Investigational Drug Substance(s)	**Durvalumab and tremelimumab**
Study Number	**ESR-17-12664**
EudraCT	**2017-003159-44**
Sponsor Code	**SOGUG-2017-A-IEC(VEJ)-1**
Version Number	**3.0.**
Date	**12/NOV/2019**

Phase II trial of durvalumab (Medi4736) plus tremelimumab with concurrent radiotherapy in patients with localized muscle invasive bladder cancer treated with a selective bladder preservation approach

Sponsor:

Spanish Oncology Genitourinary Group (SOGUG)

[redacted]

SPONSOR'S SIGNATURE PAGE

Study title: Phase II trial of durvalumab (Medi4736) plus tremelimumab with concurrent radiotherapy in patients with localized muscle invasive bladder cancer treated with a selective bladder preservation approach

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Version number and date: 3.0 – 12/NOV/2019

I have read this protocol and agree to conduct this trial in accordance with all provisions of the protocol, GCPs and the Declaration of Helsinki.

[redacted]

SOGUG Chairman	Signature	Signature date (DD-mm-YYYY)

[redacted]

Coordinating Investigator	Signature	Signature date (DD-mm-YYYY)

INVESTIGATOR'S SIGNATURE PAGE

Study title: Phase II trial of durvalumab (Medi4736) plus tremelimumab with concurrent radiotherapy in patients with localized muscle invasive bladder cancer treated with a selective bladder preservation approach

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Principal Investigator's Name	**Principal Investigator's Signature**	**Signature date (DD-mm-YYYY)**

PROTOCOL SYNOPSIS

Study Title: **Phase II trial of durvalumab (Medi4736) plus tremelimumab with concurrent radiotherapy in patients with localized muscle invasive bladder cancer treated with a selective bladder preservation approach**	
Study Number:	ESR-17-12664
Sponsor Code:	SOGUG-2017-A-IEC(VEJ)-1
***EudraCT No.*:**	2017-003159-44
***Clinicaltrials.gov*:**	NCT3702179
Clinical Phase:	Phase II
Study Duration: - Authorities submission - Trial start date - First patient - Estimated last patient in - Estimated last patient last treatment - Estimated trial completion date	 2Q 2018 (May 31, 2018) 4Q 2018 (Nov. 14, 2018) 1Q 2019 (Jan. 24, 2019) 3Q 2020 3Q 2022 2Q 2023
Investigational Product(s) and Reference Therapy: Durvalumab (MEDI4736) will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration. Tremelimumab is supplied as a sterile solution for IV infusion, filled in 20 mL clear glass vials with a rubber stopper and aluminum seal. Each vial contains 20 mg/mL (with a nominal fill of 20 mL, accounting to 400 mg/vial and a nominal fill of 1.25 mL for the 25mg/vial) of tremelimumab, in an isotonic solution at pH 5.5. Radiotherapy at doses of 46 Gy to the minor pelvis and 64-66 Gy to the bladder.	

Research Hypothesis:

Combined-modality treatment of localized muscle invasive bladder cancer including transurethral resection (TUR), radiotherapy and dual checkpoint inhibition immunotherapy could achieve pathological complete response in some patients (Twyman-Saint Victor C, Rech AJ, Maity A, et al. 2015). These patients could avoid to undergone radical surgery with radical cystectomy and preserve their bladder, without the side-effects associated with chemotherapy and surgery.

Objectives:

Primary Objectives:

To determine the efficacy of durvalumab plus tremelimumab with concurrent radiotherapy in terms of pathological response rate in patients with localized muscle invasive bladder cancer treated with bladder preservation intent.

Secondary Objective(s):

- To determine the rate of patients with bladder preserved, the rate of immediate and late salvage cystectomies and the survival with bladder preserved free of tumor, defined as the time from the start of immunotherapy to either the date of cystectomy or the date of recurrence of muscle- invasive bladder carcinoma or metastasis.
- To determine the disease-free survival, defined as the time from the start of therapy to the date of recurrence of muscle invasive bladder carcinoma or metastases, and overall survival, defined as the time from the start of immunotherapy to the date of death due to any cause.
- To assess the safety profile and tolerability of the combination of durvalumab plus tremelimumab with concurrent radiotherapy.
- To evaluate the long-term functionalism and late sequelae of the treatment in the preserved bladders.

Exploratory Objective(s):

An associated translational study will be performed to analyze and characterize changes in the tumor cell and inflammatory stroma induced by the study treatment in patients with poor response. Additionally, the predictive value of immune biomarkers on response and bladder preservation will be explored.

Exploratory objectives will be determined according the following determinations:

1. Peripheral blood:

Peripheral lymphocytes would be isolated before starting first dose and at different time points during the treatment and progression. Recently has been demonstrated that combination of anti-CTLA4 and anti-PD1 leads to striking change in characteristics of circulating leukocytes in vivo, so peripheral blood analysis might carry more information that allow us to unveil the dynamics of inflammatory and cancer cells in peripheral blood. Blood would be processed for DNA, RNA, miRNA, and exosomes studies.

2. Urine samples (only for patients included in ICO L'Hospitalet):

The samples will be collected at the time of screening period and the end of treatment visit to detect

and to quantify CD8 and CD4 lymphocytes and assess their immune profile (PD-1, TIM-3, CTLA-4, ICOS, and 4-1BB expression and TCR sequence.), in order to evaluate possible correlations between a high number of CD8-PDL1 with worse prognosis (as previously reported by Dr. Quezada, J. Exp. Med. 2018). Further analysis could be implemented and will be detailed in the final Clinical Study Report.

3. Tumor tissue:

Before treatment a fresh biopsy from primary tumor (initial TUR) will be processed to isolate DNA, RNA and paraffin embedded tissue Ventana SP263 assay will be performed, whole exome-seq (WES), and RNA-seq to get information on tumor somatic mutations, included the amino-acid change in missense mutations, and its position into the protein. Additionally, we will predict the immune-peptides repertoire for each patient, combining information about missense mutations and inferred HLA alleles. DNA from tumor will be used to analyze TCR-β chain clonality analysis to achieve information about T-cell diversity and clonality and associate to treatment benefit. Paraffin embedded tissue will be used for immunohistochemistry to study tumor inflammatory stroma (CD3; CD4; CD8; CD45RO; FoxP3, CD20, CD56; CD64; CD11b; CD68; among others), and lymphocyte exhaustion markers (PD-1; PD-L1; CD137; Granzyme B; Perforin; among others). It won't be necessary to wait to have the result of IHC to start study treatment.

A second biopsy will be performed after therapy in patients who do not achieve CR and the sample will be processed the same way as the original biopsy was. The objective of this second biopsy is to study inflammatory changes induced by treatment by immunohistochemistry and changes in T-cell clonality. WES and RNA-seq will allow us to explore whether immunoediting has a role or not in resistance to combined treatment with checkpoint inhibitors and radiotherapy, as immunogenic antigens should be silenced during the treatment.

Study Design:

This is an open, multicenter, phase II trial of the combination of durvalumab plus tremelimumab with concurrent normofractionated radiotherapy in patients with localized muscle invasive bladder cancer treated with a selective multi-modality bladder conservative approach. The study will be conducted in 7 centers with multidisciplinary teams with wide experience in multi-modality bladder preservation therapy.

The treatment consists of initial transurethral resection (TUR) of the tumor, with multiple random biopsies of normal-appearing bladder urothelium, followed by durvalumab 1500 mg i.v. plus tremelimumab 75 mg i.v., every 4 weeks for a total of 3 doses. Two weeks after the initiation of immunotherapy, normofractionated external-beam radiotherapy with high-energy photons will be started. Radiotherapy will be administered concurrently with immunotherapy at doses of 46 Gy to the minor pelvis and 64-66 Gy to the bladder. Afterwards, a urologic evaluation of response will be performed. Response is defined as an absence of invasive cancer at post-immunotherapy biopsy (≤cT1). Patients with response to immunotherapy will be candidates to bladder preservation, whereas in those with residual muscle invasive tumor the possibility of salvage radical cystectomy must be evaluated. Patients developing an isolated bladder invasive relapse during follow-up will be also possible candidates to salvage cystectomy, whereas those developing a superficial relapse in the

preserved bladder will be managed with TUR and intravesical BCG.

The primary endpoint of the study is pathological response evaluated by biopsy performed via cystoscopy at the end of the treatment. Pathological response is defined as the absence of muscle-invasive bladder cancer at post-treatment biopsy (≤cT1). The study will be conducted using a two-stage sequential design. Using the assumption that the treatment would be considered ineffective if it had a response proportion similar to radiotherapy alone (P0: 0.5) but would be of considerable interest if it had a response proportion of 70% of more (P1: 0.7), the sample size requirement is 12 patients for the first stage and 20 additional patients for the second stage. Six or more responses in the first stage were required for continuation to second stage accrual. The study was planned to have a type I error of 0.10 and a power of 80% in a one sided test.

Number of Centers:

7 centers belonging to the Spanish Oncology Genitourinary Group (SOGUG)

Number of Patients:

The total sample size will be 32 patients: 12 patients for the first stage and 20 additional patients for the second stage (see study design)

Study Population:

Patients with non-previously treated localized muscle invasive bladder cancer

Inclusion Criteria:

Patients diagnosed with urothelial carcinoma of the bladder, in clinical stages T2-4a N0 M0, who are not candidates for radical cystectomy by medical reasons, refusal or patient's choice.

1. Patients must have signed the informed consent prior to undergoing any study procedure.
2. Patients must be 18 years of age or older.
3. Patients must have ECOG performance status 0 or 1.
4. A paraffin-embedded tumor sample must be available for the associate molecular study.
5. Body weight >30 Kg.
6. Adequate normal organ and marrow function as defined in section 4.1 of this protocol.
7. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients, according to what is detailed in section 4.1 of this protocol.
8. Patient is willing and able to comply with the protocol for the duration of the study.

Exclusion Criteria:

1. Involvement in the planning and/or conduct of the study (applies to both Sponsor staff and/or staff at the study site).
2. Participation in another clinical study with an investigational product during the last 30 days.
3. Concurrent enrolment in another clinical study unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
4. Involvement in the planning and/or conduct of the study (applies to both Sponsor staff and/or staff at the study site).
5. Participation in another clinical study with an investigational product during the last 30 days.
6. Concurrent enrolment in another clinical study unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.
7. Previous treatment with radiotherapy to the bladder, systemic chemotherapy or immune checkpoint inhibitors. Prior intravesical Bacillus Calmette-Guérin (BCG) treatment for non-muscle invasive bladder cancer is allowed, 28 days prior to study.
8. Presence of regional lymph node or metastatic extension of the disease.
9. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.
10. Any concurrent chemotherapy, investigational product (IP) other than studied in this protocol, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
11. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.
12. History of allogeneic organ transplantation.
13. Active or prior documented autoimmune or inflammatory disorders, as it is detailed in section 4.2 of this protocol.
14. Uncontrolled intercurrent illness, please see section 4 of this protocol.
15. History of another primary malignancy as detailed in section 4 of this protocol.
16. History of active primary immunodeficiency
17. Active infection (see section 4 of this protocol)
18. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. Exceptions are listed in section 4 of this protocol.
19. Receipt of live attenuated vaccine within 30 days prior to the first dose of IMP

20. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control according what is detailed in this protocol (section 4)
21. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
22. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study.
23. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.
24. Known allergy or hypersensitivity to IP or any excipient

Investigational Product(s), Dose, and Mode of Administration:

Durvalumab 1500mg plus tremelimumab 75mg via IV infusion Q4W, starting on Week 0, for a total of 3 doses. N.B If a patient's weight falls to 30kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W and 1mg/kg tremelimumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg plus tremelimumab 75 mg Q4W).

Two weeks after the initiation of immunotherapy, normofractionated external-beam radiotherapy with high-energy photons will be started. Radiotherapy will be administered concurrently with immunotherapy at doses of 46 Gy to the minor pelvis and 64-66 Gy to the bladder.

Study Assessments and Criteria for Evaluation:

Safety Assessments:

Toxicity of the treatment will be assessed and graded using Common Terminology Criteria for Adverse Events CTCAE v4.03 and the Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) criteria. Patients will be evaluated weekly from the start until the end of treatment (week 12).

To monitor accurately the potential toxicity of radiotherapy associated with durvalumab and tremelimumab, an initial cohort of 5 patients will be treated. If no dose limiting toxicity is observed in ≥2 of these patients (in observation period of 12 weeks (4 weeks after RT) , the rest of patients will be treated at full doses. In contrast, if severe toxicity is observed in ≥2 of these patients, 3 additional patients will be treated. If dose-limiting toxicity is seen in one of these additional patients during observation period, the therapeutic regimen will be modified in the subsequent ones, administering full doses of durvalumab but discontinuing tremelimumab after the first dose.

Efficacy Assessments:

The primary endpoint of the study is pathological response evaluated by biopsy performed via cystoscopy at the end of the treatment. Pathological response is defined as the absence of muscle-invasive bladder cancer at post-treatment biopsy (≤cT1).

Secondary endpoints are: Rate of patients with bladder preserved, rate of immediate and late salvage cystectomies; survival with bladder preserved free of tumor, defined as the time from the start of immunotherapy to either the date of cystectomy or the date of recurrence of muscle- invasive bladder carcinoma or metastasis; disease-free survival, defined as the time from the start of therapy to the date of recurrence of muscle invasive bladder carcinoma or metastases, and overall survival, defined as the time from the start of immunotherapy to the date of death due to any cause; safety profile and tolerability of the combined-modality treatment and long-term functionalism and late sequelae of the treatment in the preserved bladders.

Statistical Methods and Data Analysis:

The primary endpoint of the study is pathological response evaluated by biopsy performed via cystoscopy at the end of the treatment. Pathological response is defined as the absence of muscle-invasive bladder cancer at post-treatment biopsy (≤cT1). The study will be conducted using a two-stage sequential _Simon optimal design. Using the assumption that the treatment would be considered ineffective if it had a response proportion similar to radiotherapy alone (P0: 0.5) but would be of considerable interest if it had a response proportion of 70% of more (P1: 0.7), the sample size requirement is 12 patients for the first stage and 20 additional patients for the second stage. Six or more responses in the first stage are required for continuation to second stage accrual. The study is planned to have a type I error of 0.10 and power of 80% one sided test.

Sample Size Determination:

The sample size requirement is 12 patients for the first stage and 20 additional patients for the second stage. Six or more responses in the first stage are required for continuation to second stage accrual.

Protection of Personal Data

The Sponsor is committed to compliance with Organic Law 3/2018, of December 5, Protection of Personal Data and guarantee of digital rights as well as Regulation (EU) 2016/679 of the European Parliament and the Council of April 27 of 2016 Data Protection (RGPD).

Protocol assessments:

Protocol Activities	Screening (≤28 Days Prior to Randomization)	Treatment Period (treatment period for durvalumab + tremelimumab and radiotherapy).											Response evaluation to therapy [j]	Follow-up [k]
		W 1	W 2	W 3	W 4	W 5	W 6	W 7	W 8	W 9	W1 0	W1 1	W12 (End of treatment visit)		
Written informed consent/assignment of patient identification number	X														
Preliminary eligibility fulfillment (investigator's opinion)	X														
Demography and history of tobacco and alcohol use	X														
Previous treatments for bladder cancer	X														
Recent formalin-fixed tumour biopsy	X														
Formal verification of eligibility criteria	X														
Medical and surgical history	X														
Hepatitis B and C; HIV	X														
Urine hCG or serum βhCG[a]	X												X		
Durvalumab administration		X				X				X					
Tremelimumab administration		X				X				X					
Radiotherapy administration				X	X	X	X	X	X						
Physical examination [b]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs (pre-, during and post-infusion vital signs assessments)[c]	X	X				X				X	X	X	X		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		
12- lead ECG [d]	X	X													
Adverse event/serious adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Serum chemistry (complete clin. chem. panel including liver enzymes)[e]	X	X	X	X	X	X	X	X	X	X			X		X
Thyroid function tests (TSH and fT3 and fT4)[f]	X					X				X			X		X
Hematology [e]	X	X	X	X	X	X	X	X	X	X			X		X
Urinalysis [g]	X					X				X			X		X
Coagulation parameters [h]	X												X		
Cystoscopy and random biopsies	X													X	
Tumour assessment (CT scan)[i]	X												X		X
Biomarker/pharmacodynamic sampling															
Peripheral blood [l]		X			X				X				X		
Fresh tumor biopsies [m]	X													X	
Urine samples [n]	X												X		

[a] Pre-menopausal female patients of childbearing potential only

[b] Full physical examination at baseline; targeted physical examination at other time points

[c] Patients will have their blood pressure and pulse measured before, during, and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- 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.

[d] ECG during screening and on cycle 1 Day 1 within 1 hr prior to the start of the first study treatment. Thereafter as clinically indicated.

[e] According what is detailed on tables 4 and 5. If screening laboratory assessments are performed within 3 days prior to 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. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated. Depending on the profile of the combination agent, the frequency of the hematology, serum chemistry and LFT testing may need to be increased to every two weeks.

[f] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[g] Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.

[h] Coagulation tests: prothrombin time, APTT and INR – to be performed at screening and EoT visit, and only as clinically indicated thereafter.

[i] Timing of CT scans:

- Initial Staging: thorax, abdomen and pelvis CT scan

- Post-therapy re-staging (week 12): thorax, abdomen and when applicable pelvis CT scan

[j] Six weeks since the end of radiotherapy. Cystoscopy and bladder biopsy will be performed for ALL patients as an efficacy determination

[k] Follow-up: Pelvis and abdomen CT scan, urine cytology and Rx Thorax every 3 months the first year, every 4 months the second year and every 6 months thereafter. Additional cystoscopy and bladder biopsy will be performed in case of detection abnormalities in the cytology or imaging studies

[l] Peripheral blood: Week 1 prior to the administration of durvalumab and tremelimumab, W2 before initiation of RT, W8 at the end of RT, and W12 at the time of tumor response

[m] Fresh tumor biopsies: A fresh biopsy sample, optional, at the time of initial TUR. Those patients who have not achieved complete response will be submitted to a fresh biopsy, if not clinically contraindicated. It will be required to send fresh and formalin fixed samples of the pathological surgical specimen from patients who are candidate to salvage cystectomy.

[n] Urine samples (Optional): only for patients included in ICO L'Hospitalet. The samples will be collected at the time of screening periode and the end of treatment visit. The first urine in the morning would be collected using a standard testing tube of 50 ml.

Table of contents

ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AChE	Acetylcholinesterase
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
APF12	Proportion of patients alive and progression free at 12 months from randomization
AST	Aspartate aminotransferase
AUC	Area under the curve
$AUC_{0\text{-}28day}$	Area under the plasma drug concentration-time curve from time zero to Day 28 post-dose
AUC_{ss}	Area under the plasma drug concentration-time curve at steady state
BCG	Bacillus Calmette-Guérin
BICR	Blinded Independent Central Review
BoR	Best objective response
BP	Blood pressure
C	Cycle
CD	Cluster of differentiation
CI	Confidence interval
CL	Clearance
C_{max}	Maximum plasma concentration
$C_{max,ss}$	Maximum plasma concentration at steady state
CR	Complete response

CSA	Clinical study agreement
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CTLA-4	Cytotoxic T–lymphocyte-associated antigen 4
$C_{trough,ss}$	Trough concentration at steady state
CXCL	Chemokine (C-X-C motif) ligand
DoR	Duration of response
EC	Ethics Committee, synonymous to Institutional Review Board and Independent Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDoR	Expected duration of response
EGFR	Epidermal growth factor receptor
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator’s Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee

IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IHC	Immunohistochemistry
IL	Interleukin
ILS	Interstitial lung disease
IM	Intramuscular
IMT	Immunomodulatory therapy
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent-to-Treat
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
mAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Minister of Health, Labor, and Welfare
miRNA	Micro-ribonucleic acid
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
NE	Not evaluable
NSCLC	Non–small-cell lung cancer
OAE	Other significant adverse event
ORR	Objective response rate
OS	Overall survival

PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PDx	Pharmacodynamic(s)
PFS	Progression-free survival
PFS2	Time to second progression
PGx	Pharmacogenetic research
PK	Pharmacokinetic(s)
PR	Partial response
q2w	Every 2 weeks
q3w	Every 3 weeks
q4w	Every 4 weeks
q6w	Every 6 weeks
q8w	Every 8 weeks
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST 1.1	Response Evaluation Criteria in Solid Tumors, version 1.1
RNA	Ribonucleic acid
RR	Response rate
RT-QPCR	Reverse transcription quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Stable disease
SNP	Single nucleotide polymorphism
SoC	Standard of Care
SOGUG	Grupo Español para el Estudio del Cáncer Urológico

sPDL1	Soluble programmed cell death ligand 1
T_3	Triiodothyronine
T_4	Thyroxine
TSH	Thyroid-stimulating hormone
TUR	Transurethral resection
ULN	Upper limit of normal
US	United States
WBDC	Web-Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

The purpose of the present study is to explore feasibility, toxicity and activity of the integration of double-checkpoint inhibition immunotherapy, associated with transurethral resection (TUR) and radiotherapy, to the treatment of localized muscle-invasive bladder cancer with selective bladder-preservation intent.

1.1. Disease background

Urothelial cancer of the bladder is the second most common genitourinary malignancy in developed countries and third most common cause of death among genitourinary tumors. Radical cystectomy has long been considered the standard treatment for patients with muscle-invasive bladder carcinoma. Because of the morbidity and decreased quality of life associated with this procedure, organ-preserving alternatives to cystectomy have been extensively explored (James ND et al, 2012; Milosevic M et al 2007; Mark RH et al, 2014; Ploussard G et al, 2014; Shipley WU et al, 1998) .

1.1.1. Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (Dunn 2004) PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor (Keir et al 2008) and to CD80 (Butte et al, 2007). PD-L1 expression is an adaptive response that helps tumors evades detection and elimination by the immune system. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g., IFNγ) and can be found on both tumor cells (TC) and tumor infiltrating IC. To address this issue is important in bladder cancer context because PD-L1 is widely expressed in urothelial tumor cells and tumor infiltrated mononuclear cells, and is correlated with a better survival in some studies (Bellmunt J et al, 2015). The binding of PD L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target TC, and protecting the tumor from immune elimination (Zou and Chen 2008). PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated (Butte et al, 2007; Paterson et al. 2011).

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28 (Granier C et al, 2017).

In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism (Stewart et al 2015).

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (Brahmer et al. 2012; Hirano et al. 2005; Iwai et al. 2002; Okudaira et al. 2009; Topalian et al. 2012; Zhang et al. 2008) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (Powles et al. 2014; Rizvi et al 2015; Segal et al 2016). In addition, high mutational burden e.g., in bladder carcinoma (Alexandrov et al. 2013) may contribute to the responses seen with immunotherapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells. (Fife and Bluestone, 2008) Blockade of CTLA-4 binding to CD80/86 by anti-CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors (Ni L et al, 2017).

Pre-clinical data has now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity (Scott Antonia, Sarah B et al, 2016). Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies whilst nivolumab and pembrolizumab, two anti-PD-1 agents and atezolizumab, an anti PD-L1 agent have been granted approvals by agencies such as the United States of America Food and Drug Administration and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and urothelial carcinoma. In addition, data from agents in the anti-PD-1/PD-L1 class shows clinical activity in a wide range of tumor types (Homet Moreno B, et al, 2015).

1.1.2. Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells (IC). It is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document.) Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. In vitro studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFNγ; Stewart et al. 2015).

As of the data cut-off (DCO) date (12 July 2017), an estimated 4067 patients have been exposed to 1 or more doses of durvalumab in ongoing AstraZeneca-sponsored Phase I to III studies, either as monotherapy or in combination, and 5911 patients where the treatment arm is blinded. Additionally, approximately 4000 patients have been exposed to 1 or more doses of durvalumab in externally-sponsored/investigator-initiated clinical trials (ESR/IITs) (see Durvalumab IB version 12, Appendix B Table 46).
Estimates of overall cumulative patient exposure based on actual exposure data from any completed clinical trials and the enrolment/randomisation schemes for ongoing open label and blinded trials are: 3723 patients received durvalumab monotherapy and 3372 received durvalumab in combination with tremelimumab. No AstraZeneca or MedImmune study has been terminated prematurely due to toxicity. Refer to the current durvalumab Investigator’s Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.3. Tremelimumab

Tremelimumab is a human immunoglobulin (Ig)G2 mAb that is directed against CTLA-4; cluster of differentiation [CD]152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. Tremelimumab completely blocks the interaction of human CTLA-4 with CD80 and CD86, resulting in increased release of cytokines (interleukin [IL]-2 and interferon [IFN]-γ) from human T cells, peripheral blood mononuclear cells and whole blood (Tarhini and Kirkwood 2008). Tremelimumab is being developed by AstraZeneca for use in the treatment of cancer.

As of the data cutoff date (12 July 2017), approximately 1617 patients have been exposed to one or more doses of tremelimumab monotherapy across the program; 574 patients from AstraZeneca/MedImmune sponsored studies and 936 patients from legacy studies (monotherapy) and 107 patients from externally sponsored studies. Details on the safety profile of tremelimumab monotherapy are summarized in Tremelimumab IB, section

5.2.2. Refer to the current tremelimumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics.

1.1.4. Durvalumab in combination with tremelimumab

Because the mechanisms of action of CTLA-4 and PD-1 are non-redundant targeting both PD-1 and CTLA-4 pathways may have additive or synergistic activity (Pardoll 2012); therefore, in addition to evaluating both agents in the monotherapy setting in a number of cancer indications AstraZeneca is also investigating the use of durvalumab + tremelimumab combination therapy for the treatment of cancer.

Study D4190C00006 is a Phase Ib dose-escalation study to establish the safety, PK/pharmacodynamics, and preliminary anti-tumor activity of durvalumab + tremelimumab combination therapy in patients with advanced NSCLC. The dosing schedule utilized is durvalumab every 2 or 4 weeks (Q2W, Q4W) up to 12 months, combined with tremelimumab Q4W up to Week 24 for 7 doses then every 12 weeks (Q12W) for 2 additional doses for up to 12 months. The study is ongoing and continues to accrue (Scott Antonia, Sarah B 2016). In addition, other clinical studies have since started looking at the combination in both NSCLC and other oncology indications.

To date more than 1000 patients have received the combination using several doses and dosing schedules. Details on the safety profile of durvalumab + tremelimumab combination therapy are summarized in Section 1.4.2. Refer to the current editions of the durvalumab and tremelimumab IBs for a complete summary of non-clinical and clinical information including safety, PK and efficacy.

1.1.5. Combination with Radiotherapy

Nonclinical studies suggest that radiotherapy may sensitize tumor cells to immune-mediated attack (McFarland 2012) by prompting release of soluble tumor antigens from killed cells as well as by increasing tumor cell surface expression of antigens and receptors mediating T-cell recognition and/or killing and enhanced efficiency of professional antigen-presenting cells (Ferrara 2009, Kershaw 2013). Together with the observation that radiation may induce expression of chemokines needed for T-cell trafficking (Kershaw 2013, Hellevik 2014), these data suggest that radiation can function as an immune adjuvant to help reverse the suppression of tumor immune responses.

As a crucial tumor immune-evasion mechanism, however, Treg-mediated immunosuppression may be a key obstacle for successful tumor immunotherapy in general, and following radiation in particular. Following sub-lethal irradiation of antigen-primed mice, antigen-specific immune suppression mediated primarily by CD4+

CD25+ Tregs develops over several weeks. The proportion of Treg to T effector populations is skewed, with higher numbers of Tregs (McFarland 2012). The influx of Treg cells into an irradiated tumor microenvironment therefore may counteract any benefit obtained from increased antigen release, enhanced antigen presentation, or influx of T effector cells. Data from mice also suggest that tumor cells may counterbalance this effect by upregulating PD-L1 in response to radiation (Deng 2014). Importantly, administration of an anti-PD-L1 antibody could greatly enhance radiation-induced tumor regression and survival in this study, providing strong support to the notion that PD-1/PD-L1 blockade may overcome immunosuppression mediated by radiation-induced PD-L1 upregulation

1.2. Research hypothesis

Combined-modality treatment of localized muscle invasive bladder cancer including TUR, radiotherapy and dual checkpoint inhibition immunotherapy could achieve pathological complete response in some patients. These patients could avoid to undergone radical surgery with radical cystectomy and preserve their bladder, without the side-effects associated with chemotherapy.

1.3. Rationale for conducting this study

Several studies have shown that long-term bladder preservation can be achieved in a significant proportion of patients with a multimodal treatment, including transurethral resection (TUR) of the bladder tumor and radiotherapy, often associated with neoadjuvant or concurrent chemotherapy (James 2012, Milosevic 2007, Mak 2014, Ploussard 2014, Shippley 1998). In these studies, only patients who achieve a pathological complete response of the muscle-invasive bladder tumor with the treatment are considered candidates for bladder preservation. In the rest of patients, salvage cystectomy should be at last recommended (Kaufman 1993, Mitin 2016). Interestingly, the survival rates observed using this approach are comparable to those expected with aggressive surgery (Mak 2014, Efstathiou 2015, Arcangeli 2016). These studies showed that this approach is clearly feasible and therefore constitutes an alternative to standard radical surgery for patients with surgical contraindication, cystectomy refusal or patient's choice. Bladder preservation via combined-modality treatment provides a considerable improvement in the quality of life of selected patients by allowing them to avoid radical cystectomy (Mak 2016, Efstathiou 2009). However, given the complexity of this multimodality treatment, it can only be performed in centers with experienced multidisciplinary teams including urologists, oncologists and radiotherapists. Our center, ICO-HUB, has a large experience in bladder preservation therapy with radiotherapy alone and associated with chemotherapy (Garcia del Muro X 2004). Recently, we conducted also a clinical trial of multimodal bladder preservation using a targeted agent, sorafenib, in combination with radiotherapy (Garcia del Muro X 2011).

The incorporation of immunotherapy, especially double-checkpoint inhibition, to the multimodality therapy of localized muscle-invasive bladder cancer could have potential important advantages over the current regimens including cisplatin-based chemotherapy. Firstly, immunotherapy habitually lack the strong toxicity of this chemotherapy, and could substitute it in the bladder-sparing regimen. Furthermore, the potential of immunotherapy might be optimal being used in a very early stage, in non-previously treated patients with low tumor burden, without presence of metastases, and without significant repercussion in the performance status. Therefore, the purpose of the present study is to explore feasibility, toxicity and activity of the integration of double-checkpoint inhibition immunotherapy, associated with TUR and radiotherapy, to the treatment of localized muscle-invasive bladder cancer with selective bladder-preservation intent.

Additionally, the availability of a recent histologic sample before the start of treatment, and a second sample after the treatment in those patients without response to the treatment, constitutes a valuable model for an associated translational study.

1.3.1. Durvalumab + tremelimumab combination therapy dose rationale

The durvalumab + tremelimumab doses and regimen selected for this study are based on evidence, the goal of selecting an optimal combination dose of durvalumab and tremelimumab that would yield sustained target suppression (sPD-L1), demonstrate promising efficacy, and have an acceptable safety profile.

Pharmacokinetics/Pharmacodynamics data

Study D4190C00006 included dose cohorts with both a Q4W and a Q2W schedule of durvalumab in combination with a Q4W schedule of tremelimumab. The Q4W schedule was included to align with the Q4W dosing of tremelimumab. PK simulations from durvalumab monotherapy data indicated that a similar area under the plasma drug concentration-time curve at steady state (AUC_{ss}; 4 weeks) was expected following both 10 mg/kg Q2W and 20 mg/kg Q4W dosing with durvalumab. The observed durvalumab PK data from the D4190C00006 study were in line with the predicted monotherapy PK data developed pre-clinically and in line with that seen in the first-time-in-human (FTIH), single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. This demonstrates similar exposure of durvalumab 20 mg/kg Q4W and 10 mg/kg Q2W, with no alterations in PK when durvalumab and tremelimumab (doses ranging from 1 to 3 mg/kg) are dosed together. While the median maximum plasma concentration at steady state ($C_{max,ss}$) is expected to be higher with 20 mg/kg Q4W (approximately 1.5 fold) and median trough concentration at steady state ($C_{trough,ss}$) is expected to be higher with 10 mg/kg Q2W (approximately 1.25 fold), this is not expected to impact the overall safety and efficacy profile, based on existing preclinical and clinical data (Scott Antonia, Sarah B 2016) .

Monotonic increases in PDx activity were observed with increasing doses of tremelimumab relative to the activity observed in patients treated with durvalumab monotherapy. There was evidence of augmented PDx activity relative to durvalumab monotherapy with combination doses containing 1 mg/kg tremelimumab, inclusive of both the 15 and 20 mg/kg durvalumab plus 1 mg/kg tremelimumab combinations.

Clinical data

In Study D4190C00006 various dose combinations have been explored, with doses of tremelimumab ranging from 1 to 10 mg/kg and doses of durvalumab ranging from 3 to 20 mg/kg. Tremelimumab was given on a Q4W schedule whilst durvalumab was explored in both a Q4W and Q2W schedule, with the goal of identifying the dose combination that best optimizes the benefit-risk profile in an acceptable range of PK and

pharmacodynamic values (Scott Antonia, Sarah B 2016).

Patients treated with doses of tremelimumab above 1 mg/kg had a higher rate of adverse events (AEs), including discontinuations due to AEs, serious AEs (SAEs), and severe AEs. Between the 10 mg/kg durvalumab + 1 mg/kg tremelimumab and 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohorts treated at the q2w schedule, the number of patients reporting any AE, Grade 3 AEs, SAEs, and treatment-related AEs was higher in the 10 mg/kg durvalumab + 3 mg/kg tremelimumab cohort than the 10 mg/kg durvalumab + 1 mg/kg tremelimumab cohort. A similar pattern was noted in the q4w regimens, suggesting that, as the dose of tremelimumab increased above 1 mg/kg, a higher rate of treatment-related events may be anticipated. Further, the SAEs frequently attributed to immunotherapy, pneumonitis and colitis, were more commonly seen in cohorts using either 3 or 10 mg/kg of tremelimumab compared to the 1-mg/kg dose cohorts. Together, these data suggest that a combination using a tremelimumab dose of 1 mg/kg appeared to minimize the rate of toxicity when combined with durvalumab. Thus, all combination doses utilizing either the 3 or 10 mg/kg doses of tremelimumab were eliminated in the final dose selection (Scott Antonia, Sarah B 2016).

In contrast, cohorts assessing higher doses of durvalumab with a constant dose of tremelimumab did not show an increase in the rate of AEs. The data suggested that increasing doses of durvalumab may not impact the safety of the combination as much as the tremelimumab dose. Further, safety data between the 10-mg/kg and 20-mg/kg cohorts were similar, with no change in safety events with increasing dose of durvalumab.

In Study D4190C00006, of all treatment cohorts, the cohort of patients treated in the 20 mg/kg durvalumab + 1 mg/kg tremelimumab group had a tolerable safety profile, but still showed strong evidence of clinical activity. No dose-limiting toxicities (DLTs) were reported in this cohort.

Preliminary clinical activity of the durvalumab and tremelimumab combination did not appear to change with increasing doses of tremelimumab. The 15- and 20-mg/kg durvalumab q4w cohorts demonstrated objective responses at all doses of tremelimumab, and increasing doses of tremelimumab did not provide deeper or more rapid responses.

Efficacy data suggested that the 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose cohort may demonstrate equivalent clinical activity to other dose combinations. Of the 14 patients in this cohort, there were 4 patients (29%) with PR, 4 patients (29%) with SD, and 2 patients (14%) with PD. Two patients were not evaluable for response (Scott Antonia, Sarah B 2016).

Altogether, the data suggested that a 20 mg/kg durvalumab + 1 mg/kg tremelimumab dose combination should be selected for further development.

Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information on the durvalumab + tremelimumab combination, including safety, efficacy and pharmacokinetics.

1.3.2. Rationale for fixed dosing

A population 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 Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on the PK of durvalumab (coefficient of ≤0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-patient variability with fixed dosing regimen.

Similarly, a population PK model was developed for tremelimumab using data from Phase 1 through Phase 3 (N=654; doses=0.01 to 15 mg/kg Q4W or Q90D; metastatic melanoma) (Wang et al 2014). Population PK model indicated minor impact of body WT on PK of tremelimumab (coefficient of ≤0.5). The WT-based (1 mg/kg Q4W) and fixed dosing (75 mg/kg Q4W; based on median body WT of ~75 kg) regimens were compared using predicted PK concentrations (5th, median and 95th percentiles) using population PK model in a simulated population of 1000 patients with body weight distribution of 40 kg to 120 kg. Similar to durvalumab, simulations indicated that both body WT-based and fixed dosing regimens of tremelimumab yield similar median steady state PK concentrations with slightly less between-patient variability with fixed dosing regimen.

Similar findings have been reported by others (Ng et al 2006; Wang et al 2009; Zhang et al 2012; Narwal et al 2013). 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 (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-patient variability in pharmacokinetic/pharmacodynamics parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and a fixed dose of 75 mg Q4W tremelimumab (equivalent to 1 mg/kg

Q4W) is included in the current study.

1.3.3. Radiotherapy dose

Radiotherapy will be administered at standard doses for radical treatment of the bladder with bladder-sparing intent. The radiotherapy schedule selected for this study has been widely used in several bladder preservation studies (James ND1, Hussain SA, Hall E, et al. Radiotherapy with or without chemotherapy in muscle-invasive bladder cancer. N Engl J Med. 2012 Apr 19;366(16):1477-88). 64 Gy in 32 fractions, given as 2 Gy/day (5 doses/week) at doses of 46 Gy to the minor pelvis (23 doses) and 64-66 Gy to the bladder (32 doses) will be administered.

1.4. Benefit-risk and ethical assessment

1.4.1. Durvalumab + tremelimumab

1.4.1.1. Overall risks

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

Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be because of inflammatory cells on specific tissues. These risks are generally events with a potential inflammatory mechanism and which may require more frequent monitoring and/or unique interventions such as immunosuppressants and/or endocrine replacement therapy. These risks include gastrointestinal AEs such as colitis and diarrhoea, pneumonitis /interstitial lung disease (ILD), renal AEs such as, nephritis and increases in creatinine, hepatic AEs such as hepatitis and liver enzyme elevations, skin events such as rash and dermatitis, endocrinopathies such as hypo- and hyperthyroidism, hypophysitis, adrenal insufficiency. diabetes mellitus type I and diabetes insipidus, and neurotoxicities such as myasthenia gravis and Guillain-Barre syndrome.

1.4.1.2. Durvalumab

ADRs in durvalumab monotherapy

The identified risks with durvalumab monotherapy include the following: cough/productive cough, pneumonitis, ILD, dysphonia, ALT/AST increased, hepatitis, diarrhoea, abdominal pain, colitis, hypothyroidism, hyperthyroidism, blood TSH increased, blood TSH decreased, adrenal insufficiency, Type 1 diabetes mellitus, hypophysitis/hypopituitarism, diabetes insipidus, blood creatinine increased, dysuria, nephritis, rash, pruritus, night sweats, dermatitis, myocarditis, pyrexia, oedema peripheral, upper respiratory tract infections, pneumonia, oral candidiasis, dental and oral

soft tissue infections, influenza, myalgia, myositis, polymyositis and infusion-related reaction.

- *Potential imAEs for durvalumab and durvalumab in combination with tremelimumab include*
    - Pancreatitis
    - Other rare or less frequent events with a potential immune-mediated aetiology, eg, pericarditis, sarcoidosis, uveitis, and other events involving the eye (eg, keratitis and optic neuritis), skin (eg, scleroderma and vitiligo), and haematological (eg, haemolytic anaemia and immune thrombocytopenic purpura), rheumatological events (polymyalgia rheumatica and autoimmune arthritis) and neuropathy/neuromuscular toxicities (eg, myasthenia gravis, Guillain Barre syndrome)

- *Hypersensitivity reactions including:*
    - Anaphylaxis and allergic reaction
    - Cytokine release syndrome
    - Immune complex disease

- Other infections

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

In monotherapy clinical studies AEs (all grades) reported very commonly (≥10% of patients) are fatigue, nausea, decreased appetite, dyspnea, cough, constipation, diarrhea, vomiting, back pain, pyrexia, abdominal pain, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 8% of patients experienced an AE that resulted in permanent discontinuation of durvalumab. and approximately 5% of patients experienced an SAE that was related to durvalumab by the study 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 (see the Dosing Modification and Toxicity Management Guidelines in appendix 1).

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

1.4.1.3. Tremelimumab

Risks with tremelimumab monotherapy are GI effects (colitis, diarrhoea, enterocolitis and intestinal perforation), endocrine disorders (hypo and hyperthyroidism, hypophysitis and adrenal insufficiency), skin effects (rash, and pruritus), elevations in lipase and amylase,

other gastrointestinal events e.g. ulcerative colitis, dehydration, nausea and vomiting; hepatic events including hepatitis, and liver enzyme elevations; pneumonitis and ILD; clinical manifestations of pancreatitis; nervous system events including encephalitis, peripheral motor and sensory neuropathies, Guillain-Barre and proximal muscle weakness; cytopenias including thrombocytopenia, anemia and neutropenia; infusion-related reactions, anaphylaxis, and allergic reactions; renal events including renal failure, acute kidney injury, nephritis, nephrotic syndrome, autoimmune nephritis and electrolyte abnormalities such as hypokalemia; autoimmune diseases including autoimmune arthritis, Sjögren's syndrome and giant cell temporal arteritis; hyperglycemia and diabetes mellitus; and pyrexia (Comin-Anduix B, Escuin-Ordinas H., 2016).

Further information on these risks can be found in the current version of the tremelimumab IB.

Using pooled data from monotherapy clinical studies AEs (all grades) reported very commonly (≥10% of patients) were diarrhea, nausea, fatigue, pruritus, decreased appetite, rash, vomiting, dyspnea, constipation, cough, pyrexia, abdominal pain, decreased weight, headache, asthenia, and anaemia. Approximately 16% of patients experienced an AE that resulted in permanent discontinuation of tremelimumab and approximately 45% of patients experienced an SAE.

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

1.4.2. Durvalumab + tremelimumab

The safety of durvalumab + tremelimumab combination therapy is being evaluated in the ongoing dose escalation and dose expansion Study 006, in patients with NSCLC, and has so far shown a manageable safety and tolerability profile.

The potential risks with the combination of durvalumab + tremelimumab are similar to those for durvalumab and tremelimumab monotherapy. Emerging data from study 006 and from combinations of other agents in the same class indicate an increased frequency and/or severity of some of these potential immune-mediated toxicities.

In durvalumab+tremelimumab combination studies at the dose of durvalumab 20 mg/kg and tremelimumab 1 mg/kg AEs (all grades) reported very commonly (≥10% of patients) are fatigue, diarrhoea, nausea, dyspnea, decreased appetite, pruritus, vomiting, anaemia, constipation, cough, abdominal pain, pyrexia, back pain, hyponatremia and rash.

Approximately 13% of patients experienced an AE that resulted in permanent discontinuation of study drug and approximately 13% of patients experienced an SAE

that was related to durvalumab and tremelimumab by the study investigator (Scott Antonia, Sarah B 2016).

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

2. STUDY OBJECTIVE

2.1. Primary objective(s)

To determine the efficacy of durvalumab plus tremelimumab with concurrent radiotherapy in terms of pathological response rate in patients with localized muscle invasive bladder cancer treated with bladder preservation intent.

2.2. Secondary objective(s)

- To determine the rate of patients with bladder preserved, the rate of immediate and late salvage cystectomies and the survival with bladder preserved free of tumor, defined as the time from the start of immunotherapy to either the date of cystectomy or the date of recurrence of muscle- invasive bladder carcinoma or metastasis.
- To determine the disease-free survival, defined as the time from the start of therapy to the date of recurrence of muscle invasive bladder carcinoma or metastases, and overall survival, defined as the time from the start of immunotherapy to the date of death due to any cause
- To assess the safety profile and tolerability of the combination of durvalumab plus tremelimumab with concurrent radiotherapy
- To evaluate the long-term functionalism and late sequelae of the treatment in the preserved bladders

2.3. Exploratory objective(s)

An associated translational study will be performed to analyze and characterize changes in the tumor cell and inflammatory stroma induced by the study treatment, in patients with poor response. Additionally, the predictive value of immune biomarkers on response and bladder preservation will be explored.

3. STUDY DESIGN

3.1. Overview of study design

This is an open-label, multicenter, phase II trial of the combination of durvalumab plus tremelimumab with concurrent normofractionated radiotherapy in patients with localized muscle invasive bladder cancer treated with a selective multimodality bladder conservative approach. The study will be conducted in a small group of centers with multidisciplinary teams with wide experience in multimodality bladder preservation therapy (7 centers belonging to SOGUG).

The treatment consisted of initial transurethral resection (TUR) of the tumor, with multiple random biopsies of normal-appearing bladder urothelium, followed by durvalumab 1500 mg i.v. plus tremelimumab 75 mg i.v., every 4 weeks for a total of 3

doses. Two weeks after the initiation of immunotherapy, normofractionated external-beam radiotherapy with high-energy photons will be started. Radiotherapy will be administered concurrently with immunotherapy at doses of 46 Gy to the minor pelvis and 64-66 Gy to the bladder. Six weeks after the end of radiotherapy as an efficacy determination, ALL patients will undergo a new cystoscopy with biopsies of the tumor bed and all residual present lesions. Response is defined as an absence of invasive cancer at post immunotherapy biopsy (≤cT1). Patients with response to immunotherapy will be candidates to bladder preservation, whereas in those with residual muscle invasive tumor the possibility of salvage radical cystectomy must be evaluated. Patients developing an isolated bladder invasive relapse during follow-up will be also possible candidates to salvage cystectomy, whereas those developing a superficial relapse in the preserved bladder will be managed with TUR and intravesical BCG.

To monitor accurately the potential toxicity of radiotherapy associated with durvalumab and tremelimumab, an initial cohort of 5 patients of first Simon Optimax stage of 12 patients, will be treated. If no dose limiting toxicity is observed in ≥2 of these patients in the 12 weeks of observation period, the rest of patients will be treated at full doses. In contrast, if severe toxicity is observed in ≥2 of these patients, 3 additional patients will be treated. If dose limiting toxicity is seen in one of these additional patients, the therapeutic regimen will be modified in the subsequent ones, administering full doses of durvalumab but discontinuing tremelimumab after the first dose.

Patients will be followed up every 3 months the first year, every 4 months the second year and every 6 months thereafter with abdomen and pelvis CT scan, Rx thorax, urine cytology. Additional cystoscopy and bladder biopsy will be performed anytime in case of detection abnormalities in the cytology or imaging studies. The study will be closed 2 years after the last patient inclusion.

3.2. Study schema

Protocol Activities	Screening (≤28 Days Prior to Randomization)	Treatment Period (treatment period for durvalumab + tremelimumab and radiotherapy).												Response evaluation to therapy[j]	Follow-up[k]
		W1	W2	W3	W4	W5	W6	W7	W8	W9	W10	W11	W12 (End of treatment visit)		
Written informed consent/assignment of patient identification number	X														
Preliminary eligibility fulfillment (investigator's opinion)	X														
Demography and history of tobacco and alcohol use	X														
Previous treatments for bladder cancer	X														
Recent formalin-fixed tumour biopsy	X														
Formal verification of eligibility criteria	X														
Medical and surgical history	X														
Hepatitis B and C; HIV	X														
Urine hCG or serum βhCG[a]	X												X		
Durvalumab administration		X				X				X					
Tremelimumab administration		X				X				X					
Radiotherapy administration				X	X	X	X	X	X						
Physical examination[b]	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Vital signs (pre-, during and post-infusion vital signs assessments)[c]	X	X				X				X	X	X	X		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X		
12- lead ECG[d]	X	X													
Adverse event/serious adverse event assessment		X	X	X	X	X	X	X	X	X	X	X	X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X		X
ECOG	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Serum chemistry (complete clin. chem. panel including liver enzymes)[e]	X	X	X	X	X	X	X	X	X	X			X		X
Thyroid function tests (TSH and fT3 and fT4)[f]	X					X				X			X		X

Hematology[e]	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**		**X**
Urinalysis[g]	**X**					**X**				**X**			**X**		**X**
Coagulation parameters[h]	**X**												**X**		
Cystoscopy and random biopsies	**X**													**X**	
Tumour assessment (CT scan)[i]	**X**												**X**		
Biomarker/pharmacodynamic sampling															
Peripheral blood[l]		**X**			**X**				**X**				**X**		
Fresh tumor biopsies[m]	**X**														
Urine samples [n]	**X**												**X**		

[a] Pre-menopausal female patients of childbearing potential only

[b] Full physical examination at baseline; targeted physical examination at other time points

[c] Patients will have their blood pressure and pulse measured before, during, and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- 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.

[d] ECG during screening and on cycle 1 Day 1 within 1 hr prior to the start of the first study treatment. Thereafter as clinically indicated.

[e] According what is detailed on tables 4 and 5. If screening laboratory assessments are performed within 3 days prior to 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. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated. Depending on the profile of the combination agent, the frequency of the hematology, serum chemistry and LFT testing may need to be increased to every two weeks.

[f] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

[g] Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.

[h] Coagulation tests: prothrombin time, APTT and INR – to be only performed at screening and EoT visit, and only as clinically indicated thereafter.

[i] Timing of CT scans:

- Initial Staging: thorax and , abdomen and pelvis CT scan

- Post-therapy re-staging (week 12): thorax, and abdomen CT scan and when applicable pelvis

[j] Six weeks since the end of radiotherapy. Cystoscopy and bladder biopsy will be performed for all patients as a efficacy determination

[k] Follow-up: Pelvis and abdomen CT scan, urine cytology and Rx Thorax every 3 months the first year, every 4 months the second year and every 6 months thereafter. Additional cystoscopy and bladder biopsy will be performed in case of detection abnormalities in the symptomatology, cytology or imaging studies

[l] Peripheral blood: Week 1 prior to the administration of durvalumab and tremelimumab, W2 before initiation of RT, W8 at the end of RT, and W12 at the time of tumor response

[m] Fresh tumor biopsies: A fresh biopsy sample, optional, at the time of initial TUR. Those patients who have not achieved complete response will be submitted to a new fresh biopsy, if not clinically contraindicated. It will be required to send fresh and formalin fixed samples of the pathological surgical specimen from patients who are candidate to salvage cystectomy.

n Urine samples (Optional): only for patients included in ICO L'Hospitalet. The samples will be collected at the time of screening periode and the end of treatment visit. The first urine in the morning would be collected using a standard testing tube of 50 ml.

3.3. Study oversight for safety evaluation

It should be documented whether or not the patient ends the trial. If for some reason abandoned, the investigator should register the reason for premature termination in the eCRF. The reasons why a patient may drop out or be removed from the trial are as listed in section 4.4.

4. PATIENT SELECTION, ENROLLMENT, RANDOMIZATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient must meet all inclusion criteria (Section 4.1) and none of the exclusion criteria (Section 4.2) for this study. Under no circumstances will there be exceptions to this rule.

4.1. Inclusion criteria

For inclusion in the study, patients should fulfill the following criteria:

1. Patients diagnosed with urothelial carcinoma of the bladder, in clinical stages T2-4a N0 M0, who are not candidates for radical cystectomy by medical reasons, refusal or patient's choice.
2. Written informed consent obtained from the patient prior to performing any protocol-related procedures, including screening evaluations
3. Age >18 years at time of study entry or Adult male or female (according to age of majority as defined as ≥18 years)

4. Patients must have ECOG performance status 0 or 1.

5. A paraffin-embedded tumor sample must be available for the associate molecular study.

6. Body weight >30 Kg.

7. Adequate normal organ and marrow function as defined below:

- Haemoglobin ≥9 g/dL
- Absolute neutrophil count (ANC ≥1.5 (or 1.0) x (> 1500 per mm3)
- Platelet count ≥100 (or 75) x 109/L (>75,000 per mm3)
- 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 physician.
- AST (SGOT)/ALT (SGPT) ≤2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤5x ULN
- Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine clearance CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

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

Females:

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

8. 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).

9. Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

4.2. Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Involvement in the planning and/or conduct of the study (applies to both sponsor staff and/or staff at the study site)

2. Participation in another clinical study with an investigational product during the last 30 days.

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

4. Previous treatment with radiotherapy to the bladder, systemic chemotherapy or immune checkpoint inhibitors. Prior intravesical BCG treatment for non-muscle invasive bladder cancer is allowed, 28 days prior to study.

5. Presence of regional lymph node or metastatic extension of the disease.

6. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab or tremelimumab may be included only after consultation with the Study Physician.

7. Any concurrent chemotherapy, investigational product (IP) other than studied in this protocol, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

8. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable.

9. History of allogeneic organ transplantation.

10. Active or prior documented 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, rheumatoid arthritis, hypophysitis, uveitis, etc]). 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 skin condition that does not require systemic therapy
- Patients without active disease in the last 5 years may be included but only after consultation with the study physician
- Patients with celiac disease controlled by diet alone

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

12. History of another primary malignancy, except for:

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence.
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated carcinoma in situ without evidence of disease.
- Non-muscle invasive bladder cancer.
- Incidental prostate carcinoma

13. History of active primary immunodeficiency

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

15. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab. 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)

16. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note: Patients, if enrolled, should not receive live vaccine whilst receiving IP and up to 30 days after the last dose of IP.

17. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy or 180 days after the last dose of durvalumab + tremelimumab combination therapy.

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

19. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study.

20. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements.

21. Known allergy or hypersensitivity to IP or any excipient

Procedures for withdrawal of incorrectly enrolled patients are presented in Section 4.5

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

4.3. Study oversight for safety evaluation

It should be documented whether or not the patient ends the trial. If for some reason abandoned the treatment should register the reason for premature termination in the eCRF. The reasons why a patient may drop out from treatment or be removed from the trial are described in the following sections.

4.4. Withdrawal of patients from study treatment

An individual patient will not receive any further investigational product if any of the following occurs:

- An individual patient will not receive any further durvalumab + tremelimumab combination therapy.
- Patient will not receive tremelimumab monotherapy in any case.
- Withdrawal of consent or lost to follow-up.
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
- Any AE that meets criteria for discontinuation, as defined in Section 10.
- Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
- Consumption of illicit drugs or other substances by the patient which, at the discretion of the investigator, may reasonably contribute to the toxicity or otherwise, interfere in some with the results.
- Pregnancy (proof of beta-HCG compatible with pregnancy, communicating pregnancy as a serious adverse event), or intent to become pregnant.
- Grade ≥3 infusion reaction.
- Request to discontinue treatment by the patient or a legal representative.
- At the specific request of the sponsor and / or research coordinators of the trial.
- Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits.
- Initiation of alternative anticancer therapy including another investigational agent.
- Development of a secondary malignant tumor requiring treatment.
- Confirmation of PD and investigator determination that the patient is no longer benefiting from treatment with durvalumab + tremelimumab. Patients who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment

Patients who are permanently discontinued from receiving investigational product will be followed for safety per Section 10 and Appendix 1, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the patient is lost to follow-up or enrolled in another clinical study. All patients will be followed for survival. Patients who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

The date and reason for treatment discontinuation should be recorded in the eCRF.

4.5. Withdrawal of patients from study

Criteria for withdrawal of the study:

1. Withdrawal of informed consent
2. Death of the patient
3. Loss of follow-up

The investigator will do everything possible to keep all patients in the study unless it is considered that the most appropriate option for the patient is to interrupt his/her participation.

If a patient refuses to continue his/her participation in the study, all end-of-study evaluations should be performed if the patient accepts or can be evaluated. The date and reason for withdrawal should be recorded in the eCRF.

4.6. Withdrawal of consent

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

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

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

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

- all further participation in the study including any further follow up (e.g., survival contact telephone calls)
- withdrawal of consent to the use of their study generated data
- withdrawal to the use of any samples

5. INVESTIGATIONAL PRODUCTS

5.1. Durvalumab and tremelimumab

AstraZeneca/MedImmune will supply durvalumab and tremelimumab to the sponsor as a solution for infusion after dilution. The sponsor will supply durvalumab and tremelimumab to the site pharmacies as a solution for infusion after dilution.

5.2. Durvalumab (MEDI4736)

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

5.3. Tremelimumab

Tremelimumab will be supplied as a 400-mg or a 25-mg vial solution for infusion after dilution. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5 and density of 1.034 g/mL. The nominal fill volume is 20.0 mL for the 400-mg vial and 1.25 mL for the 25-mg vial. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.Drug product should be kept in secondary packaging until use to prevent excessive light exposure.

5.4. Formulation/packaging/storage

The trial medication (i.e., Durvalumab and Tremelimumab) and its packaging will be labeled in accordance with annex 13 of EU to Good Manufacturing Practice. Storage will be done according IB and labeling specifications.

5.5 Dose and treatment regimens

5.5.1. Treatment regimens

Durvalumab + tremelimumab combination therapy

All patients will receive durvalumab (MEDI4736) (1500mg Q4W) in combination with tremelimumab (75 mg IV Q4W) for up to 3 doses/cycles each, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. If a patient's weight falls to 30kg or below the patient should receive weight-based dosing equivalent to 20 mg/kg of durvalumab Q4W and 1mg/kg tremelimumab Q4W until the weight improves to >30 kg, at which point the patient should start receiving the fixed dosing of durvalumab 1500mg plus tremelimumab 75 mg Q4W.

Tremelimumab will be administered first; the durvalumab (MEDI4736) infusion will start approximately 1 hour (maximum 2 hours) after the end of the tremelimumab infusion. Standard infusion time for each is one hour. If there are interruptions during infusion, the total allowed infusion time for each should not exceed 8 hours at room temperature. If

there are no clinically significant concerns after the first cycle, then, at the discretion of the Investigator, all other cycles of durvalumab (MEDI4736) can be given immediately after the tremelimumab infusion has finished.

5.5.2. Study drug preparation of durvalumab and tremelimumab

Based on average body WT of 75 kg, 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) and 75 mg Q4W tremelimumab (equivalent to 1 mg/kg Q4W) is included in the current study.

5.5.2.1. Preparation of durvalumab doses for administration with an IV bag

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

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature
- A dose of 1500mg (for patients >30kg 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 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 30.0 mL 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 20 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If patient weight falls to ≤ 30 kg weight-based dosing at 20 mg/kg will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab (MEDI4736) concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

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

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

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

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.

5.5.2.2. Preparation of tremelimumab doses for administration with an IV bag

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

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature
- A dose of 75 mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Add 3.8 mL (i.e.,75 mg of tremelimumab, with the dose volume rounded to the nearest tenth mL) to the IV bag. The IV bag size should be selected such that the final concentration is within 0.10 to 10 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

If weight falls to ≤ 30 kg, weight-based dosing at 1 mg/kg Weight-based dosing (for patients ≤30 kg) will be a administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final tremelimumab concentration ranging from 0.10 to 10 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. Appendix 2 includes an example of a weight-based dose calculation.

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

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

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

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

5.5.3. Monitoring of dose administration

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the Study Protocol.

In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event 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 in severity, study drug will be discontinued. For management of patients who experience an infusion reaction, please refer to the toxicity and management guidelines in Appendix 1.

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 study personnel must be trained to recognize and treat anaphylaxis. The study 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.

5.5.4. Accountability and dispensation of IMPs

The trial medication will be sent to the investigator's site pharmacy preceded by the Regulatory Green Light. The medication is to be used exclusively in the clinical trial according to the instructions of this trial protocol.

When a drug shipment is received, the Investigator or designee will check the amount and condition of the delivery, drug expiration date, and sign the Receipt of Shipment Form provided. The Receipt of Shipment Form should be faxed or emailed to the CRO. The original form will preliminarily be retained at the site and will be collected at the next monitoring visit by the monitor and stored in the Trial Master File at CRO. A copy remains in the Investigator File at the site. In case of shipment problems the Investigator or designee shall contact the CRA as soon as possible.

For this trial a IWRS system will be used for IMP stock management, Pharmacy or PI designee properly identified in the personnel list and tasks delegation log, will get access to the web based platform to update receptions, destructions and dispensing of IMPs. The record must be continuously updated and contain the dates, quantities and compounds of drugs received, medication identification number(s), the patient identification number to whom the trial medication was dispensed, date and quantity of medication dispensed. The system includes an audit trail that allow to unequivocal identify the staff member and the field modify at any time.

5.5.5. Disposition of unused investigational study drug

Trial medication will be monitored by the CRA at the respective hospital pharmacy prior to destruction after having completed a final inventory, when applicable. Local or institutional regulations may require immediate destruction of the study drug used for

safety reasons, e.g., cytotoxicity or to maintain the storage capacity and functionality of the storage at the site. In these cases, it may be acceptable to destroy it by the research staff, including partially used and empty vials, dispensed before a monitoring inspection, if the verification of original documents of empty boxes that indicate the information of batch number and dispensing date to the patient on the label. This documentation will be verified against the quantity shipped, dispensed, returned and destroyed.

Prior to the destruction a final trial medication reconciliation statement must be completed.

Drug supplies will be destroyed according to the legal requirements in Spain.

All trial medication inventory forms must be made available for inspection by a Sponsor authorized representative or designee and regulatory agency inspectors. The Investigator is responsible for the accountability of all used and unused study supplies at the site.

6. TREATMENT PLAN

The treatment consisted of initial TUR of the tumor, with multiple random biopsies of normal-appearing bladder urothelium, followed by durvalumab 1500 mg i.v. plus tremelimumab 75 mg i.v., every 4 weeks for a total of 3 doses.

Two weeks after the initiation of immunotherapy, normofractionated external-beam radiotherapy with high-energy photons will be started. Radiotherapy will be administered concurrently with immunotherapy at doses of 46 Gy to the minor pelvis and 64-66 Gy to the bladder.

Six weeks after the end of radiotherapy, ALL patients will undergo a new cystoscopy with biopsies of the tumor bed and all residual present lesions as an efficacy determination. In patients with persistent prominent inflammatory reaction at this moment, the cystoscopy can be performed 1-2 weeks later (6 to 8 weeks after the end of radiotherapy). Response is defined as an absence of invasive cancer at post immunotherapy biopsy (≤cT1). Patients with response to immunotherapy will be candidates to bladder preservation, whereas in those with residual muscle invasive tumor the possibility of salvage radical cystectomy must be evaluated. Patients developing an isolated bladder invasive relapse during follow-up will be also possible candidates to salvage cystectomy, whereas those developing a superficial relapse in the preserved bladder will be managed with TUR and intravesical BCG.

Patients will be followed up every 3 months the first year, every 4 months the second year and every 6 months thereafter with abdomen and pelvis CT scan, Rx thorax, urine cytology. Additionally of the mandatory efficacy cystoscopy and bladder biopsy (6w post RT), other cystoscopy and bladder biopsy will be performed in case of detection abnormalities in the cytology or imaging studies. The study will be closed 2 years after the last patient inclusion.

Replacement of patients

It is planned to replace those patients who interrupt the trial in advance (without having completed 12 weeks of treatment) and have not presented dose-limiting toxicity.
Patients who have not been taking durvalumab and tremelimumab for more than 21 days or who discontinue treatment with radiotherapy for more than 2 weeks will also be replaced.

6.1. Dose modification and toxicity management

6.1.1. Radiotherapy

Patients who, for reasons unrelated to toxicity, discontinue radiotherapy for more than 2 weeks will be excluded from the study. In the case of interruptions of less than 2 weeks, the patient will resume treatment from the point where he was interrupted.

A severe toxicity (G3-4) related to radiotherapy or due to combination of the RT+durvalumab/tremelimumab, RT will be suspended until recovery to G1. However, if it is toxicity unrelated to the RT, it will continue without variations.

6.1.2. Durvalumab and tremelimumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy and durvalumab + tremelimumab are provided in the Dosing Modification and Toxicity Management Guidelines in Appendix 1. Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab and tremelimumab should be permanently discontinued (see Section 4.4 of this protocol and the Dosing Modification and Toxicity Management Guidelines in Appendix 1).

Following the first dose of IP, subsequent administration of durvalumab and tremelimumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines in Appendix 1. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy and the durvalumab + tremelimumab regimen by the reporting investigator.
Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician. In case of severe grade 3-4 toxicity, the possibility to discontinue tremelimumab, following the administration of durvalumab alone concurrently with radiotherapy, when the toxicity will recover, should be considered.

It is planned to replace those patients who interrupt the trial in advance (without having completed 12 weeks of treatment) and have not presented dose-limiting toxicity. Patients who have not been taking durvalumab and tremelimumab for more than 21 days or who discontinue treatment with radiotherapy for more than 2 weeks will also be replaced.

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

All toxicities will be graded according to NCI CTCAE, Version 4.03 and RTOG/EORTC grading system.

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENTS

7.1. Restrictions during the study

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

Female patient of child-bearing potential

- Females of childbearing potential who are sexually active with a non sterilized male partner must use at least 1 **highly** effective method of contraception (Table 1) from the time of screening and must agree to continue using such precautions for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy. Non-sterilized 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-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 180 days after receipt of the final dose of durvalumab + tremelimumab combination therapy or 90 days after receipt of the final dose of durvalumab

monotherapy. 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.

- Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 1).

N.B Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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

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

Highly effective methods of contraception, 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 1. 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).

Table 1. ***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/ethinyl estradiol-releasing transdermal system: e.g. Ortho Evra® • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

Blood donation

Patients should not donate blood while participating in this study, or for at least 90 days following the last infusion of durvalumab or tremelimumab or 90 days after receipt of the final dose of durvalumab.

7.2. Concomitant treatment(s)

The Principal Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF.

Restricted, prohibited, and permitted concomitant medications are described in the following tables. Refer to IB's Section 6.6 for guidance on management of IP-related toxicities.

7.2.1. Permitted concomitant medications

Table 2. ***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 above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management [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

7.2.2. Excluded concomitant medications

Table 3. ***Prohibited concomitant medications***

Prohibited medication/class of drug	Usage
Any investigational anticancer therapy other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment
Any concurrent chemotherapy,	Should not be given concomitantly whilst the patient is on study treatment.

radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	(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])
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers	Should not be given concomitantly, or used for premedication prior to the I-O infusions. The following are allowed exceptions: ● Use of immunosuppressive medications for the management of IP-related AEs, ● Use 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).
Drugs with laxative properties and herbal or natural remedies for constipation	Should be used with caution through to 90 days after the last dose of tremelimumab during the study
Sunitinib	Should not be given concomitantly or through 90 days after the last dose of tremelimumab (acute renal failure has been reported with combination therapy of tremelimumab and sunitinib)
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 30 days after the last dose of IP (including SoC)
Herbal and natural remedies which may have immune-modulating effects	Should not be given concomitantly unless agreed by the sponsor

8. STUDY PROCEDURES

8.1. Schedule of study procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis

For durvalumab + tremelimumab combination+radiotherapy

- Tumor efficacy (RECIST) assessment dates are not affected by dose delays and

remain as originally scheduled, as they are based on the date of enrollment (not the date of therapy).

- All other scheduled assessments must be performed relative to the start of the dosing cycle such that all laboratory procedures, etc required for dosing should be performed within 3 days prior to dosing
- Patients may delay dosing under certain circumstances.
- Dosing may be delayed per Toxicity Management Guidelines, due to either an immune or a non-immune-related AE.
- If dosing must be delayed for reasons other than treatment-related toxicity, dosing will resume as soon as feasible
- Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumor efficacy (RECIST) . Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab and tremelimumab (see current Investigator Brochures for durvalumab and tremelimumab.

8.1.1. Screening phase

Screening procedures will be performed up to 28 days before Day 1 of Week 1, unless otherwise specified. All patients must first read, understand, and sign the IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, patients will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Confirm collection of tumor biopsy
- Review of prior/concomitant medications
- Imaging by CT scan
- Clinical laboratory tests for:

- Clinical chemistry (see Table 4)
- Hematology (see Table 5)
- Urinalysis (see Table 6)
- Coagulation (PT, PTT, INR)
- Serum pregnancy test (for women of childbearing potential only)
- Hepatitis B and C and HIV serologies
- Cystoscopy and random biopsies
- Tumor assessment (CT scan)
- Fresh tumor biopsies collection are optional. This is only for those patients who signed the substudy informed consent.
- Urine samples collection (optional; only for a patients included in ICO L'Hospitalet). The first urine in the morning would be collected using a standard testing tube of 50 ml.

8.1.2. Treatment phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

The following procedures will be performed during the treatment phase:

- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- ECG
- Review of concomitant medications
- Clinical laboratory tests for:
    - Clinical chemistry (see Table 4);
    - Hematology (see Table 5);
    - Urinalysis (see Table 6).
    - Thyroid function tests (TSH and T3 and T4)
- Adverse event/serious adverse event assessment
- Peripheral blood collection

8.1.3. End of treatment and follow-up visits

The following procedures will be performed during the end of treatment visit (w12):

- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- AE/SAE collection
- Concomitant medications
- Clinical laboratory tests for:
    - Clinical chemistry (see Table 4)
    - Hematology (see Table 5)
    - Urinalysis (see Table 6)
    - Coagulation (PT, PTT, INR)
    - Thyroid function tests (TSH and T3 and T4)
- Serum pregnancy test (for women of childbearing potential only)
- Tumor assessment by CT scan
- Peripheral blood collection
- Urine samples collection (optional; only for a group of patients).

8.1.4. Safety

Safety follow-up visits will be scheduled up to 90 days after the last dose of study treatment, the procedures to be performed are the same that for EOT visit except for peripheral blood collection and CT scan that should not been performed in this visit, unless PI criteria as per normal practice

8.1.5. Follow-up Visits

All patients will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study. It is of special interest the long-term follow-up of survival, disease free survival and the preservation of the bladder free of tumor.

Given the potential risk for delayed immune-related toxicities, safety follow-up must be performed up to 90 days after the last dose of durvalumab and tremelimumab administration.

The extended safety follow-up beyond 30 days after last study drug administration may be performed either via a site visit or via a telephone call with subsequent site visit requested in case any concerns noted during the telephone call.

8.2. Description of study procedures

8.2.1. Medical history and physical examination, electrocardiogram, weight and vital signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations will be performed on study days noted in the Schedule of Assessments.

8.2.2. Physical examination

Physical examinations will be performed according to the assessment schedule. Full physical examinations will include assessments of the head, eyes, ears, nose, and throat and the respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, dermatological, hematologic/lymphatic, and endocrine systems. Height will be measured at screening only. Targeted physical examinations are to be utilized by the Investigator on the basis of clinical observations and symptomatology. Situations in which physical examination results should be reported as AEs are described in Section 10.

8.2.3. Electrocardiograms

Resting 12-lead ECGs will be recorded at screening, baseline, (cycle 1 Day 1 within 1 hr prior to the start of the first study treatment), and as clinically indicated throughout the study. ECGs should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. In case of clinically significant ECG abnormalities, including a QTcF value >470 ms, 2 additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Situations in which ECG results should be reported as AEs are described in Section 10.3.1

8.2.4. Vital signs

Vital signs (blood pressure [BP], pulse, temperature, and respiration rate) will be evaluated according to the assessment schedules Body weight is also recorded at each visit along with vital signs.

8.2.4.1. First infusion

On the first infusion day, patients in the durvalumab + tremelimumab combination therapy group will be monitored and vital signs collected/recorded in eCRF prior to, during and after infusion of IP as presented in the bulleted list below.

BP and pulse will be collected before, during, and after each infusion at the following times (based on a 60-minute infusion):

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

If the infusion takes longer than 60 minutes, then BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. A 1-hour observation period is recommended after the first infusion of durvalumab and tremelimumab.

8.2.4.2. Subsequent infusions

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

8.2.5. Clinical laboratory tests

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the assessment schedules and as clinically indicated (see Table 4 through Table 6).

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

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

The laboratory variables to be measured are presented in Table 4 (clinical chemistry), Table 5 (hematology), and Table 6 (urinalysis).

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

The following laboratory variables will be measured:

Table 4. ***Clinical chemistry***

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

[a] Tests for ALT, 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] Bicarbonate (where available), chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at screening, on Day 0 (unless screening laboratory assessments are performed within 3 days prior to Day 0), and if clinically indicated.

[d] 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 5. ***Hematology***

Absolute neutrophil count	**Absolute lymphocyte count**
Hemoglobin	**Platelet count**

Note: For coagulation parameters, activated partial thromboplastin time and international normalized ratio are to be assessed at baseline and as clinically indicated.

Urinalysis should be done at baseline (screening) and then as clinically indicated

Table 6. ***Urianalysis***

Bilirubin	**Ketones**
Blood	**pH**
Color and appearance	**Protein**
Glucose	**Specific gravity**

Note: Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

If a patient shows an AST or ALT ≥3x ULN together with total bilirubin ≥2x ULN, refer to Appendix 1 for further instructions on cases of increases in liver biochemistry and

evaluation of Hy's Law. These cases should be reported as SAEs if, after evaluation, they meet the criteria for a Hy's law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

All patients should have further chemistry profiles performed at 30 days (±3 days), 2 months (±1 week) and 3 months (±1 week) after permanent discontinuation of IP (see Table 4).

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF. Situations in which laboratory safety results should be reported as AEs are described in Section 10.3.5.

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

8.3. Biological sampling procedures

8.3.1. Biomarker/pharmacodynamic sampling and evaluation methods

8.3.1.1. Peripheral blood

Information about peripheral blood studies will be included in the informed consent form (ICF). Blood samples for biomarker analysis will be acquired at baseline (Week 1 prior to the administration of durvalumab and tremelimumab, W2 before initiation of RT, W8 at the end of RT, and W12 at the time of tumor response).

Extraction and Manipulation Procedure:

Every peripheral blood sample extraction for translational studies will consist in 2 whole blood tubes for peripheral blood mononuclear cells (PBMCs) isolation, 2 plasma tubes and 1 serum tube. A manual with the detailed procedures of extraction and manipulation of samples will be sent to each site. Plasma and serum tubes will be kept at -80ºC and shipped to the Translational Research Laboratory 1 at the Institut Català d'Oncologia (ICO) periodically. Whole blood for cytometry will be processed using Ficoll Hypaque © and PBMCs will be frozen using FBS and DMSO, if this procedure is not available at the site, samples will be sent to the central laboratory in less than 24 hours.

The following translational studies are going to be performed:

- Correlation between changes in peripheral blood cell populations and clinical benefit. Combination of anti-CTLA4 and anti-PD1 leads to striking change in characteristics of circulating leukocytes in vivo (Rituparna et al. 2015). PBMCs will be analyzed using flow cytometry to determine the presence of activation and exhaustion

markers such as but not limited to PD1, CD137, and TIM3.

- Correlation between patient HLA type and clinical benefit and toxicity. Whole exome sequence (WES) from peripheral blood lymphocytes is going to be performed to use a comparator to WES from tumor metastasis. We are going to use this information to check the HLA types from different patient with outcome and toxicity.
- Correlation between blood circulating cytokines and clinical benefit. Changes in circulating cytokines have been associated to tumor response (Sanmamed et al. 2014). Blood samples will be evaluated to determine variation in cytokines such as but not limited to IL-1a, IL-2, IL-6, IL-8, IFNy, and TGFb.
- Identification of exosome profile in peripheral blood. Exosomes are cell-derived vesicles that are present in many and perhaps all biological fluids, including blood, urine, and cultured medium of cell cultures. The reported diameter of exosomes is between 30 and 100 nm. It is becoming increasingly clear that exosomes have specialized functions and play key role in intercellular functions, and metastatic niche preparation. On the other hand, immune cells can secrete exosomes that can act as activators of immune response. The delivery and expose of molecules such as certain heat shock proteins (HSP) that can act as damage-associated molecular pattern molecules (DAMPS) and interact to several toll-like receptors (TLRs) can activate immune response. Additionally, dendritic cell-derived exosomes express MHC I, MHC II, and costimulatory molecules and have been proven to be able to induce and enhance antigen-specific T cell responses in vivo. (Benito-Martin et al. 2015). We are going to explore tumor exosomes (basal samples), and treatment-induced immune exosomes (induced by treatment) and correlate with treatment efficacy and toxicity.

8.3.1.2. Urine samples

Urine samples samples will be optionally required from patients recruited in ICO L'Hospitalet at the time of screening period and end of treatment visit. The first urine in the morning would be collected using a standard testing tube of 50 ml.

The urine will follow the standard procedures and should be delivered to the central laboratory at the Institut Català d'Oncologia (ICO) L'Hospitalet. If for any reason the urine can not be delivered to the central laboratory immediately it can be kept at room temperature.

The samples will be collected at the time of screening period and the end of treatment visit to detect and to quantify CD8 and CD4 lymphocytes and assess their immune profile (PD-1, TIM-3, CTLA-4, ICOS, and 4-1BB expression and TCR sequence.), in order to evaluate possible correlations between a high number of CD8-PDL1 with worse prognosis (as previously reported by Dr. Quezada, J. Exp. Med. 2018). Further analysis on could be implemented and will be detailed in the final Clinical Study Report.

8.3.2. Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each patient in this study is as follows:

Table 7. ***Volume of blood to be drawn from each patient***

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	Local practice	Local practice	Local practice
	Hematology	Local practice	Local practice	Local practice
Biomarker analysis		45 mL	4	180

8.3.3 Fresh tumor biopsies

If the patient agrees to participate in the substudy a fresh tumor biopsy sample will be required at the time of initial TUR. A fragment of tumor tissue will be processed following standard procedures for formalin-fixing at the pathology unit, a suitable tumor block or 15 unstained slides 4 micrometer thick will be sent to the central laboratory. Another fragment of tumor tissue of at least 1 g of weight will be frozen immediately using an optimal cutting temperature (OCT) compound, tubes will be kept at -80ºC and shipped to the central laboratory at the Institut Català d'Oncologia (ICO) periodically. Details for the processing, labelling and shipping of the samples will be given to each site in a manual.

Tumor assessment:

For every patients who have not achieved complete response will undergo a TUR and fresh biopsy will be obtained. One sample will be fixed in formalin and two additional ones will be frozen and kept at -80ºC.

It will be required to send fresh and formalin fixed samples of the pathological surgical specimen from patients who are candidate to salvage cystectomy. For sample processing and sending please follow the same procedures explained above for the TUR.

Deep-frozen tissue will be processed according to standard laboratory procedures to isolate DNA and RNA.

The following translational studies are planned:

- Paraffin embedded tissue will be used for immunohistochemistry to study tumor inflammatory stroma (such as, but not limited to CD3; CD4; CD8; CD45RO; FoxP3, CD20, CD11b; CD68; among others), and lymphocyte exhaustion markers (PD-1; PD-L1; CD137; Granzyme B; Perforin; among others). Ventana SP263 (please see algorithm in appendix II) tumor infiltration and PD-L1 expression in tumor and stroma cells has been related to tumor response among different tumors and also in bladder cancer treated with PDL1 (Herbst et al. 2014).

- Correlation of neoantigen presentation and clinical benefit. Tumor mutational load is relevant to response to immunotherapy and has shown predictive value in bladder cancer treated with anti PDL1 (Rosenberg et al. 2016). We will perform whole exome-seq (WES), and RNA-seq to get information on tumor somatic mutations, included the amino-acid change in missense mutations, and its position into the protein. Additionally, we will predict the immune-peptides repertoire for each patient, combining information about missense mutations and inferred HLA alleles. DNA from tumor will be used to analyze TCR-β chain clonality analysis to achieve information about T-cell diversity and clonality and associate to treatment benefit.
- Correlation of gene signatures and clinical response. Sequencing data will be used to classify the tumors according to the bladder cancer TCGA (https://portal.gdc.cancer.gov/). Previous data show correlation between subgroups and response (Rosenberg et al. 2016). DNA and RNA data will be used to explore gene signatures related to Interferon signaling and T cell activation.
- Explore changes in immune infiltrate, T-cell clonality and gene expression between pre- and post-treatment samples in non-responding patients using the techniques previously explained. This will allow us to determine the changes in immune cells and tumor and make hypothesis about resistance mechanisms.

PD-L1 Testing

To ensure comparability of data across all studies of durvalumab and/or tremelimumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the Ventana SP263 assay. Testing should be restricted to the Ventana SP263 assay and should be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

The Ventana SP263 assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully reproducibility data package supporting cut-off and scoring algorithm. Following completion of ATLANTIC and HAWK clinical trials, the assay will be associated with clinical utility. In other cancer types (bladder, pancreatic, gastric, hepatocellular, triple negative breast, ovarian, esophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma, cholangiocarcinoma, small cell lung, melanoma and cervical HPV + cancers), the Ventana SP263 assay has only limited clinical performance data.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a patient's PD-L1 status is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current PD-L1 status of the tumor and considered

clinically most relevant.

- In AstraZeneca studies, the preferred sample for PD-L1 testing was less than or equal to 3 months old. In cases where a sample a less than 3 months old was not available, patients were asked to undergo a new biopsy if considered clinically appropriate by their treating physician.
- Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e., >100 tumor cells) to allow for adequate PD-L1 immunohistochemistry analyses.
- When the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen it is not older than 3 years of age. When archival samples are used to assess PD-L1 status, the age of the sample/date of collection should be captured.
- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis.

Sample data collection for PD-L1 testing

The following fields of data should be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (e-code or unique identifier)
- Specimen identifier (written on the specimen)
- Site identifier
- Specimen collection date
- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival of fresh tumor
- Tumor type
- Primary tumor location
- Metastatic tumor location (if applicable)
- Fixative

The following fields of data should be collected from PD-L1 testing laboratory:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells

- Total percent positivity of PD-L1 in infiltrating immune cells

The Ventana SP263 assay to measure PD-L1 in tumors is experimental. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

Sample processing and if indicated submission process for PD-L1 testing

Preparing Stored samples for testing

- Where samples already exist, they should be retrieved from the Biobank storage location. These blocks should undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for PD-L1 testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 status. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single block. The provision of 2 cores is advised in order to provide sufficient tissue for PD-L1 assessment.
- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 testing. To fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature.
- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for PD-L1 testing

- An overnight processing schedule into paraffin wax is recommended

Storage of tumor blocks for PD-L1 testing

- FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

Quality control of samples to be used for PD-L1 testing

- Tissue should be assessed by the site pathologist prior to PD-L1 testing.
- Each sample should be reviewed for:
- Adequate fixation
- Good preservation of morphology
- Presence of tumor tissue
- Histopathology consistent with indication
- Greater than 100 tumor cells are required to determine PD-L1 status – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.

If indicated, shipping samples to a PD-L1 testing laboratory

- When submitting sample to for PD-L1 testing the recommendation is to ship the block in order for sectioning to occur at the laboratory. Blocks should be shipped - containing enough material to be provided to allow a minimum of 5, and preferably 10, sections to be cut (each 4 microns thick) to be used for PD-L1 testing.

Sectioning instructions

Where it is not possible or indicated to ship the block to laboratory for PD-L1 testing, unstained slides should be prepared from the paraffin-embedded tumor sample block as described below:

- A minimum of 5-10 x 4 micron (µm) thick, unstained sections should be provided for PD-L1 testing.
- A new disposable microtome blade must be used for each block to prevent contamination between patient samples.
- Slides are stable under these conditions for 6 months.
- Apply one section per slide to positively-charged Superfrost glass slides.
- The sections should be dried overnight between room temperature and 37°C. Do not dry sections at temperatures above 37°C.
- Sections should be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 status

8.3.4. Future biomarker studies and sample disposal

An additional ICF will be issued to obtain consent for future biomarker research. All research performed with these samples will be subject to Ethical Committee evaluation

and approval.

If future biomarker research is not consented samples will be kept at the central laboratory and then disposed of in five years.

8.3.5. Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the patient is withdrawn from further study participation.

The Principal Investigator:

- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and the sponsor are informed about the sample disposal.

9. DISEASE EVALUATION AND METHODS

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009, Nishino et al 2013):

- Response to immunotherapy may be delayed
- Response to immunotherapy may occur after PD by conventional criteria
- The appearance of new lesions may not represent PD with immunotherapy
- SD while on immunotherapy may be durable and represent clinical benefit.

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency “Guideline on the evaluation of anticancer medicinal products in man” (EMA/CHMP/205/95/Rev.4) for immune modulating anticancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with durvalumab + tremelimumab would continue between the initial assessment of progression and confirmation for progression.

- In addition, patients may continue to receive durvalumab + tremelimumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that patients continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab + tremelimumab and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anticancer therapy other than durvalumab + tremelimumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

9.1. Efficacy variable

The main efficacy variable of the study treatment is pathological response evaluated by biopsy performed via cystoscopy at the end of the treatment. Pathological response is defined as the absence of muscle-invasive bladder cancer at post-treatment biopsy (≤cT1). Post-treatment biopsy will be performed by cystoscopy performed 6 weeks after the end of radiotherapy. Persistence of invasive cancer in the bladder is considered no response to therapy, and radical cystectomy, if feasible, would be indicated. Apparition of new lesions outside of the bladder is considered a first RECIST progression.

Confirmation of progression guidelines are set for the following reasons:

- for patient management and treatment decisions,
- in the absence of significant clinical deterioration, to promote the collection of additional scans after the first radiologic RECIST 1.1 assessment of progressive disease (PD) in order to distinguish pseudoprogression from true radiologic progression, also known as RECIST 1.1 modified for confirmation of progression,
- when scans are evaluated by Investigator and by BICR, to reduce informative censoring by Investigator assessments (Investigator assesses PD at a time-point earlier than does BICR).

Confirmed objective disease progression refers to either of the following scenarios: 1. clinical progression/deterioration followed by a radiologic verification scan (PD by RECIST 1.1); or 2. in the absence of significant clinical deterioration, radiologic PD by RECIST 1.1 followed by a second radiologic confirmation scan with PD assessed according to the specific confirmation of progression criteria listed below. RECIST 1.1 modified for confirmation of progression refers to the second scenario above. The

confirmatory scan should occur preferably at the next scheduled imaging visit and no earlier than 4 weeks following the date of the immediate prior assessment of RECIST 1.1 PD.

Immediate prior radiologic progression would be considered confirmed if any the following criteria are met in the confirmatory scan:

- ≥20% increase in the sum diameters of target lesions (TLs) compared with the nadir at 2 consecutive visits, with an absolute increase of at least 5 mm in sum of diameters compared to nadir,
- and/or significant progression (worsening) of non-target lesions (NTLs) and/or of pre-existing new lesions at the confirmatory scan time-point compared with the immediate prior time-point (Note: Pre-existing new lesions are evaluated as NTLs at the confirmatory scan time-point),
- and/or additional new unequivocal lesions at the confirmatory scan time-point.

NOTE: In order to have confirmed objective disease progression, there should be two consecutive PD's, the first PD by RECIST 1.1 and the second PD using the confirmation of progression criteria (above). If the first PD by RECIST 1.1 is not confirmed, continue with assessments until the next PD by RECIST 1.1, which in turn will need its own immediate subsequent confirmation scan.

In the absence of significant clinical deterioration, treatment with study drug may continue between the initial assessment of progression and the scan to confirm progression.

If the confirmation scan confirms progression, then the date of the prior scan with PD should be declared as the date of progression.

If progression is not confirmed, in the absence of significant clinical deterioration, then the patient should continue study drug and on-treatment assessments until the next PD which will also require a follow-up confirmation scan. **If the first PD is not confirmed by the immediate next scan, then the Investigator should not change the PD assessment of the first scan.**

If a patient discontinues treatment (and/or receives a subsequent anticancer therapy) prior to radiologic progression, then the patient should still continue to be followed until confirmed objective disease progression.

10. ASSESSMENT OF SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is

familiar with the content of this section.

10.1. Safety parameters

10.1.1. Definition of adverse events

An adverse event is the development of an undesirable medical condition (other than progression of the malignancy under evaluation) or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

10.1.2. Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the patient
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to the sponsor.

10.1.3. Durvalumab + tremelimumab adverse events of special interest

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

AESIs for durvalumab ± tremelimumab include but are not limited to events with a

potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-mediated adverse event (imAE) is defined as an AESI that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

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

AESIs observed with durvalumab ±tremelimumab include:

- Diarrhea / Colitis
- Intestinal perforation
- Pneumonitis / ILD
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Myositis/polymyositis
- 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 labs suggestive of pancreatitis - increased serum lipase , increased serum amylase).
- Myocarditis
- Other inflammatory responses that are rare with a potential immune-mediated aetiology are also considered as AESIs and include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological, rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis. It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab and tremelimumab Investigator’s Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1). These guidelines

have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 1) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

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

- Physical examination
- Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.
- Saturation of peripheral oxygen (SpO2)
- Other items
- When pneumonitis (ILD) is suspected during study treatment, the following markers should be measured where possible:

    1. ILD Markers (KL-6, SP-D) and β-D-glucan
    2. Tumour markers: Particular tumour markers which are related to disease progression.
    3. Additional Clinical chemistry: CRP, LDH

10.2. Assessment of safety parameters

10.2.1. Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03.

The determination of severity for all other events not listed in the CTCAE should be

made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

- Grade 1 (mild) An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate) An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Grade 3 (severe) An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the patient.
- Grade 4 (life threatening) An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the patient to perform activities of daily living (eating, ambulation, toileting, etc).
- Grade 5 (fatal) Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.2.1. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a non serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2. Assessment of relationship

The Investigator’s assessment of causality must be provided for all AEs (serious and non-serious); the Investigator must record the causal relationship in the eCRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An Investigator’s causality assessment is the determination of whether there exists a reasonable possibility that the study treatment caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

If the Investigator does not know whether or not the study treatment caused the event, then the event will be handled as “related to study treatment” for reporting purposes.

If the Investigator's causality assessment is “unknown but not related to study treatment”, this should be clearly documented on study records.

In addition, if the Investigator determines an SAE is associated with study procedures,

the Investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

10.3. Recording of adverse events and serious adverse events

Adverse events will be recorded eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to the sponsor.

The following variables will be collected for each AE:

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

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

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication, as explained in Section 10.2.2
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE

grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

10.3.1. Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab + tremelimumab).

During the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion.

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

The investigator is responsible for following all SAEs until resolution, until the patient returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

10.3.2. Causality collection

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

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

10.3.3. A guide to the interpretation of the causality question is found in next section. Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE report form. This includes both non-treatment–emergent (i.e., SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A

protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). The following guidelines should be used by Investigators to assess the relationship of SAEs to the protocol:

- Protocol related: The event occurred due to a procedure or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.
- Not protocol related: The event is related to an etiology other than the procedure or intervention that was described in the protocol. The alternative etiology must be documented in the study patient's medical record.

10.3.4. Adverse events based on signs and symptoms

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

10.3.5. Adverse events based on examinations and tests

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

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result or vital sign will be considered as additional information. Whenever possible, the reporting Investigator should use the clinical rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonmandated parameters should be reported as AEs.

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

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

10.3.6. Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further

evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs. Please refer to Appendix 1 for further instruction on cases of increases in liver biochemistry and evaluation of Hy's law.

10.3.7. Disease progression

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

10.3.8. New cancers

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

10.3.9. Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Regulatory Authority of the SAE as per local requirements.

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

The sponsor must inform the AEMPS of any Suspected serious or unexpected serious adverse events (SUSAR) that occur in accordance with the reporting obligations, and will concurrently forward all such reports to AstraZeneca. A copy of the report must be sent by e-mail to AstraZeneca at the time the event is reported to the AEMPS by the sponsor.

* A cover page should accompany the SAE form indicating the following:

- External Scientific Research (ESR)
- The investigator's name and address
- The trial name/title and AstraZeneca ESR reference number

* Send SAE report and accompanying cover page by way of Email to [redacted]

If a non-serious AE becomes serious, the same process described before will be followed.

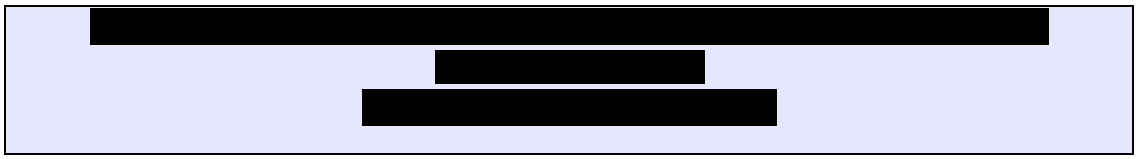
Serious adverse events that do not require expedited reporting to the AEMPS need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

The following reportable events must be submitted to the sponsor within 24 hours (or immediately for death or life-threatening events).

Serious Adverse Events

- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event).
- Occupational exposure (even if not associated with an adverse event)
- Potential drug-induced liver injury (Hy's Law cases): These events are considered important medical events and should be reported as SAEs.

Site staff should send SAE report and accompanying cover page by fax or email to sponsor/CRO's designated mailbox:



10.3.9.1. Reporting of deaths to

All deaths that occur during the study, or within the protocol defined 90 day post last dose of durvalumab + tremelimumab safety follow up period must be reported to the sponsor as follows:

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the sponsor as a SAE within **24 hours** (see Section 10.3.2 for further details). 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.

Deaths occurring after the protocol defined safety follow up period after the administration of the last dose of study drug should be documented in the Statement of Death page. If the death occurred as a result of an event that started after the defined

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

10.3.10. Other events requiring reporting

10.3.10.1. Overdose

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

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

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

The designated sponsor representative will work with the Investigator to ensure that all relevant information is provided.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 10.3.10.1. For other overdoses, reporting must occur within 30 days.

10.3.10.2. Pregnancy

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

- Pregnancy discovered before the study patient has received any study drugs.
- Pregnancy of a female partner of male patient, providing there is no restriction of male patient fathering a child.

10.3.11. Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be

reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the appropriate sponsor representatives within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The designated sponsor representative will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

10.3.12. Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 180 days after the last dose of durvalumab + tremelimumab combination therapy or 90 days after the last dose of durvalumab monotherapy, whichever is the longer time period should, if possible, be followed up and documented.

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

10.4. Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the 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 study 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 in clinical studies as medication errors:

- 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 (excluding IVRS/IWRS errors)
- Wrong drug administered to patient (excluding IVRS/IWRS errors)
- Examples of events that **do not** require reporting as medication errors in clinical studies:
    - Errors related to or resulting from IVRS/IWRS - including those which lead to one of the above listed events that would otherwise have been a medication error
    - 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
    - Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

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

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

The designated sponsor representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 10.3.10) and within 30 days for all other medication errors.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1. Description of analysis sets

11.1.1. Safety analysis set

The safety analysis set will include all patients who receive at least 1 dose of study treatment. The safety analysis set will be the primary population for evaluating treatment administration/compliance and safety.

11.1.2. Efficacy analysis set

The efficacy analysis will be a *per protocol analysis*. The efficacy analysis set will include all patients who receive at least 2 cycles of durvalumab and 3 weeks of radiotherapy. The efficacy analysis set will be the primary population for evaluating treatment efficacy.

Additionally, intention to treat analysis will be performed for efficacy data.

11.2. Methods of statistical analyses

11.2.1. Safety analyses

Safety analysis will be performed weekly during the length of the treatment and every three months later (late toxicity associated with radiotherapy). Toxicities will be graded according to NCI CTCAE, Version 4.03 and RTOG/EORTC grading system.

11.2.2. Efficacy analyses and exploratory analyses

Table 8. ***Efficacy analyses and exploratory analyses***

Objectives	Variable	Analysis	Clinical factors	Analysis population
Primary: efficacy of durvalumab plus tremelimumab with concurrent radiotherapy in terms of pathological response rate	Pathological response rate	1. Proportion estimation with a 95% confidence interval 2. Simon two stage decision rule 3. Logistic regression with clinical factors	Tumour size Tumour localization Histology Biomarkers	Per protocol
Secondary 1a: bladder preservation.	Rate of bladder preserved	1. Proportion estimation with a 95% confidence interval 2. Logistic regression with clinical factors	Tumour size Tumour localization Histology Biomarkers	Per protocol
Secondary 1b: bladder preservation.	Rate of immediate and late salvage cystectomies.	1. Proportion estimation with a 95% confidence interval 2. Logistic regression with clinical factors	Tumour size Tumour localization Histology Biomarkers	Per protocol

Secondary 1c: bladder preservation.	Time from start of immunotherapy to the date of recurrence of muscle invasive bladder carcinoma or metastases.	Kaplan Meier estimation of survival with a 95 % confidence interval	Not applicable	Per protocol
Secondary 1d: Overall survival	Time from treatment start to exitus.	Kaplan Meier estimation of survival with a 95 % confidence interval		Per protocol
Secondary 1.3: Progression free survival	Time from treatment start to tumour relapse or distant progression.	Kaplan Meier estimation of survival with a 95 % confidence interval		Per protocol
Secondary 2: Safety profile and tolerability of combination	CTCAE V4.03	1. Frequency table with adverse events, grades and relationship to study drugs and to radiotherapy treatment 2. Frequency table with severe toxicity.	Durvalumab cumulative dose, tremelimumab cumulative dose, radiotherapy treatment constraints (dose in risk organs).	Safety population
Secondary 3: To evaluate the long term functionalism and late sequel of the treatment in the preserved bladders.	Bladder control scale	Repeated measures analysis		Per protocol
Exploratory 1: Biomarkers and pathological response rate	Biomarkers and pathological response rate	Logistic regression in which respons or not Is the response and baseline biomarkers are factors to be studied	Biomarkers	Per protocol
Exploratory 2: Biomarkers evolution between baseline and surgery time	Biomarkers evaluated at baseline vs surgery evaluation	Paired t-test or Wilcoxon Signed Rank Test (depending on the natur of variables)		Per protocol

11.2.3. Interim analyses

- Safety: To monitor accurately the potential toxicity of radiotherapy associated with durvalumab and tremelimumab, an initial cohort of 5 patients will be treated. If no dose limiting toxicity is observed in ≥2 of these patients at the end of the treatment, the rest of patients will be treated at full doses. In contrast, if severe toxicity is observed in ≥2 of these patients, 3 additional patients will be treated. If dose limiting toxicity is seen in one of these additional patients, the therapeutic regimen will be modified in the subsequent ones, administering full doses of durvalumab but discontinuing tremelimumab after the first dose.
- Efficacy: The study will be conducted using a Simon “Optimal design” two-stage sequential design. An interim analysis of response will be performed at the end of the first stage, after the treatment of the first twelve patients treated. Six or more responses in the first stage were required for continuation to second stage accrual.

11.3. Determination of sample size

The study will be conducted using a two-stage sequential design. Using the assumption that the treatment would be considered ineffective if it had a response proportion similar

to radiotherapy alone (P0: 0.5) but would be of considerable interest if it had a response proportion of 70% of more (P1: 0.7), the sample size requirement is 12 patients for the first stage and 20 additional patients for the second stage. Six or more responses in the first stage were required for continuation to second stage accrual, and 19 of a total of 32 patients treated to consider the study positive. The study was planned to have a type I error of 0.10 and a power of 80%.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1. Ethics Committee

It is the responsibility of the sponsor to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, e.g., recruitment advertisements, if applicable, from the EC and Regulatory Authorities according to applicable legislation. All correspondence with the EC should be retained in the investigator and sponsor Trial Master File, when applicable according GCPs.

The only circumstance in which an amendment may be initiated prior to EC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the sponsor must notify the EC in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (Adopted by CHMP, 15 December 2016, issued as EMA/CHMP/ICH/135/1995), and the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013).
In addition, the study will be conducted in accordance with the protocol, and applicable local regulatory requirements and laws.

12.3. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

When study data are compiled for transfer to the sponsor and other authorized parties, patient names, addresses, and other identifiable data will be replaced by a numerical code based on a numbering system provided by the sponsor in order to de-identify study

patients. The study site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, the sponsor will maintain high standards of confidentiality and protection of patient's personal data consistent with applicable privacy laws.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.
The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IEC before use, and available for inspection.
The Investigator must ensure that each study patient, or her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The patient, or her legally acceptable representative, will provide her consent, by personally signing, dating and naming the appropriate informed consent document.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the EC. If the investigator determines that a patient's decisional capacity is so limited she cannot reasonably be consulted, then, as permitted by the EC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide her own consent, the source documents must record why the patient did not provide consent (e.g., , decisional impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained, or waived. If assent is obtained verbally it must be documented in the source documents.
The Investigator, or a person designated by the Investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The Investigator will retain the original of each patient's signed consent document and a copy will be provided to the patient.

13. STUDY MANAGEMENT

13.1. Training of study site personnel

- The study will be performed in centers with multidisciplinary teams (oncologists, radiotherapists, urologists) with wide experience in multimodal bladder preservation therapy trained in GCP's.
- The principal investigator will maintain a record of all center staff involved in the clinical trial (doctors, nurses and other staff involved) ensuring that they receive

appropriate training to perform the study, and that any new information of relevance to the study will be transmitted to them.

- Researchers will be instructed about the documents (Protocol, ICF, IB, etc.) procedures of the trial (selection, inclusion, treatment, safety, notifications, eCRF, among others) during the initiation visits made by monitors to each participating center prior to the study start.

13.2. Monitoring of the study

The CRO in charge of monitoring this trial is:
[redacted]

The sponsor's or representative (e.g., CRO's CRA) will maintain contact with the investigator and designated staff by telephone, and/or letter, and/or email between study visits. Monitoring visits to each investigational site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (if regionally required, the heads of the medical institutions) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with Good Clinical Practices, [redacted] SOPs and local regulatory requirements.

The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to the study protocol and data accuracy in accordance with federal regulations. All records at the investigational site, including source documents, are subject to inspection by the regulatory authorities and to review by the Ethical Committee.

13.3. Source data

Source data are defined as all data in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial that are necessary for the reconstruction and evaluation of the trial.

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases

- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, ECG recordings, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor and kept in a safe place at the site.

13.4. Study timetable and end of study

Study duration

Authorities submission	2Q 2018 (May 31, 2018)
Trial start date	4Q 2018 (Nov. 14, 2018)
First patient	1Q 2019 (Jan. 24, 2019)
Estimated last patient in	3Q 2020
Estimated last patient last treatment	3Q 2022
Estimated trial completion date	2Q 2023

14. DATA MANAGEMENT

14.1. Data Management Plan

The Data Management Plan (DMP) defines and documents the procedures necessary to ensure data quality. These activities must be followed to ensure data are properly entered, validated, coded, integrated, reconciled and reviewed.

SAP will include:

- Data source strategy
- Analysis of objectives
- Analysis of sets/ populations/subgroups
- Endpoints and covariates management
- Handling of missing values and other data conventions
- Statistical methodology

Database elaboration and validation plan will include:

- Data management plan
- DB and sintaxis elaboration and validation procedure
- Clinical coding (medication, AE, LNR) with client-specific dictionaries
- Reviewing procedure and consolidation management
- Project management of data, data validation and query resolution
- SAE Reconciliation
- Quality Assurance Audit and Quality Control Procedures

Statistical report

- Elaboration according SAP and client-specific requirements
- Reviewing process
- Final validation process

All software applications used in the collection and validation of data must be properly validated following standard computer system validation and must be compliant to all regulatory requirements.

14.2. Data Handling and Report Keeping

14.2.1. Electronic Data Capture

Data required by the protocol are collected on an electronic Case Report Form (eCRF) and entered into a validated data management system which is compliant to all regulatory requirements. As defined by ICH Guidelines, the Case Report Form (CRF) is an electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject'. In this study, CRF should refer to electronic data collection form. Data collected on the CRF must follow the instructions described in the CRF Completion Guidelines.

Any corrections to entries made on the CRF will be documented in a valid audit trail where the corrections will be fully tracked (by means of non-transferable user-name and secret password). Only data required by the protocol for the purposes of the study should be collected.

The compliance with the 21 CFR11 and EU and local guidelines of the computerized systems used are guaranteed. The e-CRF is a solution from Medical R&C, and the hardware infrastructure is hosted by Claranet Inc. that ensures high availability and also implement all the security controls regarding access to the hardware hosting the eCRF.
The e-CRF software implements all the internal security protocols and data entry recommendations, such as:

- Access limited to authorized individuals
- Audit trail
- Data encryption
- Data consistency
- Range checks and alerts.
- Backup system (systems necessary to avoid data loss and ensure data integrity)

A CRF is required and should be completed for each included patient. The Investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required.
The source documents are the hospital's or the physician's patient chart. In these cases, data collected on the CRFs must match the data in those charts.

14.2.2. Record Retention

To enable evaluations and/or audits from regulatory authorities or the sponsor, the Investigator agrees to keep all essential documents according to the GCPs, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports).

The records should be retained by the Investigator according to International Conference on Harmonization (ICH) guidelines, according to local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the Investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), the sponsor should be prospectively notified. The study records must be transferred to a designee acceptable to the sponsor, such as another Investigator, another institution, or to an independent third party arranged by the sponsor.
Investigator records must be kept for a minimum of 25 years after completion or

discontinuation of the study or for longer if required by applicable local regulations.

14.3. Sponsor Discontinuation Criteria

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, study treatment safety problems, or at the discretion of the sponsor.
If a study is prematurely terminated or discontinued, the sponsor will promptly notify the Investigator. After notification, the Investigator must contact all participating patients and the hospital pharmacy (if applicable) within 1 month. As directed by the sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

14.4. Study governance and oversight

The safety of this Study will be closely monitored on an ongoing basis by Sponsor. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

14.4.1. Trial Insurance Policy

The sponsor has contracted an insurance policy to cover the responsibilities of the investigator and other parties participating in the study, according to the applicable Spanish legislation.

14.4.2. Publication Policy

The sponsor commits to responsible publication of both the positive and negative results from its clinical trials as required by all governing regulatory and health authorities, according what is stated in article 42 of RD 1090/2015 of clinical trial.

Investigators will not publish the global study results (all sites) unless the sponsor has not done so in a suitable time period after the clinical study report (CSR) has been available. Should the Investigator(s) independently seek to publish results of this study which occur at their site(s), they must inform the study sponsor of any/all drafts (including, but not limited to papers, manuscripts or abstracts) at least 60 days before submission to the congress, meeting or journal. The sponsor and Investigator(s) will agree with all aspects related to any proposed publications with regards to the following: 1) any proposed publications will be drafted in agreement with international recommendations, such as those from the International Committee of Medical Journal Editors (ICMJE) and all elements of the Consort Statement (2010), to maintain integrity of the trial results in all communications; 2) any proposed publications will state the Clinical Research Ethics Committees which approved the trial and the funding sources of the trial; 3) any proposed publications will occur before disclosure of results to lay people; 4) any proposed publications will not report premature or partial data prior to completion of the analysis

of the overall results of the trial.

14.4.3. Authorship

The order of the authors will follow the SOGUG standard and will take into in account the researchers' contribution to the study.

15. INVESTIGATIONAL PRODUCT AND TREATMENTS

15.1. Identity of investigational product(s)

Table 9. ***List of investigational products for this study***

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	*50 mg/mL solution for infusion after dilution*	MedImmune
Tremelimumab	*20 mg/mL solution for infusion after dilution*	MedImmune

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APPENDICES

APPENDIX 1. DOSING MODIFICATION AND TOXICITY MANAGEMENT GUIDELINES FOR IMMUNE-MEDIATED, INFUSION-RELATED, AND NON-IMMUNE-MEDIATED REACTIONS (MEDI4736 MONOTHERAPY OR COMBINATION THERAPY WITH TREMELIMUMAB OR TREMELIMUMAB MONOTHERAPY)

Toxicity Management Guidelines (TMGs)

Drug Substance

Durvalumab and tremelimumab

TMG Version

17 Oct 2019, CTCAE v4.03

ANNEX TO PROTOCOL

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune-Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy)

Note: Annex is to be used in any clinical trial protocol within which patients are treated with MEDI4736 Monotherapy, MEDI4736 + Tremelimumab Combination Therapy, and/or Tremelimumab Monotherapy

VERSION HISTORY

17 October 2019, CTCAE version 4.03

The Toxicity Management Guidelines (TMGs) have been developed to assist investigators with the recognition and management of toxicities associated with use of the immune-checkpoint inhibitors durvalumab [MEDI4736] (PD-L1 inhibitor) and tremelimumab (CTLA-4 inhibitor). Given the similar underlying mechanism of toxicities observed with these two compounds, these TMGs are applicable to the management of patients receiving either drug as monotherapy or both drugs in combination. Additionally, these guidelines are applicable when either drug is used alone or both drugs are used in combination and, also, other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) are administered concurrently or sequentially as part of a protocol-specific treatment regimen. The TMGs provide information for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions that may be observed with monotherapy or combination checkpoint inhibitor regimens, with specific instructions for checkpoint inhibitor-specific dose modifications (including discontinuation) and treatment interventions. Investigators are advised however to use local practice guidelines and consult local references for the management of toxicities observed with other anti-cancer treatment.

Dosing modification and toxicity management for immune-mediated, infusion-related, and non-immune–mediated reactions associated with the use of a checkpoint inhibitor or checkpoint inhibitors in this protocol – whether that is MEDI4736 alone, tremelimumab alone, or MEDI4736 + tremelimumab in combination, or MEDI4736 +/- tremelimumab in combination with other anti-cancer drugs (i.e., antineoplastic chemotherapy, targeted agents) administered concurrently or sequentially – should therefore be performed in accordance with this Annex to Protocol, which for the purposes of submission and approval of substantial updates is maintained as a standalone document.

TMG updates are iterated by date, and issued in CTCAE version as specified in the clinical study protocol. This Annex to Protocol presents the dated version of the TMGs issued in CTCAE version 4.03.

Although the TMG versioning is independent of the protocol, the TMG Annex to Protocol should be read in conjunction with the Clinical Study Protocol, where if applicable additional references for the management of toxicities observed with other anti-cancer treatment are included in the specific section of the Clinical Study Protocol.

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v4.03)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03 (unless indicated otherwise). In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: ● Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks of the start of the immune-mediated adverse event (imAE) ● Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. 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. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).

	Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below. **Grade 4** Permanently discontinue study drug/study regimen. Note: For asymptomatic amylase or lipase levels of >2.0×ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	− More potent immunosuppressives such as TNF inhibitors (e.g., infliximab; also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. − With long-term steroid and other immunosuppressive use, consider need for Pneumocystis jirovecii pneumonia (PJP, formerly known as Pneumocystis carinii pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. − Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

Pediatric Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
The criteria for permanent discontinuation of study drug/study regimen based on CTC 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 the start of the immune-mediated event	− All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended. − The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients. − The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients ≥ 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist. − For pediatric dosing of mycophenolate mofetil, consult with 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 (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	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 (radiographic changes only):** – 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. – Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. ● If toxicity worsens, then treat as Grade 3 or Grade 4. ● 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 steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such

			as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)a – Consider Pulmonary and Infectious Disease consults. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/Colitis	**Any Grade**	**General Guidance**	**For Any Grade:**

Large intestine perforation/ Intestine perforation			– 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). – When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – 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 event, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
	Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day) (Colitis: abdominal pain; mucus or blood in stool)	Hold study drug/study regimen until resolution to Grade ≤1 ● If toxicity worsens, then treat as Grade 3 or Grade 4. ● 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 (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

	(Perforation: symptomatic; medical intervention indicated*) * “medical intervention” is not invasive	resumed after completion of steroid taper.	– If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. Caution: it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, change in bowel habits, medi-cal intervention indicated, peritoneal signs; Grade 4 Colitis: life-threatening consequences,	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). Caution: Ensure GI consult to rule out bowel

	urgent intervention indicated) (Grade 3 Perforation: severe symptoms, elective* operative intervention indicated; Grade 4 Perforation: life-threatening consequences, urgent intervention indicated) *This guidance anticipates that Grade 3 operative interventions of perforations are usually not elective		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. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Hepatitis (elevated LFTs) 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 HCC patients.**	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB > ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal	● No dose modifications. ● If it worsens, then treat as described for elevations in the row below.	– Continue LFT monitoring per protocol.
	AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5- 3.0×baseline	● Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal. ● If toxicity worsens, then treat as described for elevation in the row below.	– Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, in 1 to 2 days, consider, as necessary, discussing with study physician.

	if baseline abnormal	• If toxicity improves to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, resume study drug/study regimen after completion of steroid taper.	– If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).a Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).a
	AST or ALT >5.0×ULN if baseline normal, >5×baseline if baseline abnormal; and/or TB >3.0×ULN if baseline normal; >3.0×baseline if baseline abnormal	For elevations in transaminases ≤8×ULN and/or in TB ≤5×ULN if baseline normal, or for elevations in transaminases ≤8×baseline and/or TB ≤5×baseline if baseline abnormal: ● Hold study drug/study regimen dose until resolution to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT ≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal ● Resume study drug/study regimen if elevations downgrade to AST or ALT ≤3.0×ULN and/or TB ≤1.5×ULN if baseline normal, or to AST or ALT	– Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. – Request Hepatology consult, and perform abdominal workup and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for

		≤3.0×baseline and/or TB ≤1.5×baseline if baseline abnormal, within 14 days and after completion of steroid taper. ● Permanently discontinue study drug/study regimen if the elevations do not downgrade as described in bullet above within 14 days For elevations in transaminases >8×ULN or elevations in TB >5×ULN if baseline normal, or for elevations in transaminases >8×baseline and/or TB >5×baseline if baseline abnormal, permanently discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	treatment of cancer-related infections).[a]
Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance only for management of "Hepatitis (elevated LFTs)" in HCC patients** 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**	**Any Elevations in AST, ALT or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious Disease specialist regarding

			change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold − For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	● 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.	
	Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline**	● Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. ● If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper.	− Regular and frequent checking of LFTs (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 study physician. − If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. − If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound),

			and consider starting immunosuppressives (i.e., mycophenolate mofetil).a Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	● Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN ● Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. ● Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	− 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, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**

If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): **- Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise. For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline).** **- For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** − Consult with nephrologist. − 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, decrease in urine output, or proteinuria). − Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). − Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to 1.5×baseline; > ULN to 1.5×ULN)	No dose modifications.	**For Grade 1:** − Monitor serum creatinine weekly and any accompanying symptoms. ● If creatinine returns to baseline, resume its regular monitoring per study protocol. ● If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. − Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.

	Grade 2 (serum creatinine >1.5 to 3.0×baseline; >1.5 to 3.0×ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. ● If toxicity worsens, then treat as Grade 3 or 4. ● If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).a – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine >3.0×baseline; >3.0 to 6.0×ULN) (Grade 4: serum creatinine >6.0×ULN)	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis. – 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 or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started.

			– Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus). – IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. ● If toxicity worsens, then treat as Grade 3. ● If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:**	**For Grade 3 or 4:**

		Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or

		symptoms of pancreatic inflammation. – 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.
Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning 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	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. ● If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study	**For Grade 2 (including those with symptomatic endocrinopathy):** – 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 Type 1 DM, 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

		drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).a – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity.

		3. Doses of prednisone are ≤10 mg/day or equivalent.	– Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/ severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** – See “Any Grade” recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain Neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).

		If toxicity worsens, then treat as Grade 3 or 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	− Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. − If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**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 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** − Consider, as necessary, discussing with study physician. – Obtain Neurology consult. – Consider hospitalization. − Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. − If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). − Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade**	**General Guidance**	**For Any Grade:** − The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. − Patients should be evaluated to rule out any alternative etiology (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 Neurology consult. − Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) 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, as necessary, discussing with the study physician. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a Neurology consult.

	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 or autonomic instability.	**For Grade 2:** − Consider, as necessary, discussing with the study physician. − Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. − Obtain a Neurology consult − Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** − The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. − Consider, as necessary, discussing with the study physician. − 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). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. − Initial work-up should include clinical evaluation, BNP, cardiac enzymes, 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)
	Grade 1 (asymptomatic with laboratory [e.g., BNP] or cardiac imaging abnormalities)	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated.

			- Consider using steroids if clinical suspicion is high.
	Grade 2, 3 or 4 (Grade 2: Symptoms with mild to moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Myositis/ Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – 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, but rarely affects the extremities including hands and fingers; 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 study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein 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. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
Grade 1 (mild pain)	- 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 study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	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. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – 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 3 to 5 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 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).a

Grade 3 or 4 (pain associated with severe weakness; limiting self-care ADLs)	**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 days or if there are signs of respiratory insufficiency. For Grade 4: - Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** − Monitor symptoms closely; recommend hospitalization. − Obtain Neurology consult, and complete full evaluation. − Consider, as necessary, discussing with the study physician. − 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 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). 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. − Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

[a]ASCO Educational Book 2015 “Managing Immune Checkpoint Blocking Antibody Side Effects” by Michael Postow MD.
[b]FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP Pneumocystis jirovecii pneumonia (formerly known as Pneumocystis carinii pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	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 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 standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	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	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	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 Study Physician."

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

APPENDIX 2. DURVALUMAB DOSE CALCULATIONS

For durvalumab dosing done depending on patient weight:
1. Cohort dose: X mg/kg
2. Patient weight: Y kg
3. Dose for patient: XY mg = X (mg/kg) × Y (kg)
4. Dose to be added into infusion bag:
Dose (mL) = XY mg/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration.
The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.
5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL)/10.0 (mL/vial)

Example:
1. Cohort dose: 10 mg/kg
2. Patient weight: 30 kg
3. Dose for patient: 300 mg = 10 (mg/kg) × 30 (kg)
4. Dose to be added into infusion bag:
Dose (mL) = 300 mg/50 (mg/mL) = 6.0 mL
5. The theoretical number of vials required for dose preparation:
Number of vials = 6.0 (mL)/10.0 (mL/vial) = 1 vials

APPENDIX 3. DURVALUMAB DOSE VOLUME CALCULATIONS

For durvalumab flat dosing:
1. Cohort dose: X g
2. Dose to be added into infusion bag:
Dose (mL) = X g × 1000/50 (mg/mL) where 50 mg/mL is durvalumab nominal concentration.
The corresponding volume of durvalumab should be rounded to the nearest tenth mL (0.1 mL).
3. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL)/10.0 (mL/vial)

Example:
1. Cohort dose: 1.5 g
2. Dose to be added into infusion bag:
Dose (mL) = 1.5 g ×1000/50 (mg/mL) = 30.0 mL
3. The theoretical number of vials required for dose preparation:
Number of vials = 30.0 (mL)/10.0 (mL/vial) = 3 vials

APPENDIX 4. TREMELIMUMAB DOSE CALCULATIONS

(Not needed unless tremelimumab monotherapy arm is 10 mg/kg or fixed-dose equivalent)

For tremelimumab dosing done depending on patient weight:

1. Cohort dose: X mg/kg
2. Patient weight: Y kg
3. Dose for patient: XY mg = X (mg/kg) × Y (kg)
4. Dose to be added into infusion bag:
   Dose (mL) = XY mg/20 (mg/mL) where 20 mg/mL is tremelimumab nominal concentration.
   The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for greater than 10% change in weight.
5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
   Number of vials = Dose (mL)/20.0 (mL/vial)

Example:

1. Cohort dose: 1 mg/kg
2. Patient weight: 30 kg
3. Dose for patient: 30 mg = 1 (mg/kg) × 30 (kg)
4. Dose to be added into infusion bag:
   Dose (mL) = 30 mg/20 (mg/mL) = 1.5 mL
5. The theoretical number of vials required for dose preparation:
   Number of vials = 1.5 (mL)/20.0 (mL/vial) = 1 vials

APPENDIX 5. TREMELIMUMAB DOSE VOLUME CALCULATIONS

For tremelimumab flat dosing:
1. Cohort dose: X mg
2. Dose to be added into infusion bag:
Dose (mL) = X mg/20 (mg/mL)
s tremelimumab nominal concentration
The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL).
3. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:
Number of vials = Dose (mL)/20 (mL/vial)

Example:
1. Cohort dose: 75 mg
2. Dose to be added into infusion bag:
Dose (mL) = 75 mg/20 (mg/mL) = 3.8 mL
3. The theoretical number of vials required for dose preparation:
Number of vials = 3.8 (mL)/20 (mL/vial) = 1 vial

Phase II trial of durvalumab (Medi4736) plus tremelimumab with concurrent radiotherapy in patients with localized muscle invasive bladder cancer treated with a selective bladder preservation approach - INMUNOPRESERVE STUDY - MANUSCRIPT 2022

1. Table of Contents

The information of this analysis was done with a database downloaded on XX/XX/20XX.

2. INCLUSION CRITERIA

2.1. SCREENING FAILURES

Table 1: Screening Failure

Screening failure	N	%
No		
Yes		
Total		

Table 2: Screening failures details

Patient number	Screening failure	Reason	Safety analysis set

2.2. PATIENT POPULATIONS

Safety analysis set

The safety analysis set will include all patients who receive at least 1 dose of study treatment. The safety analysis set will be the primary population for evaluating treatment administration/compliance and safety.

Efficacy analysis set

The efficacy analysis will be a per protocol analysis. The efficacy analysis set will include all patients who receive at least 2 cycles of durvalumab and 3 weeks of radiotherapy. The efficacy analysis set will be the primary population for evaluating treatment efficacy.

Table 3: Population details

Patient number	Screening failure	Safety set	ITT	Dosis Durvalumab Week 1	Dosis Durvalumab Week 5	2 dosis Durvalumab	Radiotherapy duration (weeks)	Radiotherapy >3 weeks	PP

3. RESULTS

3.1. POPULATION AND RECRUITED PATIENTS

Analysis Population Definitions

All efficacy and safety analyses will be performed using the Safety population because all the patients (n = 32) fullfil the conditions to be included in the safety and efficacy (PP) populations, which include all patients who received at least 2 doses of Durvalumab and at least 3 weeks of radiotherapy.

Table 4: Populations and Hospital

	(N=)
Safety analysis set	
Yes	
Intention to treat population	
Yes	
Per protocol population	
Yes	
Hospital	

3.2. BASELINE CHARACTERISTICS

3.2.1. BASELINE - DEMOGRAPHIC DATA

Table 5: Baseline - Demographic Data

	(N=)
Sex	
Female	
Male	
Age at treatment (year)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Age at screening (year)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Weight (kg)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Race	
Caucasian	
Systolic Blood Pressure (mmHg)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Diastolic Blood Pressure (mmHg)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Temperature (ºC)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Height (cm)	
N	
Mean (95%CI)	

	(N=)
SD	
Median (95%CI)	
Range	
Pulse Rate (bpm)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
ECOG	
0	
1	

Table 6: Tobacco smoking history

	(N=)
Tobacco Smoking History	
Never smoker (<= 100 cigarrettes/life time)	
Former smoker (>= 1 year)	
Smoker	
Tobacco Cigarrettes Day History	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Tobacco Pack Year History	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 7: Alcohol use and others current status

	(N=)
Alcoholic drinks per day	
< 1/Day	
1-2/Day	
UK	
History Drug Abuse	
No	
Yes	
ND	
Current Drug Abuse	
No	
Yes	
ND	

3.2.2. PREVIOUS RELEVANT ILLNESSES

Table 8: Relevant illnesses

Variables		N (%)
Comorbidities	Yes	
	No	
	Total	

Table 9: All comorbidities

Variables		N (%)
Comorbidities		

3.2.3. PREVIOUS RELEVANT TREATMENTS

Table 10: Concomitant Medications

Variables		N (%)
Concomitant medications	No	
	Yes	
	Total	

Table 11: All Concomitant Medication

Variables	N (%)
ConcomitantMedication	

Table 12: Other Concomitant Medication

Variables	N (%)
Other concomitant medications	

3.2.4. CANCER HISTORY

Table 13: Baseline - Cancer History

	(N=)
Non Invasive Cancer History	
Yes	
No	
Time since Non-Invasive urothelial carcinoma diagnosis until treatment started (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Non Invasive Carcinoma Grade	
High	
Low	
UK	
BCG Treatment	
Yes	
No	
Duration BCG treatment (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Note: Patient **01-001** doesn't have information about the duration of BCG treatment.

Table 14: Non-Invasive Other Treatments

Variables	N (%)
Non-invasive other treatments	

Table 15: Baseline - Cancer History - Infiltrating carcinoma diagnose

	(N=)
Time since Infiltrating carcinoma diagnosis until treatment started (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Time since Transurethral resection date until treatment started (months)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	

	(N=)
Range	
Histological Diagnosis	
Urothelial carcinoma	
Mixed urothelial carcinoma	
Initial T Stage	
T2	
T2a	
T2b	
T3	
T4	
Initial N Stage	
N0	
Initial M Stage	
M0	
Carcinoma Grade	
Low	
High	
Previous Treatments	
Yes	
No	
Partial Cystectomy	
No	
Cancer Other Treatments	
Yes	
No	
List of Cancer Other Treatments	

3.2.5. BASELINE - HEMATOLOGY AND COAGULATION

Table 16: Hematology

	(N=)
Hemoglobin (g/dl)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Neutrophils (x10e9/l)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Limphocytes (x10e9/l)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Platelets (x10e9/l)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 17: Coagulation

	(N=)
INR	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
PTT (sec)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
PTT (ratio)	

3.2.6. BASELINE - BIOCHEMISTRY AND SEROLOGY

Table 18: Biochemistry (I)

	(N=)
Creatinine (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Albumin (g/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
CreatinineClearingValue.BasAnaBio	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Total Bilirrubin (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
AST (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
ALT (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Phosphatase (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
GGT (U/L)	
N	
Mean (95%CI)	
SD	

	(N=)
Median (95%CI)	
Range	
Urea (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
LDH (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
BUN (mg/dL)	
N	
Mean (SD)	
Median (Range)	

Table 19: Patients with creatinine clearance < 40 ml/min

Patient Number	Hospital	Creatinine clearance

Table 20: Biochemistry (II)

	(N=)
Calcium (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Magnesium (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Sodium (mEq/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Potassium (mEq/L)	
N	
Mean (95%CI)	

	(N=)
SD	
Median (95%CI)	
Range	
Chloride (mEq/L))	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Glucose (mg/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Amylase (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Bicarbonate (mEq/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Lipase (U/L)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Total Protein (g/dL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 21: Serology

	(N=)
HCV	
Negative	
HbsAg	
Negative	
HIV	
Negative	

3.2.7. BASELINE - OTHER ANALYTICS

Table 22: Thyroid Function

	(N=)
THS Value	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Free T3 (pg/mL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Free T4 (ng/mL)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 23: Urinalysis

	(N=)
Urinalysis result	
Missing data	
Negative	
Traces	
+1	
+2	
Bilirubin	
Positive	
Negative	
ND	
Blood	
Positive	
Negative	
ND	
Color/appearence	
Normal	
ND	
Glucose	
Normal	
Abnormal	
ND	
pH	
N	
Mean (95%CI)	
SD	
Median (95%CI)	

	(N=)
Range	
Ketones	
Positive	
Negative	
ND	
Specific Gravity	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
TSH (mIU/L)	
Positive	
Negative	
ND	

Table 24: Electrocardiogram

	(N=)
ECG result	
Normal	
Abnormal	
ND	
ECG QTc (msec)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 25: Pregnancy Test

Pregnancy Test (females only)	
NA	
ND	

3.2.8. PD-L1

Table 26: PD-L1 High status

	(N=)
PD-L1 High status	
Missing data	
Low/Negative	
High	

3.3. TREATMENT

3.3.1. DURVALUMAB TREATMENT

Table 27: Durvalumab compliance

	(N=)
1 dosis of Durvalumab	
No	
Yes	
2 dosis of Durvalumab	
No	
Yes	
3 dosis of Durvalumab	
No	
Yes	
Number of Durvalumab dosis	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of Durvalumab dosis	
1 dosis	
2 dosis	
3 dosis	

Table 28: Durvalumab dosage

	(N=)
Dosis of Durvalumab week 1	
1500	
Dosis of Durvalumab week 5	
1500	
Dosis of Durvalumab week 9	
1500	
None	

Table 29: Durvalumab Not administered reasons

	(N=)
Not administered reasons week 1	

	(N=)
Not administered reasons week 5	
Not administered reasons week 9	

Table 30: Durvalumab delay

	(N=)
Patients with at least one delay of Durvalumab	
No	
Yes	
Number of dosis of Durvalumab delayed	
None	
1 delay	
2 delays	
3 delays	
Dosis of Durvalumab delayed	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Durvalumab dosis delay week 1	
Yes	
No	
Durvalumab dosis delay week 5	
Yes	
No	
Durvalumab dosis delay week 9	
Yes	
No	
Reason Durvalumab dosis delay week 1	
Reason Durvalumab dosis delay week 5	
Reason Durvalumab dosis delay week 9	

3.3.2. TREMELIMUMAB TREATMENT

Table 31: Tremelimumab compliance

	(N=)
1 dosis of Tremelimumab	
Yes	
2 dosis of Tremelimumab	
Yes	
3 dosis of Tremelimumab	
No	
Yes	
Number of Tremelimumab dosis	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Number of Tremelimumab dosis	
1 dosis	
2 dosis	
3 dosis	

Table 32: Tremelimumab dosage

	(N=)
Dosis of Tremelimumab week 1	
75	
Dosis of Tremelimumab week 5	
75	
Dosis of Tremelimumab week 9	
75	

Table 33: Tremelimumab Not administered reasons

	(N=)
Not administered reasons week 1	
Not administered reasons week 5	
Not administered reasons week 9	

Table 34: Tremelimumab delay

	(N=)
Patients with at least one delay of Tremelimumab	
No	
Yes	
Number of dosis of Tremelimumab delayed	
None	
1 delay	
2 delays	
3 delays	
Dosis of Tremelimumab delayed	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Tremelimumab dosis delay week 1	
Yes	
No	
Tremelimumab dosis delay week 5	
Yes	
No	
Tremelimumab dosis delay week 9	
Yes	
No	
Reason Tremelimumab dosis delay week 1	
Reason Tremelimumab dosis delay week 5	
Reason Tremelimumab dosis delay week 9	

Table 35: List of patients with Durvalumab or Tremelimumab delay

Patient ID	Reason Durvalumab delay in week 5	Reason Tremelimumab delay in week 5

3.3.3. RADIOTHERAPY TREATMENT

Table 36: Radiotherapy treatment details

	(N=)
Radiotherapy Sessions (total number)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Radiotherapy Sessions (total number)	
10	
25	
27	
28	
30	
31	
32	
33	
35	
66	
Radiotherapy Fractions (per week)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Radiotherapy Fractions (per week)	
Missing data	
4	
5	
10	
23	
Radiotherapy Dose per Fraction (Gy)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Radiotherapy Dose per Fraction (Gy)	
Missing data	
2	
4	
Radiotherapy Doses Minor Pelvis (Gy)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Radiotherapy Doses Minor Pelvis (Gy)	
Missing data	

	(N=)
46	
51	
52	
Radiotherapy Total Dose administered in bladder (Gy)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Radiotherapy Total Dose administered in bladder (Gy)	
50	
54	
60	
61	
64	
65	
66	
Radiotherapy treatment duration (weeks)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Radiotherapy interruptions

Table 37: Radiotherapy interruptions

	(N=)
Radiotherapy Interruption	
Yes	
No	
Number of radiotherapy interruptions	
N	
Mean (SD)	
Median (Range)	
Number of radiotherapy interruptions	
1 interruption	
2 interruptions	
3 interruptions	
None	
Radiotherapy ReStart	
Yes	
No	
NA	
Total duration of radiotherapy interruptions (days)	
N	
Mean (SD)	
Median (Range)	
Radiotherapy Interruption Reason	

(N=)

List of patients with their radiotherapy interruptions details

Table 38: List of patients with their radiotherapy interruptions details

Patient ID	Hospital	Number of radiotherapy interruptions	Radiotherpay restarted	Radiotherapy interruption total duration (days)	Reason for radiotherapy interruption

3.4. END OF TREATMENT

Table 39: End of treatment details

	(N=)
Treatment duration (weeks)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
End Treatment Reason	
Unnacceptable toxicity	
AE not related to treatment	
Complete the protocol treatment	

List of patients with their end of treatment reason and treatment duration:

Table 40: End of treatment reason and treatment duration by patient

Patient ID	Hospital	Treatment duration (weeks)	End of treatment reason

3.5. MEDIAN FOLLOW-UP

Table 41: Median follow-up (overall)

	(N=)
Follow-up in months	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

3.6. MEDIAN FOLLOW-UP (ONLY ALIVE PATIENTS)

Table 42: Median follow-up (only alive patients)

	(N=)
Follow-up in months	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	

Table 43: List of patients: follow-up (months)

Patient ID	Hospital	Status	Overall Survival Time (months)

3.7. RESPONSE EVALUATION TO THERAPY

Table 44: Response evaluation: Cystoscopy details

	(N=)
Time since end of treatment until Cystoscopy (weeks)	
N	
Mean (95%CI)	
SD	
Median (95%CI)	
Range	
Cytoscopy done	
Yes	
No	
Reason response evaluation not done	

List of patients without Cystoscopy

Table 45: List of patients without Cystoscopy

Patient ID	Hospital	Cystoscopy done	Reason Cystoscopy not done	Death Reason

3.8. PRIMARY EFFICACY ANALYSIS

Efficacy of durvalumab plus tremelimumab with concurrent radiotherapy in terms of pathological response rate (Response evaluation by cystoscopy 6 weeks after end of RT).

Muscle Invasive Bladder Cancer

Table 46: Response Evaluation: Muscle-invasive bladder cancer

Muscle-invasive bladder cancer	N	%	95%CI
Cytoscopy not done			
Yes			
No			
Total			

Non Invasive Bladder Cancer

Table 47: Response Evaluation: Non Invasive Bladder Cancer

Non Invasive Bladder Cancer	N	%	95%CI
Cytoscopy not done			
Yes			
No			
Total			

Non-Invasive bladder cancer (including Muscle invasive)

Table 48: Response Evaluation: Non Invasive Bladder Cancer (including Muscle Invasive

Non Invasive Bladder Cancer	N	%	95%CI
Cytoscopy not done			
Yes (Non Invasive Bladder Cancer)			
Yes (Muscle Invasive Bladder Cancer)			
No			
Total			

Table 49: Response Evaluation: TNM

	(N=)
T Stage	
T0	
T1	
T2	
T4	
T Stage (including Not evaluated)	

	(N=)
Cytoscopy not done	
T0	
T1	
T2	
T4	
N Stage	
N0	
N Stage (including Not evaluated)	
Cytoscopy not done	
N0	
M Stage	
M0	
M Stage (including Not evaluated)	
Cytoscopy not done	
M0	

3.9. Secondary Objective 1a: Bladder preservation at 6 weeks after RT

Bladder preservation. Rate of patients with bladder preserved (at 6 weeks after RT)

Table 50: Response Evaluation: Post therapy radical surgery/salvage cystectomy required (aprox. 6 weeks after RT). Immediate salvage cystectomies

	(N=)
Radical Surgery. Immediate salvage cystectomies	
No	
Radical Surgery (including Not evaluated). Immediate salvage cystectomies	
Cytoscopy not done	
No	

Details of Response Evaluation

Table 51: List of patients with Response Evaluation Non-invasive Invasive Bladder or without Cystoscopy (6 weeks after end of RT)

Patient ID	Hospital	Muscle Invasive Bladder	Non Invasive Bladder Cancer	T Stage	N Stage	M Stage	Radical Surgery

3.10. Secondary objective 1b: Bladder preservation immediate and late salvage cystectomies

Bladder preservation: Rate of immediate and late salvage cystectomies. *"Post therapy radical/surgery cystectomy"* is used to calculate the rate at 3, 6 and 9 months (assuming a margin of one week, 7 days).

- Immediate salvage cystectomies
- Late salvage cystectomies

Table 52: Late salvages cystectomies at 3 months

Late salvages cystectomies at 3 months (all patients)	N	%	95%CI
No (Follow-up>=3m)			
Death before 3m			
Total			

Table 53: Late salvages cystectomies at 6 months

Late salvages cystectomies at 6 months (all patients)	N	%	95%CI
No (Follow-up>=6m)			
Death before 6m			
Total			

Table 54: Late salvages cystectomies at 6 months (excluding patients with Follow-up less than 6 months)

Late salvages cystectomies at 6 months (excluding patients with Follow-up less than 6 months)	N	%	95%CI
No (Follow-up>=6m)			
Total			

Table 55: Late salvages cystectomies at 9 months

Late salvages cystectomies at 9 months (all patients)	N	%	95%CI
Yes			
No (Follow-up>=9m)			
Death before 9m			
Total			

Table 56: Late salvages cystectomies at 9 months (excluding patients with Follow-up less than 9 months

Late salvages cystectomies at 9 months (excluding patients with Follow-up less than 9 months)	N	%	95%CI
Yes			
No (Follow-up>=9m)			
Total			

Table 57: Late salvages cystectomies at any time

Late salvages cystectomies at any time (all patients)	N	%	95%CI
Yes			
No			
Death			
Total			

Table 58: Late salvages cystectomies (any time) excluding deaths

Late salvages cystectomies at any time (excluding deaths)	N	%	95%CI
Yes			
No			
Total			

Table 59: List of patients with Late salvages cystectomies (any time)

Patient ID	Hospital	Late salvage cystectomy	Date Late salvage cystectomy	Time since start of treatment until late salvage cystectomy (months)

3.11. Secondary objective 1c: Bladder preservation EFS

Event Free Survival (EFS) with bladder preserved free of tumor, defined as the time from the start of immunotherapy to either the date of cystectomy or the date of recurrence of muscle-invasive bladder carcinoma or metastasis.

EFS Bladder preservation

Table 60: Bladder preservation: Event Free Survival

EFS (event)	N	%	95%CI
Event/Death			
No			
Total			

Table 61: Type of event: EFS bladder preserved

	(N=)
Type of event: EFS bladder preserved	
No	
Late salvage cystectomy/Bladder relapse	
Bladder relapse/Metastases	
Bladder relapse	
Metastases	
Death	

Table 62: Survival Median/Mean EFS

	Median	95%CI	Mean	95%CI
EFS				

3.11.1. EFS Bladder preservation estimated at 6, 12, 18 and 24 months (Kaplan-Meier)

Table 63: EFS bladder preserved at 6, 12, 18 and 24 months

EFS bladder preserved	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 6 months				
At 12 months				
At 18 months				

EFS bladder preserved	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 24 months				

Note: Estimated using Kaplan-Meier product-limit method

3.11.1.1. Figure: EFS Bladder preservation

List of patients. Events: EFS bladder preserved

Table 64: List of patients with event for EFS bladder preserved

Patient ID	Hospital	Event EFS bladder preserved	Date EFS bladder preserved

3.12. Secondary objective 1d: Event free survival (Specific)

Event Free Survival (EFS) specific:

1) M1 o N1 (metastases) is an event independently of presence of Salvage cystectomy

2) Local recurrence (bladder relapse) without Salvage cystectomy.

EFS specific

Table 65: Event Free Survival specific

EFS (event)	N	%	95%CI
Event/Death			
No			
Total			

Table 66: Type of event: EFS specific

	(N=)
Type of event: EFS specific	
No	
Bladder relapse/Metastases	
Bladder relapse	
Metastases	
Death	

Table 67: Survival Median/Mean EFS specific

	Median	95%CI	Mean	95%CI
EFS				

3.12.1. EFS specific estimated at 6, 12, 18 and 24 months (Kaplan-Meier)

Table 68: EFS specific at 6, 12, 18 and 24 months

EFS specific	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Note: Estimated using Kaplan-Meier product-limit method

3.12.1.1. Figure: EFS Specific

List of patients. Events: EFS specific

Table 69: List of patients. EFS specific

Patient ID	Hospital	Event EFS specific	Date EFS specific

3.13. Secondary objective 1e: PFS (Tumour assessment)

Time from treatment start to tumour relapse or distant progression (or death)

PFS Tumour assessment

Table 70: PFS Tumour Assessment

EFS (event)	N	%	95%CI
PD/Death			
Alive			
Total			

Table 71: Type of event: PFS Tumour assessment

	(N=)
Type of event: PFS Tumour assessment	
Alive without PD	
PD (tumour assessment)	
Death	

Table 72: Survival Median/Mean PFS Tumour assessment

	Median	95%CI	Mean	95%CI
PFS				

3.13.1. PFS Tumour assessment estimated at 6, 12, 18 and 24 months (Kaplan-Meier)

Table 73: PFS Tumour assessment at 6, 12, 18 and 24 months

PFS Tumour assessment	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Note: Estimated using Kaplan-Meier product-limit method

3.13.1.1. Figure: PFS Tumour assessment

List of patients. Events: PFS Tumour assessment

Table 74: List of patients. PFS

Patient ID	Hospital	Event PFS	Date PFS

3.14. Secondary objective 1f: Overall Survival

Time from treatment start to Death.

Overall Survival

Table 75: Overall Survival

EFS (event)	N	%	95%CI
Death			
Alive			
Total			

Table 76: Type of event: Overall Survival

	(N=)
Type of event: Overall Survival	
Alive at end of trial: Patient's decision	
Alive at end of trial according to protocol	
Death	

Table 77: Overall Survival Median/Mean

	Median	95%CI	Mean	95%CI
OS				

3.14.1. OS estimated at 6, 12, 18 and 24 months (Kaplan-Meier)

Table 78: Overall Survival at 6, 12, 18 and 24 months

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 6 months				

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 12 months				
At 18 months				
At 24 months				

Note: Estimated using Kaplan-Meier product-limit method

3.14.1.1. Figure: Overall Survival

Table 79: Details of deaths

Patient ID	Hospital	Status	Death Reason

3.15. SECONDARY OBJECTIVE: EFS MUSCLE INVASIVE

Muscle invasive events (bladder relapse) recorded in follow-up bladder disease section of the eCRD.

Table 80: EFS: Muscle invasive (patients with cystoscopy)

Muscle invasive (event)	N	%	95%CI
No			
Yes			
Total			

Table 81: Survival Median/Mean EFS Muscle Invasive

	Median	95%CI	Mean	95%CI
EFS				

3.15.1. EFS MUSCLE INVASIVE ESTIMATED AT 6, 12, 18 AND 24 MONTHS (KAPLAN-MEIER)

Table 82: EFS Muscle Invasive at 6, 12, 18 and 24 months

EFS Muscle Invasive	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Note: Estimated using Kaplan-Meier product-limit method

3.15.1.1. FIGURE: EFS MUSCLE INVASIVE

Table 83: List of patients with EFS Muscle Invasive

Patient Number	Hospital	Response evaluation at 6w after RDT: Muscle-invasive bladder cancer	Muscle invasive (patients with cystoscopy - bladder disease FU)	Date Muscle invasive	Non-Muscle invasive (patients with cystoscopy - bladder disease FU)	Date Non-Muscle invasive	Response evaluation: Non-Invasive bladder cancer (including Muscle invasive)

3.16. Secondary objective: EFS NON MUSCLE INVASIVE

Non-muscle invasive events (bladder relapse) recorded in follow-up bladder disease section of the eCRD.

Table 84: EFS: Non-Muscle invasive (patients with cystoscopy)

Non-Muscle invasive (event)	N	%	95%CI
No			
Yes			
Total			

Table 85: Survival Median/Mean EFS NON MUSCLE Invasive

	Median	95%CI	Mean	95%CI
EFS				

3.16.1. EFS NON MUSCLE Invasive estimated at 6, 12, 18 and 24 months (Kaplan-Meier)

Table 86: EFS Non-Muscle invasive at 6, 12, 18 and 24 months

EFS NON MUSCLE Invasive	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Note: Estimated using Kaplan-Meier product-limit method

3.16.1.1. Figure: EFS NON MUSCLE Invasive

Table 87: List of patients with EFS Non-Muscle Invasive

Patient Number	Hospital	Response evaluation at 6w after RDT: Muscle-invasive bladder cancer	Muscle invasive (patients with cystoscopy - bladder disease FU)	Date Muscle invasive	Non-Muscle invasive (patients with cystoscopy - bladder disease FU)	Date Non-Muscle invasive	Response evaluation: Non-Invasive bladder cancer (including Muscle invasive)

3.17. Secondary objective: METASTASES

Metastases events recorded in follow-up metastases section of the eCRD.

Table 88: EFS: Metastases

Metatases (event, includes death due to PD)	N	%	95%CI
Yes			
No			
Total			

Table 89: Survival Median/Mean EFS METASTASES

	Median	95%CI	Mean	95%CI
EFS				

3.17.1. EFS METASTASES estimated at 6, 12, 18 and 24 months (Kaplan-Meier)

Table 90: EFS METASTASES at 6, 12, 18 and 24 months

EFS METASTASES	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	95% IC
At 6 months				
At 12 months				
At 18 months				
At 24 months				

Note: Estimated using Kaplan-Meier product-limit method

3.17.1.1. Figure: EFS METASTASES

Table 91: List of patients with EFS Metastases

Patient Number	Hospital	Response evaluation at 6w after RDT: Muscle-invasive bladder cancer	Muscle invasive (patients with cystoscopy - bladder disease FU)	Date Muscle invasive	Non-Muscle invasive (patients with cystoscopy - bladder disease FU)	Date Non-Muscle invasive	Response evaluation: Non-Invasive bladder cancer (including Muscle invasive)

3.18. ESTIMATION OF CUMULATIVE INCIDENCE (COMPETING RISKS ANALYSIS)

3.18.1. CIF: MUSCLE INVASIVE BLADDER CANCER

In this section the event of interest was the relapse due to the presence of **muscle invasive bladder cancer** and the cumulative incidence is estimated in the presence of the following competitive events:

- *Death*
- *Cystectomy*

Table 92: Muscle Invasive Bladder Cancer and competitive events

	(N=)
Events (Muscle Invasive Bladder Cancer)	
Event=Death	
Event=Muscle Invasive Bladder Cancer	
No	

Table 93: List of patients with cumulative event: muscle invasive bladder cancer

Patient Number	Date treatment intiation	Events (Muscle Invasive Bladder Cancer)	Date Event/Follow-up	Time from treatment initiation	Cytoscopy	Exitus Reason	Last available date	Late salvage cystectomy date

Table 94: Cumulative Incidence of Muscle Invasive Bladder Cancer (in the presence of competitive events)

Time	Estimated Cumulative Incidence (95% CI)
6 months	
12 months	
18 months	
24 months	
36 months	

3.18.1.1. FIGURE: CIF MUSCLE INVASIVE BLADDER CANCER AND COMPETITIVE EVENTS

3.18.2. CIF: MUSCLE NON INVASIVE BLADDER CANCER

In this section the event of interest was the relapse due to the presence of **muscle non invasive bladder cancer** and the cumulative incidence is estimated in the presence of the following competitive events:

- *Death*
- *Cystectomy*
- *Muscle Invasive Bladder Cancer*

Table 95: Muscle Non Invasive Bladder Cancer and competitive events

	(N=)
Events (Muscle Non Invasive Bladder Cancer)	
Event=Death	
Event=Muscle Invasive Bladder Cancer	
Event=Muscle Non Invasive Bladder Cancer	
No	

Table 96: List of patients with cumulative event: Non-invasive muscle bladder cancer

Patient Number	Date treatment intiation	Events (Muscle Non Invasive Bladder Cancer)	Date Event/Follow -up	Time from treatment initiation	Cytoscopy	Exitus Reason	Last available date	Late salvage cystectomy date

Table 97: Cumulative Incidence of Muscle Non Invasive Bladder Cancer (in the presence of competitive events)

Time	Estimated Cumulative Incidence (95% CI)
6 months	
12 months	
18 months	
24 months	
36 months	

3.18.2.1. FIGURE: CIF MUSCLE NON INVASIVE BLADDER CANCER AND COMPETITIVE EVENTS

3.18.3. CIF: RELAPSE BLADDER CANCER

In this section the event of interest was the **relapse bladder cancer** and the cumulative incidence is estimated in the presence of the following competitive events:

- *Death*
- *Cystectomy*

Table 98: Relapse Bladder Cancer and competitive events

	(N=)
Events (Any Bladder Cancer)	
Event= Any Bladder Cancer	
Event=Death	
No	

Table 99: List of patients with cumulative event: Bladder cancer (Any type)

Patient Number	Date treatment intiation	Events (Any Bladder Cancer)	Date Event/Follow -up	Time from treatment initiation	Cytoscopy	Exitus Reason	Last available date	Late salvage cystectomy date

Table 100: Cumulative Incidence of Relapse Bladder Cancer (in the presence of competitive events)

Time	Estimated Cumulative Incidence (95% CI)
6 months	
12 months	
18 months	
24 months	
36 months	

3.18.3.1. FIGURE: CIF RELAPSE BLADDER CANCER AND COMPETITIVE EVENTS

3.18.4. CIF: METASTASES

In this section the event of interest was the **Metastases** and the cumulative incidence is estimated in the presence of the following competitive events:

- *Death*

Table 101: Metastases and competitive events

	(N=)
Events (Metastases)	
Event = Metastases	
Event=Death	
No	

Table 102: Cumulative Incidence of Metastases (in the presence of competitive events)

Time	Estimated Cumulative Incidence (95% CI)
6 months	
12 months	
18 months	
24 months	
36 months	

3.18.4.1. FIGURE: CIF METASTASES AND COMPETITIVE EVENTS

4. PROGNOSIS FACTORS FOR EFS BLADDER PRESERVATION, EFS (SPECIFIC), PFS AND OS

4.1. EFS BLADDER PRESERVATION

4.1.1. AGE

Table 103: EFS bladder preservation by age

Age at start of treatment	Age < 71 (N=)	Age ≥ 71 (N=)	Total (N=)	p value
Event Free Survival bladder preserved				
No				
Late salvage cystectomy/Bladder relapse				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival bladder preserved				
Event/Death				
No				

1. Fisher's Exact Test for Count Data
2. Pearson's Chi-squared test

Table 104: Median/mean EFS bladder preservation by age (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Age < 71				
Age ≥ 71				

Table 105: EFS bladder preservation by age estimated survival ratio

EFS bladder preservation	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Age < 71				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
Age ≥ 71				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

4.1.1.1. Figure: EFS bladder preservation vs Age (abowe or below 71)

4.1.2. GENDER

Table 106: EFS bladder preservation by gender

Sex	Female (N=)	Male (N=)	Total (N=)	p value
Event Free Survival bladder preserved				
No				
Late salvage cystectomy/Bladder relapse				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival bladder preserved				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 107: Median/mean EFS bladder preservation by gender (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Female				
Male				

Table 108: EFS bladder preservation by gender estimated survival ratio

EFS bladder preservation	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Female				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
Male				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

4.1.2.1. Figure: EFS bladder preservation vs gender

4.1.3. Stage: T2 vs. T3/T4

Table 109: EFS bladder preservation by Stage: T2 vs T3/T4

T Stage	T2 (N=)	T3/T4 (N=)	Total (N=)	p value
Event Free Survival bladder preserved				
No				
Late salvage cystectomy/Bladder relapse				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival bladder preserved				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 110: Median/mean EFS bladder preservation by Stage: T2 vs T3/T4 (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
T2				
T3/T4				

Table 111: EFS bladder preservation by Stage: T2 vs T3/T4 estimated survival ratio

EFS bladder preservation	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
T2				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
T3/T4				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

4.1.3.1. Figure: EFS bladder preservation vs Stage: T2 vs T3/T4

4.1.4. ECOG: 0 vs. 1

Table 112: EFS bladder preservation by ECOG: 0 vs. 1

ECOG.BasDatDem	0 (N=)	1 (N=)	Total (N=)	p value
Event Free Survival bladder preserved				
No				
Late salvage cystectomy/Bladder relapse				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival bladder preserved				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 113: Median/mean EFS bladder preservation by ECOG: 0 vs. 1 (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
0				
1				

Table 114: EFS bladder preservation by ECOG: 0 vs. 1 estimated survival ratio

EFS bladder preservation	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
0				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
1				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

4.1.4.1. Figure: EFS bladder preservation vs ECOG: 0 vs. 1

4.1.5. Non Invasive Cancer History: Yes vs. No

Table 115: EFS bladder preservation by Non invasive Cancer History: Yes vs. No

NonInvasiveCancerHistory.BasCancer	Yes (N=)	No (N=)	Total (N=)	p value
Event Free Survival bladder preserved				
No				
Late salvage cystectomy/Bladder relapse				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival bladder preserved				
Event/Death				
No				

1. Fisher's Exact Test for Count Data
2. Pearson's Chi-squared test

Table 116: Median/mean EFS bladder preservation by Non invasive Cancer History: Yes vs. No (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Yes				
No				

Table 117: EFS bladder preservation by Non invasive Cancer History: Yes vs. No estimated survival ratio

EFS bladder preservation	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
No				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

4.1.5.1. Figure: EFS bladder preservation vs Non invasive Cancer History: Yes vs. No

4.1.6. PD-L1: High vs. Low/Negative

Table 118: EFS bladder preservation by PD-L1: High vs. Low/Negative

PD-L1 High status	Low/Negative (N=)	High (N=)	Total (N=)	p value
Event Free Survival bladder preserved				
No				
Late salvage cystectomy/Bladder relapse				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival bladder preserved				
Event/Death				
No				

1. Fisher's Exact Test for Count Data
2. Pearson's Chi-squared test

Table 119: Median/mean EFS bladder preservation by PD-L1: High vs. Low/Negative (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Low/Negative				
High				

Table 120: EFS bladder preservation by PD-L1: High vs. Low/Negative estimated survival ratio

EFS bladder preservation	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Low/Negative				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
High				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

4.1.6.1. Figure: EFS bladder preservation vs PD-L1: High vs. Low/Negative

4.1.7. Creatinine clearance: < 60 vs ≥ 60 (mL/min)

Table 121: EFS bladder preservation by Creatinine clearance: < 60 vs ≥ 60 (mL/min)

Creatinine clearance (mL/min)	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
Event Free Survival bladder preserved				
No				
Late salvage cystectomy/Bladder relapse				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival bladder preserved				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 122: Median/mean EFS bladder preservation by Creatinine clearance: < 60 vs ≥ 60 (mL/min) (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
< 60				
≥ 60				

Table 123: EFS bladder preservation by Creatinine clearance: < 60 vs ≥ 60 (mL/min) estimated survival ratio

EFS bladder preservation	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
< 60				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
≥ 60				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

4.1.7.1. Figure: EFS bladder preservation vs Creatinine clearance: < 60 vs ≥ 60 (mL/min)

1.1. EFS BLADDER PRESERVATION UNIVARIATE AND MULTIVARIATE COX MODEL

Table 124: EFS bladder preservation univariate and multivariate Cox model

	Univariate Cox Regression					Multivariate Cox Regression					Multivariate Cox Regression (Excluding PD-L1)				
	N	Event N	HR[1]	95% CI[1]	p-value	N	Event N	HR[1]	95% CI[1]	p-value	N	Event N	HR[1]	95% CI[1]	p-value
Age at start of treatment															
Age < 71															
Age ≥ 71															
Sex															
Female															
Male															
T Stage															
T2															
T3/T4															
ECOG															
0															
1															
Non Invasive Cancer History															
Yes															
No															
PD-L1 High status															
Low/Negative															
High															
Creatinine clearance															
< 60															
≥ 60															

[1]HR = Hazard Ratio, CI = Confidence Interval; [2]Wald test

1.1.1.1. Figure: FOREST PLOT EFS bladder preservation univariate COX MODEL

Table 125: Creatinine clearance and ECOG contingency table, only patients with EFS bladder preservation

Creatinine clearance (mL/min)	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
ECOG				
0				
1				

1. Fisher’s Exact Test for Count Data

Table 126: Creatinine clearance and ECOG contingency table, only patients without EFS bladder preservation

Creatinine clearance (mL/min)	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
ECOG				
0				
1				

1. Fisher’s Exact Test for Count Data

Table 127: EFS bladder preservation multivariate model

	Multivariate Cox Regression					Multivariate Cox Regression (Excluding PD-L1)				
Characteristic	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**
Sex										
Female										
Male										
T Stage										
T2										
T3/T4										
ECOG										
0										
1										
Non Invasive Cancer History										
Yes										
No										
PD-L1 High status										
Low/Negative										
High										

[1]HR = Hazard Ratio, CI = Confidence Interval

1.2. EFS (SPECIFIC)

1.2.1. AGE

Table 128: EFS (specific) by age

Age at start of treatment	Age < 71 (N=)	Age ≥ 71 (N=)	Total (N=)	p value
Event Free Survival specific				
No				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival specific				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 129: Median/mean EFS (specific) by age (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Age < 71				
Age ≥ 71				

Table 130: EFS (specific) by age estimated survival ratio

EFS (specific)	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Age < 71				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
Age ≥ 71				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.2.1.1. Figure: EFS (specific) vs Age (abowe or below 71)

1.2.2. GENDER

Table 131: EFS (specific) by gender

Sex	Female (N=)	Male (N=)	Total (N=)	p value
Event Free Survival specific				
No				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival specific				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 132: Median/mean EFS (specific) by gender (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Female				
Male				

Table 133: EFS (specific) by gender estimated survival ratio

EFS (specific)	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Female				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
Male				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.2.2.1. FIGURE: EFS (SPECIFIC) VS GENDER

1.2.3. Stage: T2 vs. T3/T4

Table 134: EFS (specific) by Stage: T2 vs T3/T4

T Stage	T2 (N=)	T3/T4 (N=)	Total (N=)	p value
Event Free Survival specific				
No				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival specific				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 135: Median/mean EFS (specific) by Stage: T2 vs T3/T4 (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
T2				
T3/T4				

Table 136: EFS (specific) by Stage: T2 vs T3/T4 estimated survival ratio

EFS (specific)	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
T2				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
T3/T4				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.2.3.1. Figure: EFS (specific) vs Stage: T2 vs T3/T4

1.2.4. ECOG: 0 vs. 1

Table 137: EFS (specific) by ECOG: 0 vs. 1

ECOG	0 (N=)	1 (N=)	Total (N=)	p value
Event Free Survival specific				
No				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival specific				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 138: Median/mean EFS (specific) by ECOG: 0 vs. 1 (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
0				
1				

Table 139: EFS (specific) by ECOG: 0 vs. 1 estimated survival ratio

EFS (specific)	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
0				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
1				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.2.4.1. FIGURE: EFS (SPECIFIC) VS ECOG: 0 VS. 1

1.2.5. Non Invasive Cancer History: Yes vs. No

Table 140: EFS (specific) by Non invasive Cancer History: Yes vs. No

Non Invasive Cancer History	Yes (N=)	No (N=)	Total (N=)	p value
Event Free Survival specific				
No				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival specific				
Event/Death				
No				

1. Fisher's Exact Test for Count Data
2. Pearson's Chi-squared test

Table 141: Median/mean EFS (specific) by Non invasive Cancer History: Yes vs. No (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Yes				
No				

Table 142: EFS (specific) by Non invasive Cancer History: Yes vs. No estimated survival ratio

EFS (specific)	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
No				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.2.5.1. Figure: EFS (specific) vs Non invasive Cancer History: Yes vs. No

1.2.6. PD-L1: High vs. Low/Negative

Table 143: EFS (specific) by PD-L1: High vs. Low/Negative

PD-L1 High status	Low/Negative (N=)	High (N=)	Total (N=)	p value
Event Free Survival specific				
No				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival specific				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 144: Median/mean EFS (specific) by PD-L1: High vs. Low/Negative (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Low/Negative				
High				

Table 145: EFS (specific) by PD-L1: High vs. Low/Negative estimated survival ratio

EFS (specific)	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Low/Negative				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
High				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.2.6.1. Figure: EFS (specific) vs PD-L1: High vs. Low/Negative

1.2.7. Creatinine clearance: < 60 vs ≥ 60 (mL/min)

Table 146: EFS (specific) by Creatinine clearance: < 60 vs ≥ 60 (mL/min)

Creatinine clearance	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
Event Free Survival specific				
No				
Bladder relapse/Metastases				
Bladder relapse				
Metastases				
Death				
Event Free Survival specific				
Event/Death				
No				

1. Fisher's Exact Test for Count Data

Table 147: Median/mean EFS (specific) by Creatinine clearance: < 60 vs ≥ 60 (mL/min) (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
< 60				
≥ 60				

Table 148: EFS (specific) by Creatinine clearance: < 60 vs ≥ 60 (mL/min) estimated survival ratio

EFS (specific)	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
< 60				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
≥ 60				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.2.7.1. Figure: EFS (specific) vs Creatinine clearance: < 60 vs ≥ 60 (mL/min)

1.3. EFS (specific) univariate and multivariate Cox model

Table 149: EFS (specific) univariate and multivariate Cox model

	Univariate Cox Regression					Multivariate Cox Regression					Multivariate Cox Regression (Excluding PD-L1)				
Characteristic	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**
Age at start of treatment															
Age < 71															
Age ≥ 71															
Sex															
Female															
Male															
T Stage															
T2															
T3/T4															
ECOG															
0															
1															
Non Invasive Cancer History															
Yes															
No															
PD-L1 High status															
Low/Negative															
High															
Creatinine clearance															
< 60															
≥ 60															

[1]HR = Hazard Ratio, CI = Confidence Interval; [2]Wald test

1.3.1.1. Figure: FOREST PLOT EFS (SPECIFIC) univariate COX MODEL

Table 150: Creatinine clearance and ECOG contingency table, only patients with EFS (specific)

Creatinine clearance (mL/min)	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
ECOG				
0				
1				

1. Fisher’s Exact Test for Count Data

Table 151: Creatinine clearance and ECOG contingency table, only patients without EFS (specific)

Creatinine clearance (mL/min)	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
ECOG				
0				
1				

1. Fisher’s Exact Test for Count Data

1.4. PFS

1.4.1. AGE

Table 152: PFS by age

Age at start of treatment	Age < 71 (N=)	Age ≥ 71 (N=)	Total (N=)	p value
Progression Free Survival (tumour assessment)				
Alive without PD				
PD (tumour assessment)				
Death				
Progression Free Survival (tumour assessment)				
PD/Death				
Alive				

1. Fisher's Exact Test for Count Data
2. Pearson's Chi-squared test

Table 153: Median/mean PFS by age (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Age < 71				
Age ≥ 71				

Table 154: PFS by age estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Age < 71				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
Age ≥ 71				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.4.1.1. Figure: PFS vs Age (abowe or below 71)

1.4.2. GENDER

Table 155: PFS by gender

Sex	Female (N=)	Male (N=)	Total (N=)	p value
Progression Free Survival (tumour assessment)				
Alive without PD				
PD (tumour assessment)				
Death				
Progression Free Survival (tumour assessment)				
PD/Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 156: Median/mean PFS by gender (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Female				
Male				

Table 157: PFS by gender estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Female				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
Male				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.4.2.1. FIGURE: PFS VS GENDER

1.4.3. Stage: T2 vs. T3/T4

Table 158: PFS by Stage: T2 vs T3/T4

T Stage	T2 (N=)	T3/T4 (N=)	Total (N=)	p value
Progression Free Survival (tumour assessment)				
Alive without PD				
PD (tumour assessment)				
Death				
Progression Free Survival (tumour assessment)				
PD/Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 159: Median/mean PFS by Stage: T2 vs T3/T4 (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
T2				
T3/T4				

Table 160: PFS by Stage: T2 vs T3/T4 estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
T2				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
T3/T4				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.4.3.1. Figure: PFS vs Stage: T2 vs T3/T4

1.4.4. ECOG: 0 vs. 1

Table 161: PFS by ECOG: 0 vs. 1

ECOG	0 (N=)	1 (N=)	Total (N=)	p value
Progression Free Survival (tumour assessment)				
Alive without PD				
PD (tumour assessment)				
Death				
Progression Free Survival (tumour assessment)				
PD/Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 162: Median/mean PFS by ECOG: 0 vs. 1 (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
0				
1				

Table 163: PFS by ECOG: 0 vs. 1 estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
0				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
1				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.4.4.1. Figure: PFS vs ECOG: 0 vs. 1

1.4.5. Non Invasive Cancer History: Yes vs. No

Table 164: PFS by Non invasive Cancer History: Yes vs. No

Non Invasive Cancer History	Yes (N=)	No (N=)	Total (N=)	p value
Progression Free Survival (tumour assessment)				
Alive without PD				
PD (tumour assessment)				
Death				
Progression Free Survival (tumour assessment)				
PD/Death				
Alive				

1. Fisher's Exact Test for Count Data
2. Pearson's Chi-squared test

Table 165: Median/mean PFS by Non invasive Cancer History: Yes vs. No (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Yes				
No				

Table 166: PFS by Non invasive Cancer History: Yes vs. No estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
No				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.4.5.1. Figure: PFS vs Non invasive Cancer History: Yes vs. No

1.4.6. PD-L1: High vs. Low/Negative

Table 167: PFS by PD-L1: High vs. Low/Negative

PD-L1 High status	Low/Negative (N=)	High (N=)	Total (N=)	p value
Progression Free Survival (tumour assessment)				
Alive without PD				
PD (tumour assessment)				
Death				
Progression Free Survival (tumour assessment)				
PD/Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 168: Median/mean PFS by PD-L1: High vs. Low/Negative (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Low/Negative				
High				

Table 169: PFS by PD-L1: High vs. Low/Negative estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Low/Negative				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
High				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.4.6.1. Figure: PFS vs PD-L1: High vs. Low/Negative

1.4.7. Creatinine clearance: < 60 vs ≥ 60 (mL/min)

Table 170: PFS by Creatinine clearance: < 60 vs ≥ 60 (mL/min)

Creatinine clearance	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
Progression Free Survival (tumour assessment)				
Alive without PD				
PD (tumour assessment)				
Death				
Progression Free Survival (tumour assessment)				
PD/Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 171: Median/mean PFS by Creatinine clearance: < 60 vs ≥ 60 (mL/min) (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
< 60				
≥ 60				

Table 172: PFS by Creatinine clearance: < 60 vs ≥ 60 (mL/min) estimated survival ratio

PFS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
< 60				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
≥ 60				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.4.7.1. Figure: PFS vs Creatinine clearance: < 60 vs ≥ 60 (mL/min)

1.5. PFS UNIVARIATE AND MULTIVARIATE COX MODEL

Table 173: PFS univariate and multivariate Cox model

	Univariate Cox Regression					Multivariate Cox Regression					Multivariate Cox Regression (Excluding PD-L1)				
Characteristic	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**	**N**	**Event N**	**HR[1]**	**95% CI[1]**	**p-value**
Age at start of treatment															
Age < 71															
Age ≥ 71															
Sex															
Female															
Male															
T Stage															
T2															
T3/T4															
ECOG															
0															
1															
Non Invasive Cancer History															
Yes															
No															
PD-L1 High status															
Low/Negative															
High															
Creatinine clearance															
< 60															
≥ 60															

[1]HR = Hazard Ratio, CI = Confidence Interval; [2]Wald test

1.5.1.1. FIGURE: FOREST PLOT PFS UNIVARIATE COX MODEL

Table 174: Creatinine clearance and ECOG contingency table, only patients with PFS

Creatinine clearance (mL/min)	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
ECOG				
0				
1				

1. Fisher’s Exact Test for Count Data

Table 175: Creatinine clearance and ECOG contingency table, only patients without PFS

Creatinine clearance (mL/min)	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
ECOG				
0				
1				

1. Fisher’s Exact Test for Count Data

1.6. OS

1.6.1. AGE

Table 176: OS by age

Age at start of treatment	Age < 71 (N=)	Age ≥ 71 (N=)	Total (N=)	p value
Status				
Alive at end of trial: Patient's decision				
Alive at end of trial according to protocol				
Death				
Patient status				
Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 177: Median/mean OS by age (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Age < 71				
Age ≥ 71				

Table 178: OS by age estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Age < 71				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
Age ≥ 71				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.6.1.1. FIGURE: OS VS AGE (ABOWE OR BELOW 71)

1.6.2. GENDER

Table 179: OS by gender

Sex	Female (N=)	Male (N=)	Total (N=)	p value
Status				
Alive at end of trial: Patient's decision				
Alive at end of trial according to protocol				
Death				
Patient status				
Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 180: Median/mean OS by gender (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Female				
Male				

Table 181: OS by gender estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Female				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
Male				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.6.2.1. FIGURE: OS VS GENDER

1.6.3. Stage: T2 vs. T3/T4

Table 182: OS by Stage: T2 vs T3/T4

T Stage	T2 (N=)	T3/T4 (N=)	Total (N=)	p value
Status				
Alive at end of trial: Patient's decision				
Alive at end of trial according to protocol				
Death				
Patient status				
Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 183: Median/mean OS by Stage: T2 vs T3/T4 (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
T2				
T3/T4				

Table 184: OS by Stage: T2 vs T3/T4 estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
T2				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
T3/T4				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.6.3.1. Figure: OS vs Stage: T2 vs T3/T4

1.6.4. ECOG: 0 vs. 1

Table 185: OS by ECOG: 0 vs. 1

ECOG	0 (N=)	1 (N=)	Total (N=)	p value
Status				
Alive at end of trial: Patient's decision				
Alive at end of trial according to protocol				
Death				
Patient status				
Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 186: Median/mean OS by ECOG: 0 vs. 1 (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
0				
1				

Table 187: OS by ECOG: 0 vs. 1 estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
0				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
1				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.6.4.1. Figure: OS vs ECOG: 0 vs. 1

1.6.5. Non Invasive Cancer History: Yes vs. No

Table 188: OS by Non Invasive Cancer History: Yes vs. No

Non Invasive Cancer History	Yes (N=)	No (N=)	Total (N=)	p value
Status				
Alive at end of trial: Patient's decision				
Alive at end of trial according to protocol				
Death				
Patient status				
Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 189: Median/mean OS by Non invasive Cancer History: Yes vs. No (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Yes				
No				

Table 190: OS by Non invasive Cancer History: Yes vs. No estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Yes				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
No				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.6.5.1. Figure: OS vs Non invasive Cancer History: Yes vs. No

PD-L1: High vs. Low/Negative

Table 191: OS by PD-L1: High vs. Low/Negative

PD-L1 High status	Low/Negative (N=)	High (N=)	Total (N=)	p value
Status				
Alive at end of trial: Patient's decision				
Alive at end of trial according to protocol				
Death				
Patient status				
Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 192: Median/mean OS by PD-L1: High vs. Low/Negative (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
Low/Negative				
High				

Table 193: OS by PD-L1: High vs. Low/Negative estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
Low/Negative				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
High				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.6.5.2. Figure: OS vs PD-L1: High vs. Low/Negative

1.6.6. Creatinine clearance: < 60 vs ≥ 60 (mL/min)

Table 194: OS by Creatinine clearance: < 60 vs ≥ 60 (mL/min)

Creatinine clearance	< 60 (N=)	≥ 60 (N=)	Total (N=)	p value
Status				
Alive at end of trial: Patient's decision				
Alive at end of trial according to protocol				
Death				
Patient status				
Death				
Alive				

1. Fisher's Exact Test for Count Data

Table 195: Median/mean OS by Creatinine clearance: < 60 vs ≥ 60 (mL/min) (estimated by Kaplan-Meier)

	Median (months)	CI 95%	Mean	CI 95%
< 60				
≥ 60				

Table 196: OS by Creatinine clearance: < 60 vs ≥ 60 (mL/min) estimated survival ratio

OS	Events (%, total N)	Patients at risk	% estimated cumulative survival ratio	CI 95%
< 60				
At 6 months				
At 12 months				
At 24 months				
At 36 months				
≥ 60				
At 6 months				
At 12 months				
At 24 months				
At 36 months				

1.6.6.1. Figure: OS vs Creatinine clearance: < 60 vs ≥ 60 (mL/min)

1.7. OS UNIVARIATE AND MULTIVARIATE COX MODEL

Table 197: OS univariate and multivariate Cox model

	Univariate Cox Regression					Multivariate Cox Regression					Multivariate Cox Regression (Excluding PD-L1)				
	N	Event N	HR[1]	95% CI[1]	p-value	N	Event N	HR[1]	95% CI[1]	p-value	N	Event N	HR[1]	95% CI[1]	p-value
Age at start of treatment															
Age < 71															
Age ≥ 71															
Sex															
Female															
Male															
T Stage															
T2															
T3/T4															
ECOG															
0															
1															
Non Invasive Cancer History															
Yes															
No															
PD-L1 High status															
Low/Negative															
High															
Creatinine clearance															
< 60															
≥ 60															

[1]HR = Hazard Ratio, CI = Confidence Interval; [2]Wald test

1.7.1.1. FIGURE: FOREST PLOT OS UNIVARIATE COX MODEL

2. SAFETY ANALYSIS

2.1. SAFETY SUMMARY: ALL EVENTS IN OVERALL (SAFETY POPULATION)

Table 198: Safety

		N	%	LL IC 95%	UL IC 95%
SAE	No				
	Yes				
	Total				
SAE related	No				
	Yes				
	Total				
AE relationship to treatment (any treatment)	No				
	Yes				
	Total				
AE Grade≥3 related to any treatment	No				
	Yes				
	Total				
AE related to both treatments (Durva-Treme)	No				
	Yes				
	Total				
AE related to all treatments (Durva-Treme-Radiotherapy)	No				
	Yes				
	Total				
Adverse Events Related Durvalumab	No				
	Yes				
	Total				
Adverse Events Related RT	No				
	Yes				
	Total				
Adverse Events Related Tremelimumab	No				
	Yes				
	Total				
AE	Yes				
	Total				
AE Grade≥3	No				
	Yes				
	Total				

2.2. SAES

Table 199: SAEs

		N (%)
Adverse Event (CTC)		

Table 200: List of all SAEs with details

	Patient Number	AE/GRADE	Adverse Events CTCAE Other	Adverse Events Intensity	Adverse Events Related	Adverse Events Related Durvalumab	Adverse Events Related RT	Adverse Events Related Tremelimumab	Adverse Events Start Date	Adverse Events Stop Date
1										
2										

2.3. TOXICITIES

2.3.1. MOST FREQUENT TOXICITIES (RELATED TO ANY TREAT.)

Table 201: Most frequent toxicities (at least 3 pts aprox. ≥10%)

		N	%	LL IC 95%	UL IC 95%
	No				
	Sí				
	Total				
	No				
	Sí				
	Total				

Table 202: Most frequent toxicities (at least 3 pts aprox. ≥10%) according to grade

	NO		G1		G2		G3		G5		Total	
	N	%	N	%	N	%	N	%	N	%	N	%

2.3.2. Toxicities grade ≥ 3

Table 203: Toxicities with grade 3 or higher

		N (%)
Adverse Event (CTC)		

Table 204: List of all toxicities with grade 3 or higher

	Patient ID	Adverse Event (CTC)	Adverse Event (CTC specify)	AE intensity	Adverse Events Related Durva.	Adverse Events Related RT	Adverse Events Related Treme.	Date AE started	Date AE ended	Duration (days)	Continuous	SAE
1												
2												

1.1.1. AES

1.1.1.1. Most frequent AES

Table 205: Most frequent AEs (related or not to treatment) (at least 3 pts aprox. ≥ 10%)

		N	%	LL IC 95%	UL IC 95%
	No				
	Sí				
	Total				
	No				
	Sí				
	Total				

Table 206: Most frequent AEs (at least 3 pts aprox. ≥10%) according to grade

	No		G1		G2		G3		G5		Total	
	N	%	N	%	N	%	N	%	N	%	N	%

1.1.2. AES GRADE ≥ 3

Table 207: AEs with grade 3 or higher

	N (%)
Adverse Event (CTC)	

Table 208: List of all AEs with grade 3 or higher

	Patient ID	Adverse Event (CTC)	Adverse Event (CTC specify)	AE intensity	Adverse Events Related Durva.	Adverse Events Related RT	Adverse Events Related Treme.	Date AE started	Date AE ended	Duration (days)	Continuous
1											
2											