 3 days prior)	End of treatment (30 days post end of treatment ±7 days)	3 months* (±7 days)	6 months* (±7 days)	9 months* (±7 days)	12 months* (±7 days)	15 months* (±7 days)	18 months* (±7 days)	21 months* (±7 days)	24 months* (±7 days)
Written Informed Consent	x											
Eligibility	x											
Medical History[1]	x											
Cystoscopy[2]	x (within 56 days of rand)[2]				x	x		x		x		x
Physical examination and vital signs[3]	x		x	x								
Height and weight[4]	x		x	x								
WHO performance status	x		x	x	x	x	x	x	x	x	x	x
Haematology and biochemistry[5]	x		x	x								
Thyroid function tests (TSH and fT3 and fT4)[6]	x		x	x								
Urinalysis[7]	x			x								
Serum cortisol	x			x								
Coagulation parameters[8]	x											
Urine hCG or serum βhCG[9]	x		x (week 4 only)	x								
Electrocardiogram (ECG)[10]	x											
CT scan chest, abdomen and pelvis or MRI scan combined with chest CT[11]	x (within 56 days of rand)				x	x		x		x		x
Adverse events and toxicity [12]	x		x	x	x	x	x	x	x			

	Screening		Treatment	Follow-up - * from completion of chemoradiotherapy								
	Baseline (within 28 days of rand, except for cystoscopy/scans)		Day 1 of each week of chemo-radiotherapy Treatment (or within 3 days prior)	End of treatment (30 days post end of treatment)	3 months* (±7 days)	6 months* (±7 days)	9 months* (±7 days)	12 months* (±7 days)	15 months* (±7 days)	18 months* (±7 days)	21 months* (±7 days)	24 months* (±7 days)
Concomitant Medication	x											
Quality of Life (QoL) Booklet	x			x	x	x	x	x	x	x	x	x
LENT SOMA	x			x	x	x	x	x	x	x	x	x
Survival status					x	x	x	x	x	x	x	x
Blood and Urine for translational studies (optional)[13, 14]	x			x		x						

SCHEDULE OF EVENTS- Standard Chemoradiotherapy + Durvalumab

	Screening		Treatment			Follow up - * from completion of chemoradiotherapy					
	Baseline (within 28 days of rand, except for cystoscopy/scans)	REGISTRATION RANDOMISATION	Day 1 of durvalumab loading dose (or within 3 days prior)	Day 1 of each week of chemo-radiotherapy (weeks 1-3) / Day 1 of chemo-radiotherapy+ Durvalumab (week four only) (or within 3 days prior)	Durvalumab treatment (Week 8 onwards every 4 weeks) (or within 3 days prior)	3, 6, 9 and 12 months* (may be while still on durvalumab treatment) (or within 3 days prior)	End of treatment (30 days post last durvalumab treatment ±7days)	15 months* (±7 days)	18 months* (±7 days)	21 months* (±7 days)	24 months* (±7 days)
Week	- 4 weeks		- 1 week	Day 1 Weeks 1 - 4	Day 1 Weeks 8 - 48	-	-	-	-	-	-
Written Informed Consent	x										
Eligibility	x										
Medical History[1]	x										
Cystoscopy[2]	x (within 56 days of rand)[2]					X (not month 9)			X		X
Physical examination and vital signs[3]	x		X	X	X		X				
Height and weight[4]	X		X	X	X		X				
WHO performance status	X		X	X	X		X	X	X	X	X
Haematology and biochemistry[5]	x		X	X	X		X				
Thyroid function tests (TSH and fT3 and fT4)[6]	x		X	X	X		X				
Urinalysis[7]	x		X	X (week 4 only)	X		X				
Serum cortisol	x						X				
Coagulation parameters[8]	x										
Urine hCG or serum βhCG[9]	x		X	X (week 4 only)	X		X				

	Screening	Treatment			Follow up - * from completion of chemoradiotherapy					
	Baseline (within 28 days of rand, except for cystoscopy/scans)	Day 1 of durvalumab loading dose (or within 3 days prior)	Day 1 of each week of chemo-radiotherapy (weeks 1-3) / Day 1 of chemo-radiotherapy + Durvalumab (week four only) (or within 3 days prior)	Durvalumab treatment (Week 8 onwards every 4 weeks) (or within 3 days prior)	3, 6, 9 and 12 months* (may be while still on durvalumab treatment) (or within 3 days prior)	End of treatment (30 days post last durvalumab treatment ±7 days)	15 months* (±7 days)	18 months* (±7 days)	21 months* (±7 days)	24 months* (±7 days)
Week	- 4 weeks	- 1 week	Day 1 Weeks 1 - 4	Day 1 Weeks 8 - 48	-	-	-	-	-	-
Electrocardiogram (ECG)[10]	x									
CT scan chest, abdomen and pelvis or MRI scan combined with chest CT[11]	x (within 56 days of rand)				X (Not month 9)			X		X
Adverse events and toxicity[12]	x	X	X	X	X	X	X			
Concomitant Medication	x									
QoL Booklet	x				X	X	X	X	X	X
LENT SOMA	x				X	X	X	X	X	X
Survival status					X		X	X	X	X
Blood and Urine for translational studies (optional)[13,14]	x			X (week 8 only)	X (month 6 only)					
DPD test (if not already done)[15]	x									

Key

* Post completion of chemoradiotherapy

[1] Medical history to include details of previous treatment given for muscle invasive bladder cancer, details of any other conditions patient has, smoking and alcohol status.

[2] The 3 months post chemoradiotherapy treatment cystoscopy should be a rigid cystoscopy, however if there is difficulty in arranging a rigid cystoscopy (e.g. a delay of more than 4 weeks), then a flexible cystoscopy should be done so that if there is recurrence the patient can be referred for early cystectomy if appropriate. Subsequent cystoscopies can be rigid or flexible according to local policy. The baseline cystoscopy should be done within 56 days of registrationrandomisation or within 56 days of commencing neo-adjuvant chemotherapy if given. There is no need for a further cystoscopy post neo-adjuvant chemotherapy prior to registrationrandomisation if done within 56 days of starting the neo-adjuvant chemotherapy

[3] Vital signs to include blood pressure, pulse, respiratory rate, and temperature (see section 7.11). At screening a full physical examination is required. During treatment and at end of treatment a targeted physical examination can be performed which should consist of general appearance, cardiovascular, respiratory, abdominal and any other as clinically indicated.

[4] Height at baseline only.

[5] Haematology to include: basophils, eosinophils, haematocrit, haemoglobin, lymphocytes, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, and total white cell count.

Biochemistry to include: albumin, alkaline phosphatase (ALP), amylase, alanine aminotransferase (ALT) or aspartate aminotransferase (AST), calcium, creatinine, glucose, lactate dehydrogenase, lipase, magnesium, potassium, sodium, total bilirubin, total protein, urea or blood urea nitrogen, depending on local practice, uric acid, and gamma glutamyl transferase. Tests for ALT or AST, alkaline phosphatase, and total bilirubin must be conducted and assessed concurrently. If total bilirubin is ≥2×ULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin. It is preferable that both amylase and lipase parameters are assessed. For sites where only 1 of these parameters is routinely measured then either lipase or amylase is acceptable. Creatinine clearance, gamma glutamyl transferase, and magnesium testing are to be performed at baseline and if clinically indicated. If baseline laboratory assessments are performed within 3 days prior to treatment day 1 they do not need to be repeated at day 1. Results for safety bloods must be available and reviewed before commencing an infusion.

[6] Free triiodothyronine (fT3) and free thyroxine (fT4) will only be measured if thyroid stimulating hormone (TSH) is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system. If TSH is measured within 14 days prior to day 1 it does not need to be repeated at day 1.

[7] Urinalysis to include: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, colour and appearance. Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells.

[8] Coagulation tests: prothrombin time, partial thromboplastin time and international normalised ratio (INR).

[9] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the Investigator prior to commencing an infusion

[10] Baseline (single) and abnormal ECG at any time (in triplicate)

[11] The same type of scan needs to be used throughout the trial.

[12] Adverse events and laboratory safety measurements will be graded per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see protocol Appendix 4). All adverse events, whether gradable by CTCAE or not, will also be evaluated for seriousness.

[13] Optional urine and circulating tumour DNA blood samples to be collected at baseline, 30 days post end of chemoradiotherapy treatment (week 8 of durvalumab treatment for research arm), at 6 month follow up visit and at recurrence if it occurs. Full details in the translational sub-studies manual.

[14]An additional in depth translational study will run in selected centres in which urine and blood samples will be collected at baseline, week 1 and week 4 of chemoradiotherapy, 30 days post end of chemoradiotherapy, at 3, 6 and 12 months follow up visit and at recurrence if it occurs. Full details in the translational sub-studies manual.

[15] DPD test – in line with European Medicines Agency advice, all patients must undergo DPD testing before treatment. Prior test results can be used, there is no need to repeat if done prior to study entry.

ABBREVIATIONS

Abbreviation	Explanation
5FU	5-Fluorouracil
AE	Adverse Event
ALP	Alkaline phosphatase
AESI	Adverse Event of Special Interest
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BAUS	British Association of Urological Surgeons
CIS	Carcinoma *in situ*
CHI	Community Health Index
CI	Confidence Interval
CRCTU	Cancer Research UK Clinical Trials Unit
CRF	Case Report Form
CT	Computerised Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DPD	Dihydropyrimidine Dehydrogenase
ECG	Electrocardiogram
FDA	US Drug and Food Administration
fT3	Free Triiodothyronine
fT4	Free Thyroxine
GCP	Good Clinical Practice
GP	General Practitioner
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRCT	High Resolution Computer Tomography
IgG	Immunoglobulin G
ILD	Interstitial Lung Disease
imAE	Immune-Mediated Adverse Event
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IV	Intravenous
KL6	Krebs von den Lungen-6
LDH	Lactate Dehydrogenase
LENT	Late effects of normal tissue
MHRA	Medicines and Healthcare products Regulatory Agency
MMC	Mitomycin C
mNCA	Model Agreement For Non-Commercial Research
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association
ORR	Overall Response Rate
PD-1	Programmed Cell Death Protein 1

Abbreviation	Explanation
PD-L1	Programmed Death Ligand 1
PK	Pharmacokinetic
PSA	Prostate Specific Antigen
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QoL	Quality of Life
REC	Research Ethics Committee
RNA	Ribonucleic Acid
RTOG	Radiation Therapy Oncology Group
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOMA	Late effects toxicity scoring
SP-D	Surfactant Protein D
SpO2	Saturation of Peripheral Oxygen
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMG	Trial Management Group
TSH	Thyroid-Stimulating Hormone
TURBT	Transurethral resection of the bladder tumour
ULN	Upper Limit of Normal
WHO	World Health Organisation

TABLE OF CONTENTS

1 BACKGROUND AND RATIONALE

1.1 Background

Bladder cancer is the ninth most common cancer diagnosed worldwide, with an estimated 429,800 new cases each year and 165,100 cancer-related deaths reported globally in 2012 [1]. In Europe, an estimated 151,297 new cases of bladder cancer were diagnosed in 2012, with an age-standardised incidence rate (per 100,000 persons) of 17.7 for males and 3.5 for females. Overall, the annual crude incidence rate is 20.4/100,000. In 2012, there were 52,395 deaths from bladder cancer with an annual crude mortality rate of 7.1/100,000 (GLOBOCAN 2012). Approximately 90% of urothelial tumours originate in the urinary bladder, 8% originate in the renal pelvis, and 2% originate in the ureter and urethra (National Comprehensive Cancer Network 2016).

In 2014, there were 10,063 new cases of bladder cancer in the UK: 7,307 (73%) in males and 2,756 (27%) in females, giving a male: female ratio of around 27:10 [2, 3].

Overall stage at diagnosis

More bladder cancer patients with a known stage are diagnosed at an early stage (73-76% stage I or II). Only around 24% have muscle invasive bladder cancer at diagnosis [4].

This makes a total of approximately 2,000 patients in the UK with invasive disease at presentation, plus around 20% of patients with non-muscle invasive disease develop invasive recurrence, resulting in the diagnosis of approximately 4,000 cases of muscle invasive bladder cancer each year. Five-year survival rates are around 45% for muscle invasive disease [5,6].

The optimum management strategy for the control of local disease (primary bladder preservation or radical cystectomy) remains to be determined. Neoadjuvant chemotherapy prior to surgery or radiotherapy has been shown to improve survival rates [7-9]. Radical radiotherapy in combination with synchronous chemotherapy has shown to be an effective therapy [10-13] reserving salvage cystectomy for local failure especially in more elderly patients or in those with significant co-morbidity. With radiotherapy alone, between 15% and 30% of patients will ultimately lose their bladders to local failure [10,14]. In a retrospective series of 398 patients managed in Yorkshire (T2−T4, 96%), outcomes following radical cystectomy and radical radiotherapy were compared. 5-year overall survival was 36.5% (95% Confidence Interval (CI), 27.4−45.6) for radical cystectomy and 37.4% (95% CI, 32.3−42.6) for radical radiotherapy [6].

Following radical radiotherapy as sole therapy, 43.6% of patients experienced disease recurrence within the bladder and 18.8% underwent salvage cystectomy [6]. In the BC2001 trial, the 2-year cystectomy rate was 11.7% (95% CI: 7.3%-18.4%), with few invasive recurrences occurring beyond 2 years. Therefore, even in the absence of more effective systemic therapy for metastasis, improving bladder preservation will lead to an improved quality of life (QoL) for many patients. From the British Association of Urological Surgeons (BAUS) Cancer Registry we can estimate that approximately 50% of patients with stage 2 or stage 3 disease will receive radical radiotherapy as their main treatment – approximately 2,000 patients per year in the UK – with a similar number undergoing surgery.

1.2 Trial Rationale

1.2.1 Chemoradiotherapy

Chemoradiotherapy of the urinary bladder has been adopted by national and international guidelines and is a recognised standard of care for patients with muscle invasive urothelial cancer.

The results of the BC2001 randomised phase III comparison of radiotherapy alone with chemoradiotherapy with the 5-Fluorouracil (5FU)/ Mitomycin C (MMC) regimen have been recently updated. With 118 months median follow-up, adding chemotherapy to full dose radiotherapy was associated with improved 5-year bladder cancer specific survival (adjusted Hazard Ratio (HR) (95% CI): 0.73 (0.54 – 0.99), p=0.043) with a strong trend to improved overall survival (adjusted HR (95%CI): 0.81 (0.62 – 1.04), p=0.100) [15]. The previously reported improvement in the primary endpoint of loco-regional disease free survival was maintained (adjusted HR (95%CI): 0.59 (0.41 – 0.83), p=0.003) mainly driven as in the primary analysis by substantially improved invasive loco-regional control (adjusted HR (95%CI): 0.52 (0.33 – 0.81), p=0.004). Reflecting the improved loco-regional control, there was a significant reduction in the salvage cystectomy rate with concomitant chemotherapy (HR 0.54, 95% CI 0.31-0.95, p=0.03).

In both the primary[10] and 10 year updated[15] outcomes in BC2001, a 33% reduction in the risk of loco-regional recurrence was seen with a reduction of almost 50% in invasive recurrence. This improvement was consistent in pre-planned subgroup analyses and was not affected by prior neo-adjuvant chemotherapy, suggesting that neoadjuvant and concomitant chemotherapy confer separate benefits on distant and local control respectively. The improvement in loco-regional control was achieved with modest increases in acute toxicity that did not reach statistical significance with respect to grade 3 or 4 outcomes. We were particularly concerned that the more intensive therapy, particularly when given after neoadjuvant chemotherapy, did not result in impaired late bladder function. Late toxicity was measured using Radiation Therapy Oncology Group (RTOG) and late effects of normal tissue (LENT) and late effects toxicity scoring (SOMA) scales; neither measure showed a clinically significant increase with combination therapy. Likewise we were unable to detect any significant impact on bladder volume. These results are thus consistent with the bladder preservation strategy described maintaining good post treatment bladder function. This regimen thus forms the basis of the treatment cohorts in the current trial.

We have also recently reported long term QoL outcomes from BC2001 [16]. These show a transient dip in QoL at completion of chemo-radiation that recovered back to baseline by 3 months. There was no impact seen on patient reported QoL from the addition of 5FU/MMC to radiotherapy alone.

The 5FU/MMC chemoradiotherapy combination is thus well described as a base for evaluation of immune-oncology based protocols with robust long term data on safety and efficacy. The combination is well established as a standard of care within the UK and also within the USA, particularly in leading centres such as Massachusetts General Hospital/Harvard Medical School where it is one of the standard therapies used (Anthony Zeitman, personal communication).

Chemotherapy and immunotherapy

Urothelial cancer is highly immunogenic. Treatment with Programmed Death Ligand 1 (PD-L1) and Programmed Cell Death Protein 1 (PD-1) inhibiting agents have shown significant improvements achieving unprecedented durable responses and increased survival in patients with locally advanced or metastatic urothelial cancer with disease progression after platinum-based chemotherapy.

The combination of chemotherapy and immunotherapy is feasible and currently under investigation in multiple trials in a range of cancers, including bladder. Basically, there are two major ways for chemotherapy to promote tumour immunity. Firstly, by inducing immunogenic cell death, and secondly, by disrupting strategies that tumours use to evade immune recognition. This is broadly dependent on the drug, its dose, and the schedule of chemotherapy administration in relation to antigen exposure or release[17].

Radiotherapy and the immune system

Radiotherapy causes irreversible double-stranded deoxyribonucleic acid (DNA) damage which results in cytotoxicity and consequently can promote an anti-tumour immune response [17]. The underlying mechanisms are still unclear.

Radiation also affects the tumour microenvironment by inducing chemokines, which in turn promote recruitment of effector (CD8) and helper (CD4) T cells [18].

The so called “abscopal“ effect is based on radiation-induced immunogenic cell death and its effect on the tumour microenvironment which not only causes a local effect but may also induce clinical tumour regression at a site distant to or outside of the radiotherapy field[16]. Combining radiotherapy and immunotherapy has the potential to produce long term systemic effects and responses [19-22].

Combination radiotherapy and immunotherapy for the treatment of bladder cancer

The combination of radiotherapy and immunotherapy has shown promise in many tumour entities. Radiotherapy has the potential to augment the host’s immune response to cancer. Despite the common belief that radiotherapy is immunosuppressive, there is now evidence that radiotherapy leads to immunogenic cell death and stimulates a systemic anti-tumour immune response [23]. The discovery of the immunogenicity of radiotherapy has now renewed interest in combining immunotherapy with radiotherapy to further increase local and systemic anti-tumour immune responses and thus leading to improved outcomes [24,25].

Radiation in combination with checkpoint inhibitors (anti-cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) or anti PD1/ PDL1 antibodies) appears to be a promising approach[26] and is being explored in several ongoing trials including urothelial cancer. One example is PLUMMB (Pembrolizumab in Muscle Invasive/Metastatic Bladder Cancer, NCT02560636), a phase I trial to investigate the safety, tolerability, and effectiveness of pembrolizumab used in combination with radiotherapy. There is also an ongoing phase 2 trial (NCT02621151) assessing the efficacy of pembrolizumab with concurrent radiation and gemcitabine in the management of patients with muscle-invasive urothelial cancer and the aim of bladder preservation.

Currently, there is no consensus about the most efficacious fractionation of radiotherapy together with immunotherapy. The ability of radiotherapy to induce priming of anti-tumour T cells is influenced by the pre-existing tumour microenvironment, by the effects of radiotherapy on immune cells and other components that play a role in the equilibrium.

In preclinical experiments it became obvious that the host immune responses, not the radiosensitivity of cancer cells, correlate with efficacy of radiation therapy [17].

Concerning the dosing and scheduling of immunotherapy agents and the sequencing with radiotherapy there are still many unknowns and multiple studies are ongoing. Preliminary data seems to support concurrent administration [27].

Radiotherapy and durvalumab

Currently, a considerable number of trials combining immunotherapy and radiotherapy in multiple cancers are ongoing and recruiting patients. A phase Ib/II Study of Concurrent Durvalumab and Radiation Therapy (DUART) followed by adjuvant durvalumab in patients with urothelial cancer (T2-4 N0-2 M0) of the bladder is recruiting patients in the US (NCT02891161, Big Ten Cancer Research Consortium BTCRC-GU15-023). In this single centre study ten patients with palliative radiotherapy combined with durvalumab (10 mg/kg every 2 weeks) were analysed. Treatment was well tolerated (NCT01693562; EudraCT number: 2012-002206-52) [28].

Durvalumab alone or combined with chemotherapy or other immunotherapy together with radiotherapy is being investigated in head and neck cancer, glioblastoma, small cell lung cancer (NCT02701400), and non-small cell lung cancer (Swiss study tracker, SNCTP000001480).

Our hypothesis is that the known synergistic effects of chemotherapy and radiotherapy will be augmented by the addition of durvalumab. The consecutive use of adjuvant durvalumab for 12 months after completion of chemoradiotherapy plus durvalumab of the bladder we hypothesise could prevent distant relapse. This treatment concept would result in improved local control and, even more importantly, in improved metastasis free survival and overall survival times.

1.2.2 Durvalumab

Durvalumab is an engineered anti-PD-L1 antibody. The agent is currently used as monotherapy (20 mg/kg intravenous (IV) or flat dose 1500mg every 4 weeks) and in immunotherapy combinations in several ongoing and planned trials. The half-life of durvalumab is approximately 17 days.

Durvalumab background, non-clinical and clinical experience

Durvalumab is a human monoclonal antibody of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). As durvalumab is an engineered monoclonal antibody, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1 with PD-1 and cluster of differentiation 80 (CD80).

As of 12 July 2017, a total of 4067 patients have been exposed to 1 or more doses of durvalumab in ongoing open-label AstraZeneca -sponsored Phase I-III monotherapy and combination therapy studies across all indications.

Rationale for fixed dosing

A population pharmacokinetic (PK) model was developed for durvalumab using monotherapy data from a Phase I study (study 1108; N=292; doses= 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W); solid tumours). Population PK analysis indicated only minor impact of body weight on the PK of durvalumab (coefficient of ≤0.5). The impact of body weight-based (10 mg/kg Q2W or 20 mg/kg every 4 weeks (Q4W) and fixed dosing (750 mg Q2W or 1500 mg Q4W) of durvalumab was evaluated by comparing predicted steady state PK exposures (AUCss,0-28, Cmax,ss, and Cmin,sss) 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 ~75 kg). A total of 1000 patients were simulated using body weight distribution of 40–120 kg. Simulation results demonstrate that body weight -based (10 mg/kg Q2W) and fixed dosing (750 mg/kg 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).[29,30]

Similar findings have been reported by others [31-34]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies [32]. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in PK/pharmacodynamics parameters [33]. 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, we considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

In the study 1108, 42 pre-treated patients received durvalumab, the overall response rate was 31%, the median time to response was 6.3 weeks (95% CI, 5.6 to 12.1 weeks) [29]. Twelve of 13 (92.3%) had an ongoing response at last follow-up. Only 5% of patients had grade 3-4 toxicities and 64% any grade toxicity.

Concerns associated with the expected approval of these immunotherapies in Europe and the UK are mainly about the high costs and reimbursement, given only a minority of patients seem to benefit. Treatment with PD-1 or PD-L1 inhibitors (immunotherapy, check point inhibitors) in second line has become the new standard of care in the US, Europe and other parts of the world. Atezolizumab and pembrolizumab for urothelial cancer of the bladder progressing after platinum based chemotherapy, are currently subject of a National Institute for Health and Care Excellence (NICE) Single Technology Appraisals.

Although the overall response rate with immunotherapy in unselected metastatic urothelial carcinoma patients at second line are only around 15-20%, responding patients derive significant long term benefit and are the drivers of the overall survival improvement.

In May 2016, the first immunotherapy, atezolizumab, an anti-PD-L1 antibody, was US Food and Drug Administration (FDA) approved for patients with metastatic urothelial carcinoma, progressing, after platinum based chemotherapy or those unfit for chemotherapy. This was based on a response rate of 15% [35].

In May 2017, the humanised IgG4 anti-PD-1 antibody pembrolizumab (MK-3475), gained FDA approval based on the first randomised controlled phase III trial ever conducted in urothelial cancer patients in the second line setting and using an active treatment comparator [36]. In this trial pembrolizumab was superior to Investigator-choice chemotherapy for the primary endpoint of overall survival. In addition, overall response rate and in particular the duration of response are important outcome measures for urothelial cancer and with immunotherapy. The overall response rate was 21.1 % with pembrolizumab, of which 7.0% were complete responses, compared to 11.4 % overall response rate in the chemotherapy arm. The median duration of response for patients treated with pembrolizumab had not yet been reached at the time of analysis (range: 1.6+ to 15.6+ months), with 68 % of responses estimated to last for ≥ 12 months. In the chemotherapy arm, the median duration of response was 4.3 months (range: 1.4+ to 15.4+ months) – with 35 % of responses estimated to last for ≥ 12 months.

Overall risks of immunotherapies

Monoclonal antibodies directed against immune checkpoint proteins, such as PD-L1 as well as those directed against PD-1 or Cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), aim to boost endogenous immune responses directed against tumour cells. By stimulating the immune system however, there is the potential for adverse effects on other tissues.

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory or immune mediated mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine therapy. These immune mediated effects can occur in nearly any organ system, and are most commonly seen as gastrointestinal AEs such as colitis and diarrhoea, pneumonitis/interstitial lung disease (ILD), hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis and endocrinopathies including hypo- and hyper-thyroidism.

Overall risks with durvalumab

The identified risks with durvalumab monotherapy include the following: cough/productive cough, pneumonitis, ILD, dysphonia, alanine transaminase (ALT) or aspartate aminotransferase (AST) increased, hepatitis, diarrhoea, abdominal pain, colitis, cystitis non-infective, hypothyroidism, hyperthyroidism, blood Thyroid-Stimulating Hormone (TSH) increased, blood TSH decreased, adrenal insufficiency, Type 1 diabetes mellitus, hypophysitis/hypopituitarism, diabetes insipidus, pancreatitis, blood creatinine increased, dysuria, nephritis, rash, pruritus, psoriasis, night sweats, dermatitis, myocarditis, pyrexia, oedema peripheral, upper respiratory tract infections, pneumonia, oral candidiasis, dental and oral soft tissue infections, influenza, myalgia, arthralgia, myositis, polymyositis and infusion- related reaction.

Potential risks for durvalumab include:, encephalitis, subcutaneous injection site reaction, other rare or less frequent events with potential immune mediated aetiology, e.g. pericarditis sarcoidosis, uveitis and other events involving the eye (e.g.keratitis and optic neuritis), skin (e.g.scleroderma and vitiligo), and haematological (e.g., haemolytic anaemia and immune thrombocytopenic purpura), rheumatological events (polymyalgia rheumatic and autoimmune arthritis) and neuropathy/neuromuscular toxicities (e.g. myasthenia gravis, Guillain Barre syndrome). Hypersensitivity reactions including anaphylaxis and allergic reaction, cytokine release syndrome, immune complex disease, and serious infections.

In monotherapy clinical studies, Adverse Events (AE) (all grades) reported very commonly (≥15% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhoea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral oedema, headache, rash, and pruritus. Approximately 9.4% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6.5% of patients experienced a Serious Adverse Event (SAE) that was considered to be related to durvalumab by the Investigator.

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

A detailed summary of durvalumab AE data can be found in the current version of the durvalumab Summary of Product Characteristics (SmPC).

Recently, three other checkpoint inhibitors, durvalumab, nivolumab and avelumab gained FDA approval. All three approvals were based on single arm trials. So far, durvalumab is the only PD-L1 inhibitor given at 4 week intervals which adds to patient convenience and cost effectiveness.

1.3 Trial Justification

We hypothesise that the known synergistic effects of chemotherapy and radiotherapy are augmented by the addition of further therapies and specifically that checkpoint inhibitors like durvalumab can augment the effect of radiotherapy and chemotherapy in muscle invasive bladder cancer and thus can improve local control and reduce systemic spread.

The Rad-IO trial will therefore assess the combination of synchronous and adjuvant durvalumab with chemoradiotherapy using 5FU and MMC in a multi-stage design.

2 AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

2.1.1 Aims

Rad-IO is a multi-stage clinical trial which aims to determine whether patients with muscle invasive bladder cancer can safely be administered durvalumab with standard chemoradiotherapy without encountering excessive toxicity or compromising the chemoradiotherapy regimen. This protocol amendment follows confirmation that the schedule is feasible and safe in node negative patients. The amendment will add node positive patients with an initial feasibility phase followed by an efficacy based assessment.

2.1.2 Objectives

To evaluate whether durvalumab added to standard chemoradiotherapy is safe, feasible and improves outcomes. Durvalumab will be the agent evaluated.

If initial feasibility and safety outcomes are positive, we will expand to a third efficacy stage with overall survival time as the primary outcome.

The intention is for the trial to serve as a platform for evaluating additional therapies versus the current standard of care. Immunotherapies under consideration for future comparisons include the monoclonal antibodies tremelimumab and cetuximab and dose escalation of radiotherapy to the tumour bearing area of the bladder.

No more than 5 new therapies will be introduced in this trial.

Progression from the phase I/II stages of the trial to phase III will be according to a MAMS design as exemplified by STAMPEDE [37,38] and the statistical calculation for sample size will be determined according to the data from phase I/II elements of the trial.

Stage 1 of the trial will evaluate the feasibility and safety of durvalumab added to standard chemoradiotherapy. Efficacy analysis in Stage 2 can detect if there is any signal of treatment efficacy for the new therapy to warrant further research.

2.2 Outcome Measures

2.2.1 Stage 1: pilot

Safety

To evaluate the safety of the addition of durvalumab to standard chemoradiotherapy (see section 14.1 for definitions).

Feasibility

The impact of combined durvalumab and chemotherapy treatment on the radiotherapy treatment (see section 14.1 for definitions).

2.2.2 Stage 2: efficacy

The primary outcome will be disease free survival rate at 12 months post chemoradiotherapy (see section 14.1 for definitions).

Secondary outcome measures include:

- Toxicity
- Delivery of core targeted therapy (chemoradiotherapy)
- Time to local muscle invasive progression
- Time to local non-muscle invasive progression
- Time to regional nodal progression
- Time to local progression
- Time to distant progression
- Cystectomy within one year
- Quality of Life
- Overall survival time
- Disease-free survival time
- Percentage of target drug delivery

Refer to section 14.1 for definitions.

2.2.3 Stage 3: efficacy

Note, this stage is not funded as part of the current trial. However, subject to satisfactory evidence of efficacy in the first efficacy stage, we will seek further funding to expand the trial to a second efficacy stage. The primary outcome of which will be overall survival time. Secondary outcomes include:

- Acute and late toxicity
- Percentage of target drug delivery
- Time to local progression
- Time to distant progression
- Cystectomy rate
- Disease-free survival time
- Quality of Life

Definition and recording of recurrence and disease progression:

- **Local non muscle invasive progression in bladder**

  Assessed by cystoscopic findings for bladder recurrence plus concurrent pathology

  - Bladder recurrence will be classified as non-invasive if ≤ pT1, Carcinoma *In Situ* (CIS) or both

- **Local muscle invasive progression in bladder**

  Assessed by cystoscopic findings for bladder recurrence plus concurrent pathology

  - Clinical or pathological evidence of muscle wall invasion ≥ pT2

- **Regional nodal and distant progression**

  Assessed by Computerised Tomography (CT)/ Magnetic Resonance Imaging (MRI) scans. Use of FDG-PET is permitted for both initial staging and for assessment of progression.

  - Regional recurrence – defined as recurrence in lymph nodes within the true pelvis
  - Distant - defined as any recurrence beyond the true pelvis including common iliac and para aortic lymph nodes, or recurrence in non-nodal, non-vesicular pelvic structures such as bone

Details of all progression must be included on the Case Report Form (CRF) along with their subsequent clinical response.

3 TRIAL DESIGN

Rad-IO is an open-label, multicentre, multi-stage clinical trial.

3.1 Stage 1: Pilot

The first 6 patients in the research arm will be evaluated for feasibility and safety when they have completed their 3 month follow up visit post chemoradiotherapy. Further feasibility and safety evaluations will be carried out following the 3 month follow up visit for 6 research arm patients who received neo-adjuvant chemotherapy and for 6 research arm patients who didn't receive neo-adjuvant chemotherapy Following the change in the inclusion criteria to include N1-2 patients, further safety evaluations will be carried out when 6 N1-2 research arm patients have completed their 3 month follow up visit post chemoradiotherapy.. Recruitment will continue while safety and feasibility data is collected. There are no pre-defined stopping rules for stage 1.

3.2 Stage 2: Efficacy

This stage is designed as a phase II trial using disease free survival rate at 12 months post chemoradiotherapy. Patients who are assessed for stage 1 will also be included in the analysis for stage 2. Stage 2 was initially designed as a randomised comparison to allow for expansion to a third definitive stage which would focus on efficacy, with overall survival time as the primary outcome.

The original randomised design set the allocation ratio as 1:2 and, whilst patients were recruited onto the initial design, following the Covid-19 pandemic the rate of recruitment was too slow to make this design feasible. Therefore, the protocol has been amended to reflect a new trial design; changing the efficacy stage to a single arm trial with the disease-free survival rate at 12 months used as the reference assessment point. Target disease control rates will be based on data from the BC2001 trial (recently updated with 10 year outcomes [37]) and further research is subject to a significant efficacy signal in this stage plus the provision of further funding.

Given the small number of participants who were randomised to the control arm whilst the trial was recruiting to the initial design, only descriptive analysis on the safety and efficacy outcome can be drawn and no comparison with the experimental arm will be conducted. For analysis on the single arm trial design, efficacy will be evaluated at stage 2 for all patients who receive durvalumab, and the first 6 N1-2 patients recruited will be assessed for the feasibility and safety of durvalumab as outlined in section 3.1.

Changes to the study design were made for practical and ethical reasons surrounding recruitment and study power including ensuring sufficient patients, not recruiting excessively and maximising patient data already collected. In consideration of any potential bias that may arise from changing the design, all patient characteristics will be presented split by which stage they were recruited into and statistical methodologies will be explored to account for potential biases.

The trial could also be expanded to include additional agents in the evaluation in a similar MAMS design. Current candidates for further arms include radiotherapy dose escalation (depending on the outcomes for the RAIDER trial NCT02447549) or the combination of durvalumab and tremelimumab currently under evaluation in other disease sites. Addition of new arms will be via substantial amendment.

3.3 Trial Duration

For stages 1 and 2, the initial design envisaged between 132 and 159 patients to be recruited from approximately 20 UK centres over a period of two years, the trial would continue until all patients have been followed up for a minimum of five years after randomisation. However, recruitment has proved challenging in the post-Covid-19 environment despite favourable toxicity and feasibility data both from this trial as well as from other similar trials combining radiotherapy and immune checkpoint inhibition. The trial is redesigned as a single-arm trial, with a target sample size of 52 research arm patients from approximately 20 UK centres. Patients who are non-evaluable (e.g., dropped out before the primary outcome is measured) will be included in the safety and toxicity analyses. The trial will continue until all patients have been followed up for a minimum of two years after completion of chemoradiotherapy.

4 ELIGIBILITY

Eligibility should be confirmed at the point of registrationrandomisation into the trial.

4.1 Inclusion Criteria

- Age ≥18 years old
- Body weight >30kg
- Histologically proven bladder carcinoma (adenocarcinoma, transitional cell carcinoma or squamous cell carcinoma)
- Localised muscle invasive carcinoma either surgically or by imaging (T2-T4a N0 M0, or T2-T4a N1-2 M0 see Appendix 1)
- World Health Organisation (WHO) performance status grade 0 to 1
- Adequate organ and marrow function as defined below:
    - Haemoglobin ≥100 g/L
    - Absolute neutrophil count ≥1.5 x 10^9/L
    - Platelet count ≥100 x 10^9/L
    - Serum bilirubin ≤1.5 x institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their investigator. In cases of confirmed Gilbert's syndrome where serum bilirubin levels are ≥5 x ULN, referral to a liver specialist may be needed ahead of inclusion. Care should be taken to exclude other causes of raised bilirubin if there is any doubt, even in cases of known Gilbert's Syndrome.
    - ALT or AST ≤2.5 x institutional ULN
    - Calculated creatinine clearance >40 mL/min by the Cockcroft-Gault formula[39]
- Available for long-term follow-up
- Fit for a radical course of radiotherapy
- Must have a life expectancy of at least 12 weeks
- Evidence of post-menopausal status, or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    - Women <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal

treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    - Women ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
- Male and female patients of childbearing age willing to use highly effective contraception
- Patient is willing and able to comply with the protocol for the duration of the trial including undergoing treatment and scheduled visits and examinations including follow up
- Written informed consent obtained from the patient prior to performing any protocol-related procedures, including screening evaluations

4.2 Exclusion Criteria

- Uncontrolled systemic disease which would preclude the patient from participating in the trial including severe or uncontrolled cardiovascular disease (congestive heart failure New York Heart Association (NYHA) III or IV, unstable angina pectoris, history of myocardial infarction within the last 12 months, significant arrhythmias)
- Previous pelvic radiotherapy
- Bilateral hip replacements compromising accurate radiotherapy planning (with appropriate technical compensation such as MRI based planning, these patients may be included)
- Evidence of significant clinical disorder, or laboratory finding which, in the opinion of the investigator, makes it undesirable for the patient to participate in the trial
- Untreated hydronephrosis with complete blockage of drainage from the affected kidney. Patients with hydronephrosis can be included if the kidney/ureter has been stented or nephrostomy has been inserted or if the blockage is only partial.
- Prior participation in another trial (within the previous 30 days) or concurrent enrolment in another clinical trial, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
- Any unresolved toxicity Common Terminology Criteria for Adverse Events (CTCAE) Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
    - Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Trial Office.
    - Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Trial Office.
- Any previous treatment with a PD-1 or PD-L1 inhibitor, including durvalumab.
- Current or prior use of immunosuppressive medication within 14 days prior to registrationrandomisation†, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. The following are exceptions to this criterion:
    - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., 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 (e.g., CT scan premedication)
- Current use of brivudin, sorivudin, and analogues
- Patients with an active non-infective pneumonitis

- History of active primary immunodeficiency
- Any concurrent chemotherapy*, Investigational Medicinal Product (IMP), biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable
- Major surgical procedure other than transurethral resection of the bladder tumour (TURBT), as defined by the Investigator, within 30 days prior to registrationrandomisation†
- History of allogenic organ transplantation
- Active autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, hypophysitis, uveitis, etc]) requiring systemic treatment within 3 months prior to registrationrandomisation or documented history of clinically severe autoimmune or inflammatory disorder.

  The following are exceptions to this criterion:

  - Patients with vitiligo or alopecia
  - Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
  - Any chronic condition that does not require systemic therapy
  - Patients without active severe disease in the last 5 years may be included but only after consultation with the trial physician
  - Patients with coeliac disease controlled by diet alone

- Uncontrolled intercurrent illness, including but not limited to, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal 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 patient to give written informed consent
- History of another primary malignancy except for:

  - Malignancy treated with curative intent and with no known active disease ≥2 years before registrationrandomisation and of low potential risk for recurrence
  - Non-muscle invasive bladder tumours
  - NCCN low risk prostate cancer (T1/T2a, Gleason 6 PSA <10)
  - Adequately treated non-melanoma skin cancer or lentigo maligna

- Metastatic disease
- Acute, serious (e.g. Herpes zoster, chickenpox) or active infection including TB (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), evidence of prior, quiescent TB is not an exclusion, hepatitis B (known positive Hepatitis B Virus (HBV) surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive human immunodeficiency virus (HIV) 1/2 antibodies). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV Ribonucleic Acid (RNA).
- Bone marrow depression after radiotherapy or treatment with other antineoplastic agents
- Pancytopenia or isolated leucopoenia/thrombopenia or haemorrhagic diathesis
- Receipt of live attenuated vaccine within 30 days prior to registrationrandomisation†. Note: patients should not receive live vaccine whilst receiving trial drugs and up to 3 months after the last dose of IMP. Note: vaccines commonly used for COVID-19 and influenza are all permitted.
- Serious liver impairment

- Known homozygotic for dihydropyrimidine or known complete absence of dihydropyrimidine dehydrogenase (DPD) activity
- Patients undergoing management for non-malignant disease which may interact with any of the trial treatments
- Female patients who are breastfeeding
- Known allergy or hypersensitivity to any of the trial IMPs or any of the trial drug excipients
- Known clinical contra-indications to any of the trial IMPs
- Judgement by the Investigator that the patient is unsuitable to participate in the trial and the patient is unlikely to comply with trial procedures, restrictions and requirements

Please Note:

* Patients may have received neo-adjuvant according to local clinical practice, with as a minimum no radiological progression from baseline pre neo-adjuvant imaging. There is no need to repeat the cystoscopy post neo-adjuvant chemotherapy if the pre-chemotherapy assessment was done within 56 days of starting neo-adjuvant chemotherapy.

† Patients should not receive immunosuppressive medication, live attenuated vaccine or undergo a major surgical procedure post-registrationrandomisation and prior to commencing trial treatment, see also section 7.7 for prohibited concomitant medication

5 SCREENING AND CONSENT

5.1 Screening

Potential patients will be identified via clinic referrals or Multi-disciplinary Team meetings. The Investigators will ensure that a screening log of all potential patients (i.e., only those with muscle invasive bladder cancer, not all bladder cancer patients) is maintained. This log will include limited information about the potential patient (e.g. date of birth and sex), and the date and outcome of the screening process (e.g. enrolled into trial, reason for ineligibility, or refused to participate).

See the Schedule of Events and section 7.11 for details of the screening tests which need to be completed prior to trial entry.

Please Note: Patients who have received neo-adjuvant chemotherapy are eligible for this study.

An Eligibility Checklist should be completed for each patient. Baseline pathology and screening data will be captured on a Baseline Form.

5.2 Informed Consent

It is the responsibility of the Investigator or an appropriately trained designee who has been delegated this task on the Site Signature and Delegation Log (e.g. Registrar or Clinical Research Fellow) to obtain written informed consent from each patient prior to performing any trial-related procedure. A Patient Information Sheet is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial, to the patient. The Investigator must also stress that the patient is completely free to refuse to take part in, or withdraw from, the trial at any time. The patient must be given ample time (at least 24 hours) to read the Patient Information Sheet and to discuss their participation in the trial with others outside of the site research team. The patient must be given an opportunity to ask questions, which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial they must sign and date the latest version of the Informed Consent Form. The Investigator or designee must then sign and date the form. To minimise the need for additional visits, the consent form and patient information sheet can be

provided to the patient to take away and read. Consent can be confirmed verbally,, where a patient consents verbally, they will have to confirm this electronically either via text, email with or without a photograph or scan of the signed Informed Consent Forms, by audio-recorded message (e.g. answerphone) or by post. Unless the wet copies of the forms were posted to the research team, patients who provide consent remotely should bring the wet copies of the forms along to their next hospital appointment. The designated research team member will then countersign the original forms. This verbal and electronic consent will be annotated in the patient's medical notes.' A copy of the Informed Consent Form must be given to the patient, a copy filed in the hospital notes, and the original placed in the Investigator Site File. Once the patient has been entered into the trial, the patient's trial number must be entered on the Informed Consent Form maintained in the Investigator Site File. In addition, if the patient has given explicit consent, a copy of the signed Informed Consent Form must be sent to the Trial Office for review.

Details of the informed consent discussions must be recorded in the patient's medical notes, these must include date of, and information regarding, the initial discussion; and the date informed consent was obtained, with the name of the trial and the version number of the Patient Information Sheet and Informed Consent Form used. Throughout the trial, the patient must have the opportunity to ask questions about the trial. In addition, any new information which may be relevant to the patient's continued participation in the trial must be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient, in which case the process described above must be followed, and the patient's right to withdraw from the trial must continue to be respected.

Electronic copies of the Patient Information Sheet and Informed Consent Form are available from the Trial Office and must be printed or photocopied onto the headed paper of the local institution.

Patients will be asked to consent for the collection of tumour tissue, additional blood and urine samples and access to imaging for translational work (see section 9).

If the patient agrees to enter the trial and, with their prior consent, their General Practitioner (GP) must also be informed that they are taking part. A GP Letter is provided electronically for this purpose.

Following registrationrandomisation (but prior to commencing treatment) patients opting to participate in the optional Quality of Life (QoL) Sub-study should be given the QoL Booklets. Prior to completing the baseline QoL Booklets a member of the Research Team should discuss the completion of the QoL Booklet with the patient and answer any questions they may have. Once the Booklets have been completed by the patient the Site Research Team should check to make sure that all of the questions have been completed and that in particular that the date the QoL Booklet was completed has been accurately recorded.

Patients should also be given the LENT SOMA questionnaire for completion.

The baseline LENT SOMA questionnaire and if applicable the QoL Booklet should be returned to the Trial Office by using the pre-paid envelope provided.

6 TRIAL ENTRY

As soon as the patient is considered eligible the Investigator should enter the patient into the trial by completing the RegistrationRandomisation Form on the electronic Remote Data Capture (eRDC) system.

https://www.cancertrials.bham.ac.uk

Login details for the website will be provided by the Trial Office as part of site initiation.

If the electronic Case Report Form system is unavailable registration can also be performed by telephone by completing a paper RegistrationRandomisation Form and calling the Trial Office on:

☎ 0121 414 3793 or 0121 415 8544

9am-5pm Monday to Friday

The following information will be requested at registrationrandomisation:

- Name of site, Investigator and person registering/randomising the patient
- Patient's full name, full postal address, date of birth, National Health Service (NHS) number, or in Scotland the Community Health Index (CHI), and hospital number
- Confirmation that the patient is eligible for the trial

Randomisation will be performed according to a 1:2 ratio (Control Arm vs. Research Arm) using a minimisation program with the following stratification variables:

- Neo-adjuvant chemotherapy vs. No neo-adjuvant chemotherapy

Patients in the feasibility stage will be allocated to one of the two treatment arms:

- Control Arm (MMC + 5FU plus radiotherapy)
- Research Arm (durvalumab plus MMC + 5FU plus radiotherapy)

The randomisation is not blinded, and therefore both participant and the Site Research Team will know which treatment pathway has been allocated to the patient.

At the end of the registrationrandomisation procedure the patient will be allocated to the appropriate treatment arm (Control Arm or Research Arm) and given a unique trial number. A RegistrationRandomisation Confirmation Report should be printed and filed in the Investigator Site File.

The Responsible Pharmacist will be notified by the Trial Office via e-mail that a patient has been entered onto the trial. They will be instructed to log onto the eRDC system where they will be able to print a Pharmacy Notification Report which will provide details of the patient's treatment allocation, this will authorize the Responsible Pharmacist to release trial medication to the patient.

The completed and signed Eligibility Checklist, RegistrationRandomisation Form (if completed on paper), signed Informed Consent Form, the LENT SOMA questionnaire and (if applicable) QoL Booklet should then be sent to the Trial Office in the post.

7 TREATMENT DETAILS

Prior to trial entry patients may have received neo-adjuvant chemotherapy according to local clinical practice.

Treatment should start as soon as possible after registrationrandomisation and within a maximum of 4 weeks. Patients receiving neo-adjuvant chemotherapy prior to trial participation should start trial treatment as soon as possible after completing neo-adjuvant treatment and sufficient resolution of any relevant side

effects. Trial treatment should start no later than 3 months after neo-adjuvant treatment has completed (see also section 7.5.1).

7.1 Trial Treatment

Control Arm:

Radical radiotherapy to the whole bladder, 55 Gy in 20 fractions beginning day 1 of week 1 and given concurrently over 4 weeks, plus synchronous chemotherapy with mitomycin C 12mg/m^2 given day 1 week 1 and 5FU 500mg/m^2/day given week 1 days 1-5 and week 4 days 22-26 by continuous intravenous infusion.

Research Arm:

One week prior* to starting synchronous chemoradiotherapy patients will receive a fixed loading dose of 1500 mg durvalumab followed by a dose of 1500mg durvalumab every 4 weeks for up to a maximum of 12 months with the last administration on week 48 (i.e. 13 doses in total) unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

**Administration of the loading dose must occur between 5 and 10 days before the initiation of chemoradiotherapy*

Please note: If a patient's weight falls to 30kg or below the patient should receive weight-based dosing equivalent to 20mg/kg of durvalumab every 4 weeks until the weight improves to >30kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg every 4 weeks.

7.2 Investigational Medicinal Products

MMC, 5FU and durvalumab will all be classed as IMPs for this trial.

Full details of the IMPs are contained in the Pharmacy Manual, which also lists the Pharmacists' responsibilities, details of labelling, record keeping for prescribing, dispensing, and accountability of the IMPs. The Pharmacy Manual will be sent to the Responsible Pharmacist.

7.2.1 Mitomycin C

MMC is a chemotherapeutic agent licenced for use in bladder cancer. It is off patent and is available from a number of manufacturers. It acts as an anti-tumour antibiotic. It is activated in the tissues to an alkylating agent, which disrupts DNA in cancer cells by forming a complex with DNA, and also acts by inhibiting division of cancer cells, by interfering with the biosynthesis of DNA.

7.2.2 5- Fluorouracil

5FU is an antineoplastic agent licensed by the European Medicines Agency for use in the management of common malignancies, but not specifically bladder cancer. 5FU is an analogue of uracil, a component of RNA. The drug is believed to function as an antimetabolite. After intracellular conversion to the active deoxynucleotide, it interferes with the synthesis of DNA, by blocking the conversion of deoxyuridylic acid to thymidylic acid by the cellular enzyme thymidylate synthetase. Fluorouracil may also interfere with RNA synthesis.

7.2.3 Durvalumab

Durvalumab is a human monoclonal antibody that blocks PD-L1. It is manufactured by AstraZeneca and is licenced in the UK for the treatment of locally advanced, unresectable non-small cell lung cancer in adults whose tumours express PD-L1 on ≥1% of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy. For the purposes of this trial it is being used outside of its licenced indication.

7.2.3.1 Formulation, packaging and storage of durvalumab

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500mg vial solution for infusion after dilution. The solution contains 50mg/mL durvalumab, 26mM histidine/histidine-hydrochloride, 275mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10mL. Investigational product vials should be stored at 2°C to 8°C and must not be frozen. Drug product should be kept in original packaging until use to prevent prolonged light exposure. Durvalumab must be used within the individually assigned expiry date on the label.

7.2.3.2 Preparation of durvalumab doses for administration with an intravenous bag

The dose of durvalumab for administration must be prepared using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 30 days at 2°C to 8°C
- 24 hours at room temperature (up to 25°C)

From a microbiological point of view, the prepared solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C or 12 hours at room temperature (up to 25°C), unless dilution has taken place in controlled and validated aseptic conditions.

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

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

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes). The total allowed time should not exceed 8 hours at room temperature. Do not co-administer other drugs through the same infusion line.

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

7.2.3.3 Monitoring of dose administration

Patients will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Events. Patients are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of trial drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the Investigator. If the infusion-related reaction is Grade 3 or higher in severity, trial drug will be discontinued. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature.) For management of patients who experience an infusion reaction, please refer to Appendix 2.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and trial personnel must be trained to recognize and treat anaphylaxis. The trial site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

7.3 Supplies of Investigation Medicinal Products and Labelling

MMC and 5FU are commercially available and should be prescribed from hospital pharmacy stocks. Any generic or branded formulation approved for use in the UK is acceptable. Local standard operating procedures and guidelines must be followed. IMPs should be labelled with Annexe 13 compliant labels, supplied by the Trial Office.

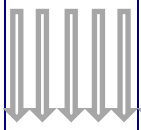
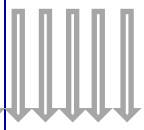
Durvalumab will be supplied directly to sites by Sharp Clinical Services.

Pharmacies will be provided with a Pharmacy Manual which contains full details of labelling, storage, prescribing, dispensing, destruction and accountability of IMPs.

7.4 Treatment Schedule

It is intended that all treatments will be given in an out-patient setting and according to the schedule stated below.

Figure 1. Treatment schedule

Week -1	Week 1	Week 2	Week 3	Week 4	Week 8-48 (on a 4-weekly basis)	
						**Durvalumab 1500 mg**
						**MMC 12 mg/m²**
						**5FU (continuous 5 day infusion)** **500mg/m² /24h**
						**Radiotherapy** **55Gy 20 fractions to bladder plus nodal radiotherapy if node-positive.** ***Target dose for clinically uninvolved nodes 46Gy in 20 fractions*** **In-field concurrent boost to up to 51Gy in 20 fractions to macroscopic disease, subject to meeting all relevant dose constraints**

7.5 Investigational Medicinal Product Administration

7.5.1 Durvalumab

A fixed dose of 1500mg will be administered 4 weekly on day 1 of each week starting one week prior* to commencement of chemoradiotherapy (week -1 day 1) up to a total of 48 weeks (13 doses in total).

**Administration of the loading dose must occur between 5 and 10 days before the initiation of chemoradiotherapy.*

From week 4 onwards durvalumab can be administered within ± 3 days of each scheduled timepoint.

The first dose of durvalumab should commence as soon as possible after registrationrandomisation and within a maximum of 4 weeks. If the patient had neo-adjuvant chemotherapy, treatment should commence as soon as possible after the last treatment of neo-adjuvant chemotherapy and sufficient resolution of any relevant toxicities. Durvalumab treatment should start no later than 3 months after neo-adjuvant treatment has finished. The neo-adjuvant chemotherapy cycle is defined as finishing on day 21 for a 3 week schedule or day 28 for a 4 week schedule, not the day of last chemotherapy infusion.

Dose should be administered over approximately 1 hour intravenous infusion; if interrupted during infusion, the infusion start to completion should not exceed 8 hours.

Patients who have a dose interruption due to toxicity or reasons other than treatment-related toxicity at any point, may resume treatment as soon as is feasible and complete the 12-month treatment period as per original schedule. Dosing intervals may be shortened as clinically feasible but the omitted dose will not be replaced if subsequent time between two consecutive doses is less than 22 days (based on the half-life of durvalumab).

7.5.2 Mitomycin C

MMC will be given on day 1 of week 1 of treatment only, as an intravenous bolus at a dose of 12mg/m^2, prior to starting radiotherapy.

Follow instructions for preparation and administration in the SmPC for MMC.

7.5.3 5-Fluorouracil

5FU will be given as a continuous intravenous infusion at 500mg/m2/day for 5 days corresponding to fractions 1-5 (week 1 days 1-5) and 16-20 (week 4 days 22-26) of radiotherapy. The initial daily dose should not exceed 1g. This treatment will involve the placement of a Hickman line for the duration of therapy or the temporary use of a long peripheral line such as a PICC line, which will be inserted by a suitably trained nurse under local anaesthetic. This will allow treatment to be given on an out-patient basis using an ambulatory 5FU infusion pump, which will enable patients to attend the radiotherapy department daily during chemotherapy. Patients can be treated as in-patients if needed.

Follow instructions for preparation and administration in the SmPC for 5FU.

7.5.4 Radiotherapy

During weeks 1-4 of trial treatment patients must be treated with CT planned radical radiotherapy to deliver a dose of 55 Gy in 20 fractions to the whole bladder. The radiotherapy must be delivered over 4 weeks with 5 days of treatment, followed by a 2 day break. For node positive patients, radiotherapy will also be given concurrently to pelvic lymph nodes (details in the Radiotherapy Treatment Planning Guidelines). Target dose for clinically uninvolved nodes 46Gy in 20 fractions with in-field concurrent boost to up to 51Gy in 20 fractions to macroscopic disease, subject to meeting all relevant dose constraints. It is recommended that nodal radiotherapy is delivered with intensity modulated radiotherapy (IMRT) techniques.

It is recommended that all radiotherapy treatments are booked for afternoon slots to allow for the durvalumab and chemotherapy infusions to take place beforehand.

Please refer to the Radiotherapy Treatment Planning Guidelines for details regarding Quality Assurance. For all centres with or without previous NCRN quality assurance, the Facility

Questionnaire for Centres Participating in National Clinical Trials must be submitted to the National Radiotherapy Trials QA team (http://www.rttrialsqa.org.uk).

Planning and Technique

Planning should occur 2-3 weeks prior to treatment. For full details of the planning and quality assurance assessments, please refer to the Radiotherapy Treatment Planning Guidelines, which can be found in the Investigator Site File.

7.6 Dose Modifications

7.6.1 Dose modification and toxicity management for durvalumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab are provided in Appendix 2. Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune-mediated AEs (imAE). Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

All toxicities will be graded according to NCI CTCAE, Version 4.0.

7.6.2 Dose modifications and treatment alterations for chemotherapy

The chemotherapy schedules in Rad-IO are in widespread use and sites will be familiar with managing the toxicity associated with these drugs, the following guidance is provided to encourage a consistent approach but investigators may use local toxicity management guidelines. Comprehensive and detailed guidance for the management of specific toxicity of individual agents is outside the remit of this protocol.

5-Fluorouracil

The principal toxicities of 5FU are diarrhoea and mucositis (see tables 1 and 2). Neutropenia is expected to be minimal at this dose and schedule. In the BC2001 trial grade 3/4 haematological toxicity was <5%. Non-haematological toxicity was mainly urinary (frequency, nocturia) and lower bowel (diarrhoea), but grade 3/4 toxicity was not significantly increased when compared to radiotherapy alone. There was an increase in grade 1-2 toxicity compared to radiotherapy alone but not sufficient to compromise the delivery of the radiotherapy. Dose modifications are thus based on those used in BC2001.

Mild diarrhoea can be controlled with a low residue diet or with suitable anti-diarrhoeals such as loperamide or codeine. Less common is plantar palmar (Hand-Foot) syndrome (erythema and desquamation of the skin of the hands and feet). This is unlikely given the short duration of therapy but can be managed with pyridoxine 50mg once daily if it occurs. In the context of synchronous therapy, the diarrhoea is the most likely toxicity that may be dose limiting. Grade 4 toxicity should be rare at the doses proposed and should be reported to the Trial Office immediately. Proposed dose modifications are summarised in tables 1 and 2.

Table 1. Diarrhoea

CTCAE grade	Grade 1	Grade 2	Grade 3	Grade 4
Treatment	No change	Reduce infusion dose by 125mg/m^{P2}P/day Continue radiotherapy Consider low residue diet with Loperamide	Discontinue infusion permanently Consider interrupting radiotherapy (until symptoms resolve to grade I)	Stop all therapy Inform Trial Office, reassess weekly

Table 2. Mucositis

CTCAE grade	Grade 1	Grade 2	Grade 3	Grade 4
Treatment	No change	Reduce infusion dose by 125 mg/m²P/day. Continue radiotherapy	Discontinue infusion permanently Continue radiotherapy unless diarrhoea also present	Stop all therapy Inform Trial Office, re-assess weekly

Occasionally, angina may be precipitated. 5FU infusion should stop immediately if this occurs. Please inform the Trial Office if such an event occurs.

Myelosuppression, nausea and vomiting were unusual in the BC2001 trial[10]. In the event of grade 3 neutropenia, thromobocytopenia or anaemia, 5FU should be stopped if the infusion is in progress. If this occurs during the first block of 5FU the second block should be omitted. If this occurs during the 2 week break between infusions, the second treatment should be omitted unless recovery to grade 1 or less by the scheduled date of the second infusion. If grade 3 myelotoxicity occurs at any point during the second block of 5FU then the treatment should be stopped and not re-started.

Non-haematological toxicities occurred at similar frequencies in the radiotherapy only and combination therapy arms of BC2001, with no excess of grade 3 toxicity with chemoradiation, grade 1-2 toxicities were more frequent and should be managed as per table 1. Simple anti-emetics such as oral metoclopramide should be used for control.

Mitomycin C

The major toxic effect of MMC is myelosuppression. Pulmonary toxicity has also been reported and should be managed symptomatically. Note that lung toxicity is a side effect associated with durvalumab treatment and has specified dose modification instructions provided in Appendix 2.

7.6.3 Dose modifications and treatment alterations for radiotherapy

The principle adopted in the BC2001 trial was that modifications should be made to the radio-sensitising treatments before changing the radiotherapy schedule. This should also be followed in this trial. One of the outcome measures will be the effect of the radio-sensitisation on delivery of radiotherapy. In BC2001 we were able to demonstrate no effect from 5FU/MMC on radiotherapy dose intensity, mainly achieved by modest reductions in the administration of 5FU in the fourth week of therapy.

Radical radiotherapy to the bladder has both short and long-term side effects. The immediate side effects include cystitis, acute small bowel reactions, and proctitis. Later side effects include telangiectasia of the bladder and bowel, chronic proctitis and tiredness. In addition, loss of bladder volume, reduction in urethral closure pressure and detrusor instability can occur in association with frequency, urgency and urge incontinence. Damage to the rectal mucosa can cause long-term rectal blood loss.

For any grade 4 radiotherapy related toxicities, radiotherapy should be delayed until toxicity is resolved to grade 2 or less. In such circumstances and when it is secured that the side effect is not immunotherapy related, chemotherapy and durvalumab will continue until the final week of radiotherapy. If treatment is delayed more than 1 week then the radiotherapy should be discontinued.

For Grade 3 diarrhoea consider delaying radiotherapy until diarrhoea resolves to Grade 1, as per table 1. Durvalumab can be the cause of diarrhoea and if in doubt it should be treated like immunotherapy The risk of gastro-intestinal toxicity may increase in patients with positive pelvic nodes due to the larger field.

7.7 Concomitant Medication

Please refer to the SmPCs for all known contraindications for mitomycin C and 5FU. Any contraindicated therapy should not be given to patients on the trial. If a patient being considered for the trial is currently receiving a contraindicated therapy, then the patient can be enrolled on the trial only if the patient is able to discontinue such treatment.

7.7.1 Concomitant medications with durvalumab

Permitted concomitant medications

Table 3. Supportive Medications

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

Excluded concomitant medications

Table 4. Prohibited Concomitant Medications

Prohibited medication/class of drug:	Usage:
Any investigational anticancer therapy other than those under investigation in this trial	Should not be given concomitantly whilst the patient is on trial treatment
Monoclonal antibodies against CTLA-4, PD-1, or PD-L1 other than those under investigation in this trial	Should not be given concomitantly whilst the patient is on trial treatment
Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this trial	Should not be given concomitantly whilst the patient is on trial treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (e.g., by local surgery or radiotherapy)

Prohibited medication/class of drug:	Usage:
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	Should not be given concomitantly, or used for premedication prior to the immunotherapy infusions. The following are allowed exceptions: • Use of immunosuppressive medications for the management of IMP-related AEs • Use in patients 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 patient (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc)
Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors (EGFR TKIs)	Should not be given concomitantly Should be used with caution in the 90 days post last dose of durvalumab Increased incidences of pneumonitis (with third generation EGFR TKIs) and increased incidence of transaminase increases (with 1st generation EGFR TKIs) has been reported when durvalumab has been given concomitantly
Live attenuated vaccines	Should not be given through 3 months after the last dose of IMP (including standard of care)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the Trial Office

7.8 Restrictions During the Trial

7.8.1 Contraception

Female patient of child-bearing potential

Females of childbearing potential (see section 4.1 for definition) who are sexually active with a non-sterilised male partner must use at least 1 **highly** effective method of contraception (Table 5) from the time of screening and must agree to continue using such precautions for 6 months after the last dose of IMP. Non-sterilised male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential

Non-sterilised males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 6 months after receipt of the final dose of IMP. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

Table 5. Highly Effective Methods of Contraception* (<1% Failure Rate)

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

[a]This is also considered a hormonal method

* Highly effective methods of contraception, is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in Table 5. Note that some contraception methods are not considered highly effective (e.g., 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).

7.8.2 Blood donation

Patients should not donate blood while participating in this trial for at least 90 days following the last infusion of durvalumab or until after 4-5 x the half-life of MMC, 5FU or until the time specified in the prescribing information of MMC, 5FU whichever is the longest.

7.9 Treatment Compliance

Treatment compliance will be measured at each clinic visit and recorded in the Treatment Form. All dose modifications, delays and omissions must be recorded. If treatment is permanently discontinued due to toxicity, a Treatment Discontinuation Form must be completed.

7.10 Trial Treatment Discontinuation and Withdrawal of Consent

7.10.1 Treatment discontinuation

Patients should discontinue trial treatment in the following circumstances:

- Delay of more than 21 days in starting the next cycle of treatment due to toxicity
- Progressive disease according to clinical investigations or radiographic investigations
- Participant becomes pregnant, despite appropriate contraceptive measures
- Any AEs that meets criteria for discontinuation as defined in Appendix 2
- Infusion reaction >Grade 3 following durvalumab administration
- If, at the Investigator's discretion, it is considered to be in the best interest of the patient.

The end of treatment investigations must be performed within 30 days following the last trial treatment.

All participants who discontinue due to AEs including clinical laboratory abnormalities must be overseen until the event has stabilised, or until the event or laboratory value returns to baseline level, which should be documented on the AE form. The patient will then continue on standard trial follow up.

7.10.2 Patient withdrawal

Patients are free to withdraw from the trial at any time without affecting their care.

In the event of a patient's decision to withdraw from the trial, the Investigator must ascertain from which aspects of the trial the patient wishes to withdraw and record the details on the Withdrawal Form and in the patient's medical notes. All information and samples collected up until the point of retraction will be retained and analysed.

If a patient chooses to stop treatment only, the patient should discontinue treatment but continue to be assessed in accordance with the protocol.

If a patient wishes to withdraw from the trial schedule (i.e., including trial specific assessments), but is willing for further data to be supplied to the Trial Office, then further routine "follow-up" data (e.g. progression status, survival, further treatment) will continue to be supplied by the Investigator to the Trial Office.

If a patient wishes to stop participating in a sub-study, e.g. the QoL study, the patient should continue in the main trial, but further QoL data must not be collected for that particular patient after the date of discontinuing the sub-study.

7.11 Schedule of Assessments

7.11.1 Baseline assessments

Baseline assessments should be performed within 28 days prior to registrationrandomisation, the exceptions to this being the cystoscopy and CT or MRI scan which should be performed within 56 days prior to registrationrandomisation. This data will be collected on the Baseline Form.

Baseline screening assessment should take place within 6 weeks of TURBT or completion of neoadjuvant chemotherapy if administered.

Baseline tests will consist of:

- Full physical examination and vital signs including blood pressure, pulse, temperature and respiratory rate
- WHO performance status
- Height and weight
- Medical history to include details of previous treatment given for muscle invasive bladder cancer, details of any other conditions patient has, smoking and alcohol status
- Clinical laboratory tests for:
    - Haematology (see Table 6)
    - Biochemistry (see Table 7)
    - Thyroid function tests - Thyroid Stimulating Hormone (TSH), free triiodothyronine (fT3) and free thyroxine (fT4) will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an AE related to the endocrine system.
    - Coagulation (prothrombin time, partial thromboplastin time, international normalised ratio (INR))
    - Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of IMP and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the Investigator prior to commencing an infusion
    - Serum cortisol
    - Urinalysis (see Table 8)
- DPD test – Prior test results can be used, there is no need to repeat if done prior to study entry.
- Cystoscopy (not required if done within 56 days of starting neo-adjuvant chemotherapy)
- 12 lead electrocardiogram (ECG), should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g. 30 minutes) to confirm the finding
- CT scan chest, abdomen and pelvis or MRI scan combined with chest CT (prior to neo-adjuvant chemotherapy (if given) and a repeat scan post neo-adjuvant chemotherapy within 56 days of registration)
- Toxicity assessment by CTCAE version 4.0 – including all previous toxicities due to the neo-adjuvant treatment, particularly any changes to the Glomerular Filtration Rate
- Concomitant medication review
- The patient should complete the LENT SOMA questionnaire (see section 5.2 for more information)
- Blood and urine samples will also be collected from patients who have given consent for this. Refer to the translational sub-studies manual for full details.

Following registrationrandomisation but prior to commencing treatment patients consenting to the optional QoL sub-study should also be asked to complete the baseline QoL Booklet (see section 5.2 for more information).

Please also note that for those trial patients that have consented to the optional tissue collection and imaging sub-studies, tumour tissue may be requested as well as access to imaging data.

Table 6. Haematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Haematocrit	Neutrophils
Haemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular haemoglobin	Total white cell count
Mean corpuscular haemoglobin concentration	

Table 7. Biochemistry (Serum or Plasma) Laboratory Tests

Albumin	Lipase[b]
Alkaline phosphatase[a]	Magnesium[c]
Alanine aminotransferase or Aspartate aminotransferase[a]	Potassium
Amylase[b]	Sodium
Calcium	Total bilirubin[a]
Creatinine[c]	Total protein
Gamma glutamyltransferase[c]	Thyroid Stimulating Hormone [d]
Glucose	Urea or blood urea nitrogen, depending on local practice
Lactate dehydrogenase	Uric acid

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

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

[c] Calculated creatinine clearance, gamma glutamyl transferase, and magnesium testing are to be performed at baseline, on Day 1 of treatment (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if clinically indicated.

[d] If TSH is measured within 14 days prior to day 1 it does not need to be repeated at day 1. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system

Table 8. Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

[a] Microscopy should be used as appropriate to investigate white blood cells and use the high-power field for red blood cells

7.11.2 First durvalumab dose (week -1)

If baseline laboratory assessments are performed within 3 days prior to treatment day 1 they do not need to be repeated at day 1.

- Targeted physical examination (based on symptoms)
- Vital signs including blood pressure, pulse, temperature and respiratory rate must be measured at the following time points:
    - At the beginning of the infusion (at 0 minutes)
    - At 30 minutes during the infusion (30±5 mins)
    - At the end of the infusion (at 60 minutes ±5 minutes)
    - In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated

  If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or more frequently if clinically indicated.
- WHO performance status
- Weight
- Haematology (see Table 6) and biochemistry tests (see Table 7)
- Thyroid function tests - fT3 and fT4 will only be measured if TSH is abnormal
- Urinalysis (see Table 8)
- For women of childbearing potential only, urine hCG or serum βhCG pregnancy test
- Toxicity assessment by CTCAE version 4.0

7.11.3 During treatment

All patients will be assessed by the following methods at the start of each week whilst receiving trial treatment. Assessments to be performed on day 1 of treatment (or within 3 days prior).

- Targeted physical examination (based on symptoms)
- Vital signs including blood pressure, pulse, temperature and respiratory rate.
  For Durvalumab infusions vital signs must be measured at the following time points:
    - At the beginning of the infusion (at 0 minutes)
    - At 30 minutes during the infusion (30±5 mins)
    - At the end of the infusion (at 60 minutes ±5 minutes)
    - In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (i.e., 90 and 120 minutes from the start of the infusion) (±5 minutes) – only if clinically indicated
- WHO performance status
- Weight
- Haematology (see Table 6) and biochemistry tests (see Table 7)
- Toxicity assessment by CTCAE version 4.0
- Thyroid function tests - fT3 and fT4 will only be measured if TSH is abnormal
- For women of childbearing potential only, urine hCG or serum βhCG pregnancy test every 4 weeks prior to each 4 weekly treatment
- For those patients that have consented to the optional sub-study, blood and urine samples will also be collected

7.11.4 During durvalumab treatment only

- Urinalysis (see Table 8)

7.11.5 End of treatment assessment

An end of treatment assessment should be performed at 30 days (+/- 7 days) after completion of protocol defined treatment for the relevant arm. The following assessments should be made:

- Targeted physical examination (based on symptoms)
- Vital signs including blood pressure, pulse, temperature and respiratory rate
- WHO performance status
- Weight
- Haematology (see Table 6) and biochemistry tests (see Table 7)
- Thyroid function tests - fT3 and fT4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an AE related to the endocrine system.
- Urinalysis (see Table 8)
- Serum cortisol
- Toxicity assessment by CTCAE version 4.0
- Patients complete the LENT SOMA questionnaire
- Consenting patients to complete the QoL Booklet
- For women of childbearing potential only, urine hCG or serum βhCG pregnancy test
- For those patients that have consented to the optional sub-study, blood and urine samples will also be collected

The Trial Office shall post the LENT SOMA questionnaire and, for consenting patients only, a QoL Booklet to coincide with the End of treatment assessment. The completed QoL Booklet and LENT SOMA questionnaire should be returned by the patient to the Trial Office in the pre-paid envelope provided.

7.11.6 Follow-up

Patients should be followed up every 3 months (+/- 7 days*) up to 2 years from completion of chemoradiotherapy treatment. The following assessments should be performed for all patients:

- Cystoscopy (at 3, 6, 12, 18 and 24 months visits*) at 3 months this should be a rigid cystoscopy unless access issues prevent this happening in a timely manner, in which case flexible cystoscopy is permitted; all subsequent cystoscopies may be rigid or flexible according to local policy.
- CT chest, abdomen and pelvis or MRI scan combined with chest CT (at 3, 6, 12, 18 and 24 months visits*)
- WHO performance status
- Toxicity assessment by CTCAE version 4.0 (at 3, 6, 9, 12, 15 month visits*)
- Patients completion of LENT SOMA questionnaire (at 3, 6, 9, 12, 18 24 months visits and end of treatment*)
- For those patients that have consented to the optional sub-study, blood and urine samples will also be collected.

** For patients receiving durvalumab assessment at 3, 6, 9 and 12 months may be during treatment. Assessments should be done within 3 days prior.*

The Trial Office shall post the LENT SOMA questionnaire and, for consenting patients only, a QoL Booklet to coincide with each follow up time point. The completed QoL Booklet and LENT SOMA questionnaire should be returned by the patient to the Trial Office in the pre-paid envelope provided.

Survival status will also be assessed at each visit.

Follow-up data after 2 years will be obtained via NHS registries with no trial specific follow-up visits required.

7.12 Management of Progression

Patients with disease progression must discontinue the trial treatment and be treated according to local clinical practice.

If a patient stops trial treatment prematurely, this should be recorded on the relevant treatment form. The relevant progression form(s) should also be completed.

All these patients must continue on trial follow-up for survival, and QoL if consented, unless they explicitly withdraw consent for this. For those patients that have consented to the optional sub-study, blood and urine samples will also be collected at disease progression.

8 PATIENT QUESTIONNAIRES

8.1 LENT SOMA Questionnaire

The LENT SOMA analytical scales were developed in 1995 by the EORTC and RTOG to measure the acute and late effects in normal tissues after cancer treatments, specifically radiotherapy[40]. The Clinical Outcomes Group based at the Christie NHS Foundation Trust developed validation studies for these questionnaires and have further adapted the questionnaire to develop patient questionnaires.

8.2 Quality of Life Sub-study

Cancer treatments may produce adverse effects that diminish patient QoL, even when tumour regression or extended survival is achieved, the acceptance of any new treatment regimen may be critically dependent on QoL consequences. Thus a detailed assessment of QoL changes is an important aspect of this trial.

Consent for participation in the QoL Sub-study will be included on the main trial consent form, and information will be provided in the Patient Information Sheet.

Refusal to consent to the QoL sub-study will not be a reason to exclude patients from participating in the rest of the trial.

In order to assess QoL we will be using the EORTC QLQ-C30 and EORTC QLQ-BLM30 questionnaires.

The QoL Sub-study will utilise the following questionnaires:

- EORTC QLQ-C30 (version 3.0) is a 30 item questionnaire developed to assess generic aspects of QoL of cancer patients; such as physical, psychological and social functions[41]. It is composed of 5 multi-item scales (physical, role, social, emotional and cognitive functioning) and 9 toxicity related single items.
- EORTC QLQ-BLM30 (version 3.0) is the Muscle Invasive Bladder Cancer specific module designed to be used with EORTC QLQ-C30. It includes 24 items with questions on urinary symptoms, sexual function, urostomy issues, catheter use, and body image. This questionnaire is in the process of being validated but has been widely used in clinical trials[42].

Both questionnaires have been developed by the European Organization for Research and Treatment.

Participation in this sub-study is optional for patients. Enrolment will be offered to all patients consented into the trial.

Participating patients will be provided with the validated questionnaires at the following time points:

- Prior to commencing protocol defined treatment (baseline)
- At the end of treatment assessment (30 days post treatment discontinuation)
- 3, 6, 9, 12, 15, 18, 21 and, 24 months post chemoradiotherapy

Sites will be provided with a supply of the baseline QoL Booklets at site initiation.

Prior to completing the baseline QoL Booklet a member of the Research Team should discuss the questionnaires with the patient and answer any questions they may have. The baseline QoL Booklet should be returned to the Trial Office by the Research Team.

Subsequent QoL Booklets will be posted out to patients by the Trial Office with a pre-paid envelope for the return of completed booklet. A copy of the completed booklets will not be sent to site.

Patients will be sent a reminder to complete the QoL booklet 1 month after the booklet should have been received.

9 TRANSLATIONAL SUB-STUDIES

Participation in the following translational sub-studies is optional and patients will be invited to give consent to each one. Translational sample collection is subject to funding provisions. The Trial Office will notify sites whether they are permitted to collect translational sub-study samples.

9.1. Tumour tissue

Patients in the trial will be invited to give consent for their tumour tissue and related normal tissue such as non-tumour bearing bladder to be retrospectively collected and used for ethically approved biomarker discovery and validation studies. This consent will include tissue from subsequent procedures such as cystoscopic biopsy or cystectomy. These studies will seek to correlate biological markers with clinical outcomes, including response to targeted therapy and chemotherapy, response to radiotherapy and risk of relapse.

Samples collected from patients for the in-depth study will be immediately processed either at the collecting site or after transfer to the translational collaborating group at the Institute of Cancer Research, London (or other designated partner organisation).

9.2. Urine and blood samples

Participating centres also have the option of taking part in urine and blood translational studies. There will be two studies, one open to all sites and one open only to selected sites with facilities for rapid real time sample processing. The former study comprises collection of urine and blood samples at baseline, 30 days post chemoradiotherapy, 6 months post chemoradiotherapy and, where applicable, on relapse.

The latter in-depth study will collect additional urine and blood samples at baseline, week 1 (Day 1) and week 4 (Day 22) of chemoradiotherapy, 30 days post chemoradiotherapy, 3, 6 and 12 months post chemoradiotherapy and, where applicable, on relapse. Samples collected for the in-depth study will be immediately processed either at the collecting site or after transfer to the translational collaborating group at the Institute of Cancer Research, London (or other designated partner organisation). The in depth study will include the extraction, storage and analysis of items of special interest such as urinary lymphocytes tumour and normal tissue DNA, RNA and analysis of histological changes associated with the tumour and treatment.

Initial sample processing for the study open to all sites will be carried out in separate University of Birmingham laboratories or other suitable location such as the Institute of Cancer Research, London (or other designated partner organisation). Items to be studied will include free DNA in blood, urine and urine pellets and the relationship to tumour DNA mutations. Changes in the immune profile of lymphocyte derived DNA will also be analysed in the same samples. The precise details of the work to be carried out will be the subject of a separate ethical application. Management of the samples will pass to this new project once ethically approved. Sample processing for the in-depth study will commence at the recruiting site and may involve other laboratories such as (but not limited to) those at the Institute of Cancer Research, London. Samples can be passed directly from the collecting site to the Institute of Cancer Research (or other designated laboratory) without needing to be transferred to or via Birmingham.

9.3. Imaging sub-study

All patients will be invited to give consent for access to cancer imaging (CT scans, bone scans, MRI and PET scans, both at baseline and during follow up) and associated data collected for this trial for subsequent transfer and analysis via image banks under ethically approved research protocols.

Full details of these sub-studies are given in a separate translational sub-studies manual.

10 ADVERSE EVENT REPORTING

The collection and reporting of AEs will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 3. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the SmPCs for the IMPs used in this trial.

10.1 Reporting Requirements

10.1.1 Reporting Period

Investigators must record details of all AEs, and report any SAEs, occurring from time of signature of Informed Consent Form until 90 days after the last exposure to all of the trial treatments. If an event that starts post the defined safety follow up period noted above is considered to be due to a late onset toxicity to trial treatments then it should be reported as an SAE if the event is thought to be unexpected by the Investigator.

10.1.2 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 3 for definition) should be reported, with the exception of abnormal laboratory results which should only be reported as an AE if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment.

10.1.2.1 Durvalumab Adverse Events of Special Interest

An Adverse Event of Special Interest (AESI) is one of scientific and medical interest specific to understanding of the IMP and may require close monitoring. An AESI may be serious or non-serious.

AESIs observed with durvalumab include:

- Diarrhoea, colitis and intestinal perforation
- Pneumonitis, Interstitial Lug Disease (ILD)
- ALT or AST increases, hepatitis, hepatotoxicity
- Neuropathy, neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Endocrinopathies (i.e. events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash, dermatitis
- Nephritis, blood creatinine increases
- Pancreatitis (or laboratory results suggestive of pancreatitis - increased serum lipase, increased serum amylase)
- Cardiac disorders (myocarditis)
- Myositis, polymyositis

- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab SmPC. More specific guidelines for their evaluation and treatment are described in detail in Appendix 2.

10.1.3 Serious Adverse Events

Investigators should report AEs that meet the definition of an SAE (see Appendix 3 for definition) on a SAE Form (see section 10.4).

10.1.4 Death

Please note where death is not due (or not clearly due) to progression of the disease, the AE causing the death **must be** reported to the Trial Office as a SAE. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. Deaths with an unknown cause should always be reported as a SAE.

10.2 Overdose

An overdose is defined as a subject receiving a dose of IMP in excess of that specified in this protocol.

Any overdose with or without associated AEs/SAEs, is required to be reported within 24 hours (one business day) of knowledge of the event to the Trial Office.

If the overdose results in an AE, this must also be recorded on an AE Form. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalisation, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab.

10.3 Hepatic Function Abnormality

For patients receiving durvalumab, hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law* case in a trial patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours (one business day) of knowledge of the event to the Trial Office, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to durvalumab has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to durvalumab, the decision to continue dosing of the trial patient will be based on the clinical judgment of the Investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the trial patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the site without delay.

Each reported event of hepatic function abnormality will be followed by the Investigator and evaluated by the Trial Office.

*Hy's Law criteria: ALT and/or AST>3 x ULN + bilirubin >2 x ULN without initial findings of cholestasis and in the absence of any alternative cause

10.4 Serious Adverse Event Reporting Procedure

10.4.1 Site

10.4.1.1 Adverse Events

AEs should be reported on an AE Form (and where applicable on an SAE Form). An AE Form should be completed at each visit and returned to the Trial Office. AESI related to durvalumab will be captured on the Treatment Toxicity Form (for durvalumab).

AEs will be reviewed using the CTCAE, version 4.0 (see Appendix 4). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded. A pre-existing condition should not be reported as an AE, unless the condition worsens, or episodes increase in frequency, during the AE reporting period.

10.4.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in the Investigator Site File.

AEs defined as serious and which require reporting as an SAE should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be emailed to the Trial Office using the contact details listed below as soon as possible and no later than 24 hours after first becoming aware of the event.

To report an SAE, email the SAE Form to:

Reg@trials.bham.ac.uk
Cc: radio@trials.bham.ac.uk
Include "RadIO SAE" in the subject line

On receipt the Trial Office will allocate each SAE a unique reference number. This number will be emailed to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trial Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE acknowledgment email received from the Trial Office should be filed with the SAE Form in the Investigator Site File.

For SAE Forms completed by someone other than the Investigator, the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trial Office, a copy kept in the Investigator Site File.

Investigators should also report SAEs to their own Trust in accordance with local practice.

10.4.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

10.4.2 Trial Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the applicable Reference Safety Information) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

10.4.3 Reporting to the Competent Authority and Research Ethics Committee

10.4.3.1 Suspected Unexpected Serious Adverse Reactions

The Trial Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days.

All other events categorised as SUSARs will be reported within 15 days.

10.4.3.2 Serious Adverse Reactions

The Trial Office will report details of all SARs (including SUSARs) to the MHRA and REC annually from the date of the Clinical Trial Authorisation, in the form of a Development Safety Update Report.

10.4.3.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

10.4.3.4 Other safety issues identified during the course of the trial

The MHRA and REC will be notified immediately if a significant safety issue is identified during the course of the trial.

10.4.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the Investigator Site File.

10.4.5 Data Monitoring Committee

The independent Data Monitoring Committee (DMC) will review all SAEs.

10.4.6 Manufacturer of durvalumab

The Trial Office will report all SAEs to the AstraZeneca Patient Safety Team within 24 hours (one business day) of becoming aware of the event.

10.5 Monitoring Pregnancies for Potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

If a patient becomes pregnant during the course of the trial, trial treatment should be discontinued immediately.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the Trial Office within 1 working day. Where the patient's partner is pregnant consent must first be obtained and the patient should be given a Release of Medical Information Form to give to their partner. If the partner is happy to provide information on the outcome of their pregnancy they should sign the Release of Medical Information Form.

The outcome of all pregnancies should be followed up and documented even if the patient has discontinued trial treatment. Outcome data should be provided on a follow-up Pregnancy Notification Form.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities, birth defects, neonatal death, spontaneous miscarriages, and induced abortion should be reported on an SAE Form.

The Trial Office will report pregnancies to the AstraZeneca Patient Safety Team within 5 calendar days for SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

10.6 Medication Error

For the purposes of this clinical trial a medication error is an unintended failure or mistake in the treatment process that either causes harm to the patient or has the potential to cause harm to the patient.

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 trial site staff or patient.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error

Examples of events to be reported as medication errors include:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong patient received the medication
- Wrong drug administered to patient

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

- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the trial, then the Investigator or other site personnel must inform the Trial Office within one day i.e. immediately but **no later than 24 hours** of becoming aware of it.

The Trial Office will report relevant information about medication errors to AstraZeneca within 5 calendar days if there is an SAE associated with the medication error and within 30 days for all other medication errors.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Collection

This trial will use an electronic remote data capture (eRDC) system to capture the CRF data. Paper CRFs will also be available as a backup. Access to the eRDC system will be granted to individuals by the Trial Office.

https://www.cancertrials.bham.ac.uk

The Investigator and site staff will ensure all data from subject visits are promptly entered into the eRDC in accordance with the trial specific User Manual and CRF Completion Guidelines. The CRF must be completed by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log). The exceptions to this are the Eligibility Checklist, SAE Form and Deviation Form which can be completed by an authorised member of the site research team but must be co-signed by the Investigator.

For the purposes of this trial SAE Forms and QoL Booklets will be captured on paper and entered onto the eRDC system by the Trial Office. The original QoL Booklets will be returned to the Trial Office and will be regarded as source data. For paper CRF the completed originals should be sent to the Trial Office and a copy filed in the Investigator Site File.

Entries on the paper CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on the CRF should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The CRF may be amended from time to time by the Trial Office throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the CRF must be implemented by participating sites immediately on receipt.

11.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, Investigator Site Files, Pharmacy File, patients' hospital notes, copies of CRFs, etc.) at their site are securely retained for at least 25 years after the end of the trial. Do not destroy any documents without prior approval from the Cancer Research UK Clinical Trials Unit (CRCTU) Document Storage Manager.

12 QUALITY MANAGEMENT

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU) according to the current guidelines for Good Clinical Practice (GCP). Participating sites will be monitored by CRCTU staff to confirm compliance with the protocol, and the protection of patients' rights as detailed in the Declaration of Helsinki (see Appendix 5).

12.1 Site Set up and Initiation

All sites will be required to sign a Model Agreement For Non-Commercial Research (mNCA) prior to participation. In addition, all participating Investigators will be asked to sign the necessary agreements, registration forms and supply a current CV to the Trial Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trial Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trial Office must be informed immediately of any change in the site research team.

12.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the trial Quality Management Plan. Additional on-site monitoring visits may be triggered by poor CRF return, poor data quality, low SAE reporting rate, excessive toxicity and excessive number of patient withdrawals or deviations. If a monitoring visit is required, the Trial Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the CRCTU trial staff access to source documents as requested.

12.3 Central Monitoring

Trial Office staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trial Office staff will check incoming CRF for compliance with the protocol, data consistency, missing data and timing. Where a patient has given explicit consent, sites are also requested to send in copies of signed Informed Consent Forms for in-house review. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group, and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the REC and MHRA.

12.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Trial Office of any MHRA inspections.

12.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the Trial Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

The Trial Office will report Serious Breaches to the Sponsor, MHRA, REC and where applicable the Principal Investigator and site Research and Development (R&D) Department.

13 END OF TRIAL DEFINITION

The end of trial will be 6 months after the last patient recruited has a minimum of 2 years follow-up. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trial Office will notify the MHRA and REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

14 STATISTICAL CONSIDERATIONS

14.1 Definitions of Outcome Measures

Stage 1: Pilot

Primary Outcome

Safety: AEs will be graded using the CTCAE version 4.0. Acute toxicity defined as related AEs experienced during treatment and late toxicity defined as related AEs reported at a time more than three months from completion of treatment. The number of patients experiencing each event will be reported by type and severity.

Feasibility: Defined as the impact on radiotherapy treatment and assessed by days delay to start of radiotherapy, days extension in length of planned radiotherapy and stopping radiotherapy early.

Safety and Feasibility analysis will be conducted on the first 6 research arm patients once they have all completed their 3 month follow up visit post chemoradiotherapy.

Secondary Outcome

Feasibility and safety evaluations as defined above will be repeated for the first 6 research arm patients who received neo-adjuvant chemotherapy and the first 6 research arm patients who didn't receive neo-adjuvant chemotherapy.

The analysis will be conducted once all 12 patients have completed their 3 month follow up visit post chemoradiotherapy.

Feasibility and safety evaluations will also be conducted on the first 6 research arm patients with node positive disease once they have all completed their 3 month follow up visit post chemoradiotherapy.

Stage 2: Efficacy

Primary Outcome

- **Disease-free survival rate:** Defined as the proportion of disease-free patients at 12 months post chemoradiotherapy. Disease events include:

- Diagnosis of distant metastases
- Diagnosis of loco-regional nodal disease
- Diagnosis of new muscle invasive tumour in the bladder
- Diagnosis of non-muscle invasive tumour in the bladder
- Diagnosis of upper tract urothelial cancer
- Death from bladder cancer

Patients who were randomised to the control arm that existed as part of the initial study design will be summarised separately and will not be compared with data obtained from the experimental arm. This is due to an insufficient number being recruited before the trial design changed.

Secondary Outcomes for Stage 2

Toxicity

Toxicity will be graded as per the safety outcome in the pilot stage. Rate of occurrences of AEs of Grade 3 or higher will be reported along with all AESI.

Delivery of core target therapy (chemoradiotherapy)

Defined as the impact on radiotherapy treatment and assessed by days delay to start of radiotherapy, days extension in length of planned radiotherapy and stopping radiotherapy early.

Time to local muscle invasive progression

Defined as the number of whole days between the date of registration/randomisation and the date of detection of local muscle invasive bladder cancer or death from bladder cancer, whichever occurs first. Patients with no evidence of local muscle invasive disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Time to local non-muscle invasive progression

Defined as the number of whole days between the date of registration/randomisation and the date of detection of local non-muscle invasive bladder cancer or death from bladder cancer, whichever occurs first. Patients with no evidence of local non-muscle invasive disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Time to regional nodal progression

Defined as the number of whole days between the date of registration/randomisation and the date of detection of loco-regional recurrence in lymph nodes within the true pelvis or death from bladder cancer, whichever occurs first. Patients with no evidence of regional nodal disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Time to local progression

Defined as the number of whole days between the date of registration/randomisation and the date of the first local progression or death from bladder cancer, whichever occurs first. Local progression includes detection of local muscle invasive disease, local non-muscle invasive disease or regional nodal disease. Patients with no evidence of local disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Time to distant progression

Defined as the number of whole days between the date of registration/randomisation and the date of detection of distant progression or death from bladder cancer, whichever occurs first. Patients with no evidence of distant progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Cystectomy within one year

Defined as the proportion of patients who undergo a cystectomy within one year of registration/randomisation.

Quality of life

QoL will be assessed at baseline, end of treatment (30 days post treatment discontinuation) and at 3, 6, 9, 12, 15, 18, 21 and 24 months post chemoradiotherapy, using the questionnaires EORTC QLQ-C30 and QLQ-BLM30.

Overall survival time

Defined as the number of whole days between the date of registration/randomisation and date of death from any cause. Patients who do not die during the course of the trial will be censored at the last date of assessment.

Percentage of target drug delivered

Defined as the amount of durvalumab being administered as a proportion of the protocol defined dose.

Disease-free survival time

Defined as the number of whole days between the date of registration/randomisation and the date of detection of any disease event (defined above) or death from bladder cancer, whichever occurs first. Patients with no evidence of progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Patients with disease still present at 3 month imaging will be categorised as having never been disease free, these patients' disease free survival time will be 0 days. Patients with no evidence of disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

Stage 3: Efficacy

Primary outcome:

Overall survival time: Defined as above.

Secondary outcomes for stage 3

Time to local progression, distant progression, acute/late toxicity and quality of life are defined as above.

Percentage of target drug delivered

Defined as the amount of durvalumab being administered as a proportion of the protocol defined dose.

Cystectomy rate

Defined as the proportion of patients who undergo a cystectomy.

Disease-free survival time

Defined as the number of whole days between the date of randomisation and the date of detection of any progression of bladder cancer or death from bladder cancer, whichever occurs first. Patients with no evidence of progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

14.2 Analysis of Outcome Measures

All analyses will be conducted on an intention to treat basis.

Counts and proportions

Counts will be presented including both the numerator and denominator**.** Proportions will be calculated using exact methodology and reported with confidence intervals.

Time-to-event outcomes

Kaplan-Meier estimates will be produced for all time to event outcomes. Median and 12 and 24 month 'survival' estimates will be presented with confidence intervals. Survival estimates stratified by whether or not patients received neo-adjuvant chemotherapy will also be investigated.

Quality of Life outcomes

QoL data will be analysed using methods suitable for the analysis of longitudinal data, and which account for informative dropout.

14.3 Planned Interim Analysis

Safety reports will be presented to the DMC, to assess feasibility and safety in the pilot stage, once the first 6 patients in the research arm have all completed their 3 month follow up visit post completion of chemoradiotherapy. A further safety report will be presented to the DMC once 6 patients on the research arm who received neo-adjuvant chemotherapy and 6 patients on the research arm who didn't receive chemoradiotherapy have all completed their 3 month post chemoradiotherapy visit. A third safety analysis will take place once 6 node positive patients on research arm complete chemoradiotherapy treatment with 3 month follow-up.

The DMC will then meet at least annually to review information relating to trial recruitment, trial conduct, data completeness, treatment compliance, safety and outcome data.

14.4 Planned Final Analyses for Stage 2

This amendment changes the second stage from a randomised to a single arm design focusing on the research arm only. The primary outcome measure for the Phase II efficacy component is the proportion of patients who remain disease-free 12 months post- completion of chemoradiotherapy. The Phase II efficacy analysis will include all patients from stage 1 and stage 2. Patients who are non-evaluable will be included in the safety and toxicity analyses but the primary outcome analysis will be based on 47 evaluable research arm patients. All patients will be assessed for toxicity and be followed for survival endpoints.

Final analysis for the primary outcome for stage 2 will be used to evaluate whether or not further investigation is warranted. Further investigation is not warranted if the disease control rate at 12 months post chemoradiotherapy is lower than 60% (based on BC2001 data). If the rate is greater than or equal to 75%, it would definitely warrant further investigation. If the observed disease control rate falls between 60% and 75%, the decision to recommend further studies will be based on secondary outcome measures including toxicity and QoL but will also depend on external factors such as emergent data from other similar studies.

14.5 Power Calculations for Stage 2

The original trial design was powered to detect a hazard ratio of 0.6, this equates to an improvement in disease free survival rate at 2 years from 50% to 66%. As this was the first efficacy stage of a MAMS design aiming to evaluate a direct, but non-definitive comparison of durvalumab plus standard care vs standard care alone, with the aim of identifying a positive signal of efficacy with durvalumab, a relaxed significance level of 0.2 (one-sided)was utilised. The power was set to 90% to balance the

number of patients that are required for this initial stage vs those that will be required in subsequent stages to maintain an adequate power level for the definitive evaluation of durvalumab, Between 132 and 159 patients need to be randomised to observe the 70 events required to evaluate disease free survival time, Table 10 shows the expected follow up time required to observe the required number of events for analysis.

Table 10. Event Rate

Assumed recruitment rate per month	Total Number of Patients	Events	Expected time from trial opening to reaching required number of events for analysis
5.5	132	69	50 months
6.67	159	70	43 months

Once the required number of events occurred if the observed hazard ratio is less than 0.823 it would be considered that the evidence was sufficient to warrant continuing to Stage 3 for further investigation.

The original trial was designed using the nstage (v3.0.1) and artpep packages in Stata® v14.2

The redesign allows inclusion of node positive patients. A site survey suggests that this will increase the recruitment rate by maybe 10% but also more importantly, this represents a group with no established standard of care. The results would thus have significant novelty. As durvalumab has systemic as well as potential primary treatment enhancement activity, it is reasonable to postulate an improvement in outcomes of bladder non-invasive, bladder invasive, pelvic nodal and distant metastatic recurrence. Data from the experimental arm of BC2001 suggests around a 20% loco-regional failure rate in the first year of follow up. Metastasis free survival in those without locoregional failure was also around 70-75%. Patients with one endpoint were censored from the other so the aggregate failure rate in this population is around 40% at 1 year.

The primary outcome measure for stage 2 is disease free survival rate at 12 months post chemoradiotherapy. Consider the average disease control rate at 12 months is 60% (and further investigation is not warranted if lower rate than this was obtained). Assume that durvalumab added to chemoradiotherapy improves the disease control rate to 75% (and anything above this would definitely warrant further investigation). To detect the minimal clinically important effect (i.e., 15% improvement in the disease control rate) at 80% power with a relaxed one-sided alpha of 10%, 47 evaluable research arm patients are required (with 33 events required for a Go decision). Considering an additional 10% patients to take into account withdrawals and non-evaluable patients, the target sample size for the efficacy stage is 52 research arm patients.

15 TRIAL ORGANISATIONAL STRUCTURE

15.1 Sponsor

The sponsor of the trial is University of Birmingham.

15.2 Coordinating Centre

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

15.3 Trial Management Group

The Chief Investigator, Co-investigators, Trial Statistician, Trial Management Team Leader (or deputy), Trial Coordinator, Clinical Trials Monitor and patient representative will form the Trial Management Group (TMG). The TMG will be responsible for the day-to-day conduct of the trial, meeting at regular intervals. They will be responsible for the set-up, promotion, on-going management of the trial, the interpretation of the results and preparation and presentation of relevant publications.

15.4 Trial Steering Committee

The independent Trial Steering Committee will be set up with an independent chairperson to oversee the trial. Membership will be composed of selected TMG members, independent clinicians and at least one patient representative. Select members of the TMG will report to this committee. The Trial Steering Committee will meet shortly before commencement of the trial and at least once a year (usually by teleconference), the meetings will usually be arranged to coincide with trial milestones. The Trial Steering Committee will oversee the conduct of the trial, monitoring progress including recruitment, data completeness, losses to follow-up, and deviations from the protocol. They will make recommendations about conduct and continuation of the trial to the sponsor.

15.5 Data Monitoring Committee

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further patients. The DMC will operate in accordance with a trial specific charter based upon the template created by the Damocles Group. The DMC will meet to assess feasibility and safety in the pilot stage after 6 patients on the research arm have completed their 3 month post chemoradiotherapy follow up visit. A further safety report will then be presented to the DMC once 6 research arm patients who received neo-adjuvant chemotherapy, 6 research arm patients who didn't receive neo-adjuvant chemotherapy and 6 research arm patients with node positive disease have completed their 3 month post chemoradiotherapy follow up visit. The DMC will meet at least annually thereafter. Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TMG who will convey the findings of the DMC to the Trial Steering Committee. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise patient safety.

15.6 Finance

This trial is an investigator-initiated and investigator-led trial funded by AstraZeneca/MedImmune who will supply durvalumab free of charge as well as funding the trial costs.

Individual per patient payment will be made to NHS Trusts to cover NHS Research costs.

16 ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association *General Assembly, Somerset West, Republic of South Africa, October 1996 (see Appendix 5).*

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments, the General Data Protection Regulation 2016/679 and the Data Protection Act 2018 and Human Tissue Act 2004 (England, Wales and Northern Ireland) and 2006 (Scotland)) and GCP. This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. REC and Health and Care Research Wales approval will also be obtained.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain Formal Confirmation of Capacity and Capability from their local R & D Department and provide evidence of this to the Trial Office. Sites will not be permitted to enrol patients until this has been obtained.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

17 CONFIDENTIALITY AND DATA PROTECTION

The University of Birmingham is the Data Controller for this trial. Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation 2016/679 and the Data Protection Act 2018. Data will be processed under Article 6 (i) (performance of a task carried out in the public interest) and Article 9 (j) (necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes in accordance with Article 89(1)). Information about how information is handled can be found in the Cancer Research UK Clinical Trials Units and University of Birmingham's privacy policies (https://www.birmingham.ac.uk/research/activity/mds/trials/crctu/crctu-privacy-notice.aspx).

With the patient's consent their full name, date of birth, NHS number, or in Scotland CHI number, and hospital number will be collected at trial entry to allow tracing through the Cancer Registries, and NHS Digital to assist with long-term follow-up. Patients' full postal address will also be collected at trial entry in order for the Trial Office to be able to post the LENT SOMA questionnaires and QoL booklets directly to patients during trial follow up. Patients will be identified using only their unique trial number, initials, and date of birth on the CRF and correspondence between the Trial Office and the participating site. However patients are asked to give permission for the Trial Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process and may also be forwarded to other health care professionals involved in the treatment of the patient (e.g. patient's GP).

The Investigator must maintain documents not for submission to the Trial Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

Representatives of the trials unit may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

The Trial Office will maintain the confidentiality of all patients' data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given consent for data transfer (e.g. AstraZeneca, laboratory staff). Anonymised patient level data may be shared in accordance with the CRCTU Data Sharing Policy.

18 INSURANCE AND INDEMNITY

The University of Birmingham has in place Clinical Trials indemnity coverage for this trial which provides cover to the University for harm which comes about through the University's, or its staff's, negligence in relation to the design or management of the trial and may alternatively, and at the University's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

19 PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer-reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of University of Birmingham. Intellectual property rights will be addressed in the mNCA between Sponsor and site.

The results of the trial will be published on a clinical trials registry and a lay summary made available on the Cancer Research UK website.

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APPENDIX 1 – TUMOUR STAGING - TNM CLASSIFICATION 8TH EDITION [42]

Note, this amendment updates the TNM system used by the trial from the 7th to the 8th Edition of the UICC System as the nodal classifications differ and the current system better fits the definition needed for assessment of nodal disease.

T - Primary Tumour

Tx Primary tumour cannot be assessed
T0 No evidence of primary tumour
Ta Non-invasive papillary carcinoma
Tis Carcinoma in situ: “flat tumour”
T1 Tumour invades subepithelial connective tissue
T2 Tumour invades muscle
- T2a Tumour invades superficial muscle (inner half)
- T2b Tumour invades deep muscle (outer half)

T3 Tumour invades perivesical tissue:
- T3a microscopically
- T3b macroscopically (extravesical mass)

T4 Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
- T4a Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
- T4b Tumour invades pelvic wall or abdominal wall

N - Regional Lymph Nodes

Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2 Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N3 Metastasis in a common iliac lymph node(s)

M - Distant Metastasis

M0 No distant metastasis
- M1a Non-regional lymph nodes
- M1b Other distant metastasis

APPENDIX 2 - DURVALUMAB TOXICITY MANAGEMENT GUIDELINES

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy –October 2022

General Considerations Regarding Immune-Mediated Reactions

These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs).

Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., National Comprehensive Cancer Network (NCCN), European Society of Medical Oncology (ESMO)) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section.

Early identification and management of imAEs is essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying imAEs. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids.

Based on the severity of the imAE, durvalumab and/or tremelimumab should be withheld and corticosteroids administered. Upon improvement to Grade ≤ 1, corticosteroid should be tapered over ≥ 28 days. More potent immunosuppressive agents should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider the need for glucose monitoring.

Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.

Considerations for Prophylaxis for Long Term use of Steroids for Patients Receiving Immune Checkpoint Inhibitor Immunotherapy

- **Infection Prophylaxis: Pneumocystis jirovecii pneumonia (PJP), antifungal and Herpes Zoster reactivation**
- **Gastritis: Consider prophylaxis for patients at high risk of gastritis (e.g. NSAID use, anticoagulation) when the patient is taking steroid therapy**
- **Osteoporosis: Consider measures for prevention and mitigation of osteoporosis .**

Relevant Society Guidelines for Management of imAEs

These society guidelines are provided as references to serve in support of best clinical practice and the TMGs. Please note, these were the current versions of these guidelines at the time of updating TMGs. Please refer to the most up to date version of these guidelines.

1. Brahmer JR, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. J Immunother Cancer 2021;9:e002435
2. Brahmer JR, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018;36(17):1714-1768.
3. Haanen JBAG, et al. Management of toxicities for immunotherapy: European Society for Medical Oncology (ESMO) clinical practice guidelines for diagnosis, treatment, and follow-up. Annals Oncol 2017;28(Suppl4):i119-i1142.

4. Sangro B, et al. Diagnosis and management of toxicities of immune checkpoint inhibitors in hepatocellular carcinoma. J Hepatol 2020;72(2):320-341.

5. Thompson JA, et al. National Comprehensive Cancer Network Guidelines: Management of immunotherapy-related toxicities version 1.2022. Published February 28, 2022.

Pediatric Considerations Regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTCAE grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid ≤ a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks of** initiating corticosteroids.	– All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. – The recommendations for steroid dosing (i.e., mg/kg/day) provided for adult patients should also be used for pediatric patients. – The recommendations for intravenous immunoglobulin (IVIG) and plasmapheresis use provided for adult patients may be considered for pediatric patients. – The infliximab 5 mg/kg IV one time dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For subsequent dosing and dosing in children < 6 years old, consult a pediatric specialist. – For pediatric dosing of mycophenolate mofetil, consult a pediatric specialist. – With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology with similar clinical presentation (e.g. infection, progressive disease). − Monitor patients for signs (e.g. tachypnoea) and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Evaluate patients with imaging and pulmonary function tests, including other diagnostic procedures as described below. − Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related etiologies excluded, and managed as described below. − Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up (including clinically relevant culture specimens to rule out infection), and high- resolution computed tomography (CT) scan. − Consider Pulmonary and Infectious Diseases consults.
	Grade 1	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1** − Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up, and then as clinically indicated.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of	**For Grade 2** − Monitor symptoms daily and consider hospitalization, as clinically indicated. − Consider Pulmonary and Infectious Diseases Consults; – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent).

		steroid taper (≤10 mg prednisone or equivalent).	– Consider HRCT or chest CT with contrast, Repeat imaging study as clinically indicated – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy. such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider, discussing with Clinical Study Lead.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Hospitalize the patient – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. – Consider starting anti-infective therapy if infection is still a consideration on the basis of other diagnostic testing despite negative culture results – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression,

	study protocol for defining the CTCAE grade/severity)		other medications, or infections), including testing for *Clostridium difficile* toxin, etc. – Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs, and ileus). – Consider further evaluation with imaging study with contrast. – Consult a gastrointestinal (GI) specialist for consideration of further workup. – **WHEN SYMPTOMS OR EVALUATION INDICATE AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION.** – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor closely for worseningsymptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 – If toxicity improves to Grade ≤1, then study drug/study regimen can be	**For Grade 2** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes

		resumed after completion of steroid taper (<10 mg prednisone, or equivalent).	(e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Consider further evaluation with imaging study with contrast. – Consider consult of a gastrointestinal (GI) specialist for consideration of further workup. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 days despite therapy with 1 to 2 mg/kg IV methylprednisolone, reconsult GI specialist and, if indicated, promptly start additional immunosuppressant agent such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.** – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.** – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** – For patients treated with durvalumab monotherapy, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (≤10 mg prednisone per day, or equivalent). – For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study	**For Grade 3 or 4** – Urgent GI consult and imaging and/or colonoscopy as appropriate. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – If still no improvement within 2 days, continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.

		investigator, in discussion with AstraZeneca Clinical Study Lead. **<u>For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy,</u>** **Permanently discontinue both durvalumab and tremelimumab for 1) Grade 3 diarrhea/colitis or 2) Any grade of intestinal perforation** **Grade 4** Permanently discontinue study drug/study regimen.	– **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis ***Infliximab should not be used for management of immune-related hepatitis.*** **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate transaminases (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP]) and total bilirubin .
	ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN	– No dose modifications. – If it worsens, then consider holding therapy.	– Continue transaminase and total bilirubin monitoring per protocol.
	ALT or AST > 3 ≤ 5 x ULN or total bilirubin > 1.5 ≤ 3 x ULN	– Hold study drug/study regimen dose until ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN. Resume study drug/study regimen after completion of steroid taper (<10 mg prednisone or equivalent). – Permanently discontinue study drug/study regimen for any case meeting Hy's law laboratory criteria (AST or ALT >3× ULN AND	– Regular and frequent checking of transaminases and total bilirubin (e.g., every 1 to 2 days) until transaminases and total bilirubin elevations improve or resolve. – If no resolution to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN in 1 to 2 days, consider discussing with Clinical Study Lead, as needed.

		bilirubin ≥2 × ULN without initial findings of cholestasis (i.e., elevated ALP) and in the absence of any alternative cause.	– If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	ALT or AST > 5- ≤ 10 x ULN	– Hold study drug/study regimen. Resume study drug/study regimen if elevations downgrade to ALT or AST ≤ 3 x ULN or total bilirubin ≤ 1.5 x ULN after completion of steroid taper (<10 mg prednisone, or equivalent). – **If in combination with tremelimumab, do not restart tremelimumab.**	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – Perform Hepatology Consult, abdominal workup, and imaging as appropriate. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.**
	Concurrent ALT or AST > 3 x ULN and total bilirubin > 2 x ULN ALT or AST > 10 x ULN OR total bilirubin > 3 x ULN	Permanently discontinue study drug/study regimen.	– Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressant.(e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.** – Perform Hepatology Consult, abdominal workup, and imaging as appropriate.
Hepatitis (elevated transaminases and total bilirubin) ***Infliximab should not be used for management of immune-related hepatitis.***	**Any Elevations of AST, ALT, or T. Bili as Described Below**	**General Guidance**	**For Any Elevations Described** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate AST, ALT, ALP, and T. Bili. – For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg).

THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients (or secondary tumour involvement of the liver with abnormal baseline values [BLV])			– For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (HBcAb)+: Evaluate for both HBV and HCV as above.
See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	Isolated AST or ALT >ULN and ≤2.5×BLV,	– No dose modifications. – If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. – For all transaminase elevations , see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	
	ALT or AST > 2.5- ⩽ 5X BLV and ⩽ 20xULN	– Hold study drug/study regimen dose until resolution to AST or ALT ≤2.5×BLV . – If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤2.5×BLV , resume study drug/study regimen after completion	– Regular and frequent checking of Transaminases and total bilirubin (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead.

	of steroid taper (<10 mg prednisone, or equivalent).	– If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
ALT or AST >5-7X BLV and ≤ 20X ULN OR concurrent 2.5-5X BLV and ≤ 20XULN AND total bilirubin > 1.5 - < 2 x ULN	– Withhold durvalumab and permanently discontinue tremelimumab – Resume study drug/study regimen if elevations downgrade to AST or ALT ≤2.5×BLV and after completion of steroid taper (<10 mg prednisone, or equivalent). – Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤2.5×BLV within 14 days	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g.,., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Study Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used.**

	ALT or AST > 7 X BLV OR > 20 ULN whichever occurs first OR bilirubin > 3ULN	Permanently discontinue study drug/study regimen.	**Same as above (except recommend obtaining liver biopsy early)**
Nephritis and/or renal dysfunction	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). − Consider Consulting a nephrologist. − Consider imaging studies to rule out any alternative etiology − Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decreased urine output, or proteinuria). Follow urine protein/creatinine ratio every 3-7 days
	Grade 1	No dose modifications.	**For Grade 1** − Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. − Consider hydration, electrolyte replacement, and diuretics, as clinically indicated. − Consider nephrologist consult if not resolved within 14 days, or earlier as clinically indicated
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion	**For Grade 2** − Consider including hydration, electrolyte replacement, and diuretics as clinically indicated − Follow urine protein/creatinine ratio every 3-7 days − Carefully monitor serum creatinine as clinically warranted.

		of steroid taper (<10 mg prednisone, or equivalent).	– Consult nephrologist and consider renal biopsy if clinically indicated. – Start prednisone 0.5 – 1 mg/kg/day if other causes are ruled out – If event is persistent beyond 5 days or worsens, increase to prednisone up to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup. When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Carefully monitor serum creatinine daily. – Follow urine protein/creatinine ratio every 3-7 days – Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days of steroids or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consider additional workup and prompt treatment with an immunosuppressant
Rash or Dermatitis **(Including Pemphigoid)**	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). **HOLD STUDY DRUG IF GRADE 3 PEMPHIGOID OR SEVERE CUTANEOUS ADVERSE REACTION (SCAR)[1] IS SUSPECTED.**

			– **PERMANENTLY DISCONTINUE STUDY DRUG IF SCAR OR GRADE 3 PEMPIGOID IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade 2** – Consider dermatology consult and skin biopsy, as indicated. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 1 week or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3	**For Grade 3** – Hold study drug/study regimen until resolution to Grade ≤1 or baseline. – If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent).	**For Grade** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. – Consider, as necessary, discussing with Clinical Study Lead.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 4** – Reconsult a dermatologist. Consider skin biopsy (preferably more than 1) as clinically feasible. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.

			– Consider hospitalization. – Monitor the extent of rash [Rule of Nines]. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Consider consulting an endocrinologist for endocrine events. – Consider discussing with Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)). If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide

			assessment of early morning adrenocorticotropin hormone (ACTH), cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	– For Grade 2-4 endocrinopathies <u>other than hypothyroidism and type 1 diabetes mellitus (T1DM)</u>, consider holding study drug/study regimen dose until acute symptoms resolve. – Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10 mg prednisone, or equivalent). – Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement. – **Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.** – **Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. <u>Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.</u>** – For patients with normal endocrine workup (laboratory assessment or magnetic resonance imaging (MRI) scans), repeat laboratory assessments/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g. disease progression,

	study protocol for defining the CTCAE grade/severity)		viral infection, concomitant medications, substance abuse). – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis – Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modifications.	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant gastroenterology specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Consider Gastroenterology referral
	Grade 2	**Consider holding study drug/regimen**	**Grade 2** – Consider IV hydration – Consider Gastroenterology referral

	Grade 3, or 4	**For Grade 3** Hold study drug/study regimen until resolution of elevated enzymes and no radiologic findings If no elevation in enzymes or return to baseline values, then resume study drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration
Nervous System Disorders			
Aseptic Meningitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include headache, photophobia, and neck stiffness, nausea/ vomiting which may resemble an infectious meningitis. – Patients may be febrile. – Mental status should be normal	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available
	Any Grade	Permanently discontinue study drug/study regimen	**For Any Grade** – Consider neurology consult – Consider MRI brain with and without contrast with pituitary protocol and a lumbar puncture for diagnosis. – Exclude bacterial and viral infections. (ie HSV) – Consider IV acyclovir until polymerase chain reactions are available – Consider, as necessary, discussing with Clinical Study Lead.(Last bullet) – Consider hospitalization.

			– Once infection has been ruled out promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.
Encephalitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** – Symptoms may include Confusion, altered behaviour, headaches, seizures, short-term memory loss, depressed level of consciousness, focal weakness, and speech abnormality. –	**For Any Grade** – Consider neurology consult – Consider testing including MRI of the brain with and without contrast, lumbar puncture, electroencephalogram (EEG) to evaluate for subclinical seizures, ESR, CRP, antineutrophil cytoplasmic antibody (ANCA) (if vasculitic process suspected), thyroid panel including TPO and thyroglobulin and additional autoantibodies to rule out paraneoplastic disorders. – Exclude bacterial and viral infections. (i.e. HSV)Consider IV acyclovir until polymerase chain reactions are available.
	Grade 2	**For Grade 2** Permanently discontinue study drug/study regimen.	**For Grade 2** – Consider, as necessary, discussing with the Clinical Study Lead. – Once infection has been ruled out methylprednisolone 1–2 mg/kg/day – For progressive symptoms or if oligoclonal bands are present consider methylprednisolone 1 g IV daily for 3–5 days plus IVIG or plasmapheresis
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider, as necessary, discussing with Clinical Study Lead. – Consider hospitalization. – Once infection is ruled out, start methylprednisolone 1 g IV daily for 3–5 days for progressive symptoms consider adding IVIG or plasmapheresis
Transverse Myelitis	**Any Grade**	**General Guidance** – Permanently discontinue immunotherapy – Consider MRI of the spine and brain	**For Any Grade** – Consider neurology consult – Inpatient care – Consider prompt initiation of high methylprednisolone pulse dosing – Strongly consider IVIG or plasmapheresis

		– Once imaging is complete, consider lumbar puncture Consider testing to rule out additional aetiologies: B12, HIV, rapid plasma reagin (RPR), ANA, anti-Ro/La antibodies, aquaporin-4 IgG, myelin oligodendrocyte glycoprotein (MOG) IgG, paraneoplastic panel for anti-Hu and anti-CRMP5/CV2	
Peripheral neuropathy	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade** – Patients should be evaluated to rule out any alternative etiology for neuropathy (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.
	Grade 1	No dose modifications.	**For Grade 1** – Consider discussing with the Clinical Study Lead, as needed. – Monitor symptoms for interference with ADLS, gait difficulties, imbalance, or autonomic dysfunction
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2** – Consult a neurologist. – Consider EMG/NCS

			– Consider discussing with the Clinical Study Lead, as needed. – Observation for additional symptoms or consider initiating prednisone 0.5–1 mg/kg orally – If progression, initiate methylprednisolone 2–4 mg/kg/day and treat as GBS – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Consider discussing with Clinical Study Lead, as needed. – Recommend hospitalization. – Monitor symptoms and consult a neurologist. – **Treat per Guillain-Barré Syndrome recommendations**
Guillain-Barré Syndrome (GBS)		General Guidance	– Recommend hospitalization – Obtain neurology consult – Obtain MRI of spine to rule out compression lesion – Obtain lumbar puncture – Antibody tests for GBS variants – Pulmonary function tests – Obtain electromyography (EMG) and nerve conduction studies – Frequently monitor pulmonary function tests and neurologic evaluations – Monitor for concurrent autonomic dysfunction – Initiate medication as needed for neuropathic pain
	Grade 2-4	Grade 2-4 Permanently discontinue	**Start IVIG or plasmapheresis in addition to methylprednisolone 1 gram daily for 5 days, then taper over 4 weeks.**
Myasthenia gravis		General Guidance	– Obtain neurology consult – Recommend hospitalization – Obtain pulmonary function tests

			– Obtain labs: ESR, CRP, creatine phosphokinase (CPK), aldolase and anti-striational antibodies – Consider cardiac exam, ECG, troponin, transthoracic echocardiogram for possible concomitant myocarditis – Obtain electromyography (EMG) and nerve conduction studies – Consider MRI of brain/spine to rule out CNS involvement by disease – Avoid medications that might exacerbate MG (e.g. beta blockers, some antibiotics, IV magnesium)
	Grade 2	Permanently discontinue	– Consider pyridostigmine 30mg three times daily and gradually increase based on symptoms (max dose 120mg four times daily) – Consider starting low dose prednisone 20mg daily and increase every 3-5 days. (Target dose 1mg/kg/day. Max dose 100mg daily)
	Grade 3-4	Permanently discontinue	– Start methylprednisolone 1-2mg/kg/day. Taper steroids based on symptom improvement – Start plasmapheresis or IVIG – Consider rituximab if refractory to plasmapheresis or IVIG – Frequent PFT assessments – Daily neurologic evaluations
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade** – Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (ECG), echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with

			baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
	Grade 2, 3 or 4	– If Grade 2-4, permanently discontinue study drug/study regimen.	**For Grade 2-4** – Monitor symptoms daily, hospitalize. – Consider cardiology consultation and a prompt start of high-dose/pulse corticosteroid therapy – Supportive care (e.g., oxygen). – If no improvement consider additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis or other therapies depending on the clinical condition of the patient, based on the discretion of the treating specialist consultant r or relevant practice guidelines. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/ Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for	**General Guidance**	**For Any Grade** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

	defining the CTCAE grade/severity)		– Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, and; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the Clinical Study Lead. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.
	Grade 1	– No dose modifications.	**For Grade 1** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult.

		– Consider, as necessary, discussing with the Clinical Study Lead.
Grade 2	– Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2** – Monitor symptoms daily and consider hospitalization. – Consider Rheumatology or Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the Clinical Study Lead. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 days, consider additional – immunosuppressive therapy such as TNF inhibitors (e.g., infliximab), IVIG or plasmapheresis, or other therapies based on the discretion of the treating specialist consultant or relevant practice guideline **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
Grade 3	**For Grade 3** – Hold study drug/study regimen dose until resolution to Grade ≤1. – Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30	**For Grade 3** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant.

		days or if there are signs of respiratory insufficiency.	– If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether patient may require IV IG, plasmapheresis.
	Grade 4	**For Grade 4** Permanently discontinue study drug/study regimen.	**Grade 4** – Monitor symptoms closely; recommend hospitalization. – Consider Rheumatology and/or Neurology consult – Consider discussing with the Clinical Study Lead, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as a TNF inhibitor (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**

[1] SCAR terms include Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), Erythema Multiforme, Acute Generalized Exanthematous Pustulosis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) and Drug-induced hypersensitivity syndrome.

Other–Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – The Clinical Study Lead may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Monitor as clinically indicated
Grade 2	– Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. – If toxicity worsens, then treat as Grade 3 or Grade 4. – Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. – Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and society guidelines. (See page 4).
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

Infusion-Related Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade** − Manage per institutional standard at the discretion of investigator. − Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For Grade 1** The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event. **For Grade 2** − The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. − Subsequent infusions may be given at 50% of the initial infusion rate.	**For Grade 1 or 2** − Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. − Consider premedication per institutional standard or study protocol prior to subsequent doses. − Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** − Manage severe infusion-related reactions per institutional standard, appropriate clinical practice guidelines, and society guidelines.

Non-Immune-Mediated Reactions

Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2-3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Clinical Study Lead."

List of Abbreviations

AChE	Acetylcholinesterase	ILD	Interstitial lung disease
ACTH	Adrenocorticotropic hormone	imAE(s)	Immune-mediated adverse event(s)
ALT	Alanine aminotransferase	INR	International normalized ratio
ASCO	American Society of Clinical Oncology	IU	International units
AST	Aspartate aminotransferase	IV	Intravenous
(T) Bili	(Total) Bilirubin	IVIG	Intravenous immunoglobulin
BNP	B-type natriuretic peptide	LDH	Lactate dehydrogenase
BUN	Blood urea nitrogen	LFTs	Liver function tests
CRP	C-reactive protein	LLN	Lower limit of normal
CSP	Clinical Study Protocol	MRCP	Magnetic resonance cholangiopancreatography
CT	Computed tomography	MRI	Magnetic resonance imaging
CTCAE	Common Terminology Criteria for Adverse Events	NCCN	National Comprehensive Cancer Network
CTLA-4	Cytotoxic T-lymphocyte antigen-4	NCI	National Cancer Institute
DILI	Drug-induced liver injury	PD-L1	Programmed cell death ligand-1
ECG	Electrocardiogram	PJP	Pneumocystis jirovecii pneumonia
ECHO	Echocardiogram	PO	By mouth
ESMO	European Society of Medical Oncology	SCAR	Severe cutaneous adverse reaction
GI	Gastrointestinal	SITC	Society for Immunotherapy of Cancer
HBcAb	Hepatitis B core antibody	SJS	Stephen Johnson Syndrome
HBeAg	Hepatitis B envelope antigen	T1DM	Type 1 diabetes mellitus
HBsAg	Hepatitis B surface antigen	T3	Triiodothyronine
HBV	Hepatitis B virus	T4	Thyroxine
HCC	Hepatocellular cancer	TEN	Toxic Epidermal Necrolysis
HCV	Hepatitis C virus	TMG(s)	Toxicity management guideline(s)
HgA1c	Hemoglobin A1C	TSH	Thyroid stimulating hormone
ICI(s)	Immune checkpoint inhibitor(s)	ULN	Upper limit of normal

APPENDIX 3 – DEFINITION OF ADVERSE EVENTS

Adverse event

Any untoward medical occurrence in a patient or clinical study subject participating in the study which does not necessarily have a causal relationship with the treatment received.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an adverse reaction. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event

An untoward occurrence that:

Results in death

Is life-threatening*

Requires hospitalisation** or prolongation of existing inpatients' hospitalisation

Results in persistent or significant disability or incapacity

Consists of a congenital anomaly/ birth defect

Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

New malignant tumours reported during the study should generally be assessed as an SAE†

† Medical judgement on an individual event basis should be applied to clarify whether the malignant tumour event should be assessed and reported as an SAE or an AE. 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 and so should only be reported as an AE. Also, some types of malignant tumours, which do not spread remotely after a routine treatment that does not require hospitalisation, may be assessed as AEs; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

The above instruction applies only when the malignant tumour is a new malignant tumour (i.e., it is not the tumour for which entry into the study is a criterion and that is being treated by the IMP under study 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 (e.g., Richter's transformation of B cell chronic lymphocytic leukaemia into diffuse large B cell lymphoma) should not be considered a new malignant tumour.

Serious Adverse Reaction

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

A SUSAR should meet the definition of an adverse reaction, unexpected adverse reaction and SAR.

Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) SmPC for a licensed product).

When the outcome of an adverse reaction is not consistent with the applicable product information the adverse reaction should be considered unexpected.

APPENDIX 4 – COMMON TOXICITY CRITERIA GRADINGS

AEs will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0

The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX 5 – WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians in biomedical research involving human patients

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964

and amended by the

29th World Medical Assembly, Tokyo, Japan, October 1975

35th World Medical Assembly, Venice, Italy, October 1983

41st World Medical Assembly, Hong Kong, September 1989

48th General Assembly, Somerset West, Republic of South Africa, October 1996

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human patients must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human patients.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person patient recruited to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human patients. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. Basic principles

a. Biomedical research involving human patients must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

b. The design and performance of each experimental procedure involving human patients should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the Investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

c. Biomedical research involving human patients should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human patient must always rest with a medically qualified person and never rest on the patient of the research, even though the patient has given his or her consent.

d. Biomedical research involving human patients cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the patient.

e. Every biomedical research project involving human patients should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the patient or to others. Concern for the interests of the patient must always prevail over the interests of science and society.

f. The right of the research patient to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the patient and to minimize the impact of the study on the patient's physical and mental integrity and on the personality of the patient.

g. Physicians should abstain from engaging in research projects involving human patients unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

h. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

i. In any research on human beings, each potential patient must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the patient's freely-given informed consent, preferably in writing.

j. When obtaining informed consent for the research project the physician should be particularly cautious if the patient is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

k. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the patient is a minor, permission from the responsible relative replaces that of the patient in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

I. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical research combined with professional care (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-therapeutic biomedical research involving human Patients (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The patient should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The Investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the patient.

Rad-IO

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☎ **0121 414 3793 or 0121 415 8544 (Mon to Fri 9 am to 5 pm)**

SERIOUS ADVERSE EVENT REPORTING

Email SAE Forms to:

✉ **Reg@trials.bham.ac.uk**

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