Investigational Drug	Durvalumab (MEDI4736)
Study Number	*ESR-18-13485*
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A PHASE II STUDY OF CAPECITABINE PLUS CONCOMITANT RADIATION THERAPY FOLLOWED BY DURVALUMAB (MEDI4736) AS PREOPERATIVE TREATMENT IN RECTAL CANCER

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PROTOCOL SIGNATURE PAGE

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EudraCT number: 2018-004758-39

The undersigned agree and confirm that:

The following protocol has been agreed and accepted and the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the ICH GCP guidelines, the European Directive, 2001/20/CE, Italian Decree 211/2003, Promoter SOP's and other regulatory requirements as amended.

The confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor/Promoter.

The findings of the study will be made publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and any discrepancies from the study as planned in this protocol will be explained.

Stefano Tamberi

Chief Investigator	Signature	Date

Elisabetta Petracci

Trial Statistician	Signature	Date

By signing this document I am confirming that I have read the protocol for the above study and I agree to conduct the study in compliance with the protocol andICH GCP

Principal Investigator	Signature	Date

PROTOCOL SYNOPSIS

Clinical Protocol *ESR-18-13485*

Study Title: A phase II study of capecitabine plus concomitant radiation therapy followed by durvalumab (MEDI4736) as preoperative treatment in rectal cancer.
Acronym: PANDORA
Protocol Number: ESR -18-13485
EudraCT: 2018-004758-39
Clinical Phase: II
Study Duration: Enrollment: 24 months Follow up: 5 years Total study duration: 7 years
Investigational Product and Reference Therapy: Durvalumab (MEDI4736) will be supplied in glass vials containing 500 mg of durvalumab as a liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration after dilution.

Research Hypothesis:

The standard treatment for locally advanced rectal cancer is preoperative chemo-radiation therapy. The combination of capecitabine plus long course radiotherapy (RT) is accepted as standard therapy. Surgery is usually performed after 8-10 weeks after the end of chemo-radiation therapy (CT/RT).
Pathologic Complete remission (pCR) can be considered as surrogate end point of efficacy of treatment in terms of disease free survival (DFS). Clinical complete remission (cCR) is an important endpoint for "wait and see" strategy.

In the PACIFIC trial in non-small cell lung cancer (NSCLC) the patients were treated with durvalumab maintenance after CT/RT for locally advanced tumour. Treatment was administered 1 to 42 days after the patients had received chemoradiotherapy without evidence of significant more toxicity than placebo arm. "Abscopal effect" is proposed as mediator of systemic effects after localized radiotherapy. Time to documented abscopal response ranged between less than one and 24 months, with a median reported time of 5 months. Preclinical data points heavily toward a strong synergy between radiotherapy and immune treatments. Recent reports already illustrate that such a systemic effect of radiotherapy is possible when enhanced by targeted immune treatments. However, several issues concerning dosage, timing, patient selection and toxicity need to be resolved before the abscopal effect can become clinically relevant.

In this study the investigators hypothesize that the addition of durvalumab after standard CT/RT for the treatment of locally advanced rectal cancer may improve the pathological response rate.

Objectives:

Primary Objective:

1. Determine the pathological complete response rate (pCR) in patients with rectal cancer treated with standard neo-adjuvant chemotherapy with capecitabine and radiation followed by durvalumab and surgery.

Secondary Objectives:

1. Determine safety of treatment with durvalumab;
2. Determine clinical complete remission rate (cCR) after durvalumab treatment, before surgery;
3. Determine disease-free survival (DFS).

Exploratory Objective:

1. Biological translational analysis of tumor biomarkers

Study Design:

This is a prospective phase II, open label, single arm, multi-centre study to evaluate activity of an innovative sequence on capecitabine plus concomitant radiation therapy followed by durvalumab in patients with rectal cancer without distant metastasis. The enrollment period will be of 24 months. Eligible patients will be initiated to a standard concomitant chemoradiation therapy for 5 weeks (radiotherapy at dose of 45-50 Gy in 25-28 fractions combined with capecitabine 825 mg/mq PO twice daily). One week after the end of CT/RT patients will be treated with durvalumab for 3 administrations. Patient will undergo surgery after 10-12 weeks from the end of CT/RT and the surgical piece will be analyzed. After surgery patients will be followed up for 5 years, according to clinical practice.

Number of Centers:

7

Number of Patients:

60

Study Population:

The study will be conducted in a hospital outpatients clinical setting. Patients will be recruited from a population of patients previously evaluated at the participating institution or referred by others.

Inclusion Criteria:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and Data Privacy Directive obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.
2. Age $\geq$ 18 years at time of study entry.
3. Eastern Cooperative Oncology Group (ECOG) 0 or 1.
4. Histological diagnosis of adenocarcinoma of rectum.
5. Clinical stage II and III rectal adenocarcinoma, assessed by thorax abdomen pelvis with contrast Computed tomography (CT) scan, pelvi Magnetic resonance imaging (MRI) scan, pancolonscopy.
6. Able to swallow oral medication.
7. Body weight >30kg.
8. Adequate normal organ and marrow function as defined below:

- Haemoglobin ≥9.0 g/dL
- Absolute neutrophil count (ANC) ≥ 1500 per mm^3
- Platelet count ≥100.000 per mm^3
- 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 haemolysis 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
- Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976).

9. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women of childbaring potential or male patients with a female partner of childbearing potential must agree to use at least 1 highly effective method of contraception from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy) as detailed in section 7.1. Women will be considered post-menopausal if they have been amenorrhoeic 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 amenorrhoeic 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 amenorrhoeic 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).

10. 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.
11. Must have a life expectancy of at least 12 weeks.

Exclusion Criteria:

1. Previous treatment for local advanced rectum cancer.
2. 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.
3. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab.
4. History of hypersensitivity to fluorouracil.
5. Known Dihydropyrimidine dehydrogenase (DPD) deficiency.
6. 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 study drug 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 e.g., cervical cancer in situ

7. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at

physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

8. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
9. Major surgical procedure within 28 days prior to the first dose of treatment.
10. History of allogenic organ transplantation.
11. 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

12. 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
13. History of leptomeningeal carcinomatosis.
14. History of active primary immunodeficiency.
15. 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.
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 highly effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.
18. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
19. 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.

20. Patients unable to follow the Protocol procedures and to sign the informed consent. In the case of patients' incapable of giving informed consent, it must be provided and signed by guardians or legal representative. Patients incapable must also sign the agreement to the extent that they are able to do so.

Investigational Product, Dose and Mode of Administration:

After careful staging, patients will be initiated to a standard concomitant chemoradiation therapy with radiotherapy at dose of 45-50 Gy in 25-28 fractions combined with capecitabine 825 mg/mq PO twice daily 7 days/week, for 5 weeks. At the end of treatment patients will undergo a lesion biopsy. One week after the end of CT/RT patients will be treated with 1500 mg IV Q4W durvalumab for 3 administrations. From week 9 to 10 after neoadjuvant therapy will be performed re-staging with CT and MRI scan. Surgery will be performed at week 10-12 from the end of CT/RT and the surgical piece will be analyzed.

Study Assessments and Criteria for Evaluation:

Activity Assessments:

After 10-12 weeks from the end of CT/RT patients will undergo surgery. The surgical piece will be analyzed both by local pathologist and by central laboratory; paraffin embedded tissue section will be shipped to central laboratory for centralized assessment of response.
The primary endpoint is the pathological complete response (pCR) rate after durvalumab treatment
The secondary endpoints are the clinical complete remission rate (cCR) after durvalumab treatment, before surgery, and disease-free survival (DSF). Complete clinical responses to treatment will be evaluated with clinical, endoscopic and radiological assessment to look for evidence of residual disease.
The disease-free survival will be evaluated during a follow up of 5 years.

Safety Assessments:

The safety assessment will be mainly based on the frequency of adverse events, including all serious adverse events. Each serious and non serious event occurring by the time of informed consent signature up to 90 days after end of Durvalumab treatment will be recorded in the medical chart and in the eCRF. The severity of the event according to NCTCAE 5.0) and the relationship to study drugwill be encoded as appropriate. Adverse events will be summarized by presenting the number and percentage of patients who experienced any adverse event, an adverse event in a specific organism apparatus and a specific adverse event.

Statistical Methods and Data Analysis:

The data collected from all the centers will be summarized in relation to demographic variables, baseline characteristics and activity and safety assessments. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. The primary analysis will be based on the calculation of the proportion of patients with complete pathological response and corresponding confidence intervals after durvalumab treatment.
As for the secondary endpoints, cCR and treatment safety will be computed similarly as for the primary endpoint. DFS will be estimated by using Kaplan-Meier approach.

Sample Size Determination:

To reach the primary aim, the sample size has been estimated by using the optimal Simon's two-stage design. Assuming a pCR rate of 15% with standard regimen, the study treatment proposed will be considered worthwhile in case of a pCR rate of 30% or greater. Assuming an $\alpha = 0.05$ and $\beta = 0.20$ (power = 0.80), in the first stage of the study, 19 patients will be accrued. If there are 3 or fewer pCR in these 19 patients, the study will be stopped for futility. Otherwise, if there are ≥4 responses, 36 additional patients will be accrued for a total of 55 evaluable patients. Assuming a 10% of dropout a total of 60 patients will be enrolled in this study. The null hypothesis of pCR=15% will be rejected if ≥13 or more pCR are observed in 55 patients.

SCHEDULE OF STUDY ASSESSMENTS

	Screening			**CT/RT**				**Endoscopy Re-staging**	**Durvalumab treatment**						**Re-staging**	**Surgery**	**Durvalumab Safety follow-up**			**Follow-up**	
Timing	-8 weeks to -1 days	-6 weeks to -1 days	-4 weeks to -1 days	Day 1[a]	1 wk ±3 d	3 wks ±3 d	5 wks ±3 d	6 wks ±3 d	6 wks ±3 d		10 wks ±3 d		14 wks ±3 d		14 wks to 15 wks ±3 d	15-17 wks ±5 d	18 wks±3 d	22±1 wks	26±1 wks	every 4 months after surgery first 2 years	then every 6 months after surgery for 3 years
									before infusion	C1	before infusion	C2	before infusion	C3							
Informed Consent																					
Informed consent: study procedures[b]			X																		
Study procedures																					
Medical history and demography			X																		
Concomitant medications			X																		
Recording of any change in concomitant medication				X	X	X	X		X		X		X								
Eligibility criteria			X																		
Physical exam			X	X	X	X	X		X		X		X							X	X
Vital signs[c]			X	X	X	X	X		X	X[l]	X	X[m]	X	X[m]						X	X
ECOG performance status			X	X	X	X	X		X		X		X							X	X
AE/SAE assessment [l]				X	X	X	X		X		X		X								

ECG[d]			X	As clinically indicated					X		As clinically indicated				X						
Laboratory Assessments																					
Clinical chemistry			X	X[f]	X	X	X		X		X		X				X	X	X		
Hematologye			X	X[f]	X	X	X		X		X		X								
Coagulation			X																		
Creatinine Clearance			X	X[f]	X	X	X		X		X		X								
TSH (reflex free T3 or free T4[g])			X						X		X		X								
Hepatitis B and C and HIV			X																		
Urinalysis			X						X		X		X								
CEA			X																	X	X
Pregnancy test			X[i]																		
Treatment administration																					
CT/RT (825 mg/mq bid capecitabina + 45-50 Gy RT				Cape every d, RT 5 d per wk for 5 wks																	
Durvalumab 1500 mg Q4W										X		X		X							
Surgery																X					
Activity evaluations																					
Endoscopy with tumour biopsy	X							X												X[n]	X[n]
Tumor evaluation (CT and MRI) [h]		X													X					X	X
Sample shipment for centralized pathologic response evaluation																X					
PRO EQ-5D-3L			X						X						X						
Sample collection for translational analysis	X							X													

[a] Every effort should be made to minimize the time between patient registration and starting treatment.
[b] If imaging procedures were performed for alternate reasons prior to signing consent, these can be used for screening purposes with consent of the patient, if performed within a window of 6 weeks from study entry.
[c] Body weight is recorded at each visit along with vital signs.
[d] Any clinically significant abnormalities detected require triplicate ECG results.
[e] Serum or plasma clinical chemistry (including LFT monitoring) and hematology may be performed more frequently if clinically indicated.
[f] If screening clinical chemistry and haematology assessments are performed within 7 days prior to Day 1 of CT/RT therapy, they do not need to be repeated at Day1.
[g] Free T3 or free T4 will only be measured if TSH is abnormal or if there is clinical suspicion of an AE related to the endocrine system.
[h] If intravenous CT contrast material is contraindicated because of hypersensitivity reaction Abdomen MRI plus Chest HRTC is required.
[i] For women of childbearing potential only. A urine or serum pregnancy test is acceptable. Women of childbearing potential are required to have a pregnancy test within 7 days prior to the first dose of study drug and then every 4 weeks. Pregnancy test may occur on Day 1, but results must be available and reviewed by the treating physician or Investigator prior to commencing an infusion
[l] 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 ofdurvalumab.
[m] BP, pulse and other vital signs should be measured, collected/recorded 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.
[n] Sigmoidoscopy should be performed every 6 months after surgery for the first two years, the extension to a pancolonscopy should be performed 1 year after surgery, then 3 years and finally every 5 years in the presence of colon free of lesions.
[l] For AEs/SAEs reported during screening, additional information such as medical history and concomitant medications may be needed

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

C Cycle; ECG Electrocardiogram; ; qXw Every X weeks; qXw Every X weeks; T_3 Triiodothyronine; T_4 Thyroxine; TSH Thyroid-stimulating hormone.

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ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APC	Antigen-presenting cells
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
CL	Clearance
C_{max}	Peak concentration
$C_{max,ss}$	Peak concentration at steady state
C_{min}	Trough concentration

Abbreviation or special term	Explanation
$C_{min,ss}$	Trough concentration at steady state
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CT/RT	Chemioradiotherapy
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
DC	Disease control
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Disodium edetate dihydrate
Fc	Fragment crystallizable
FFPE	Formalin fixed paraffin embedded
FSH	Follicle-stimulating hormone
FTIH	First-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCl	Hydrochloride
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IGF	Insulin-like growth factor
IgG1	Immunoglobulin G1
IgG2	Immunoglobulin G2
IGSF	Immunoglobulin superfamily
IHC	Immunohistochemistry
IL	Interleukin
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous(ly)
MAb	Monoclonal antibody
MDSC	Myeloid-derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	Micro ribonucleic acid
MOA	Mechanism of action
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Abbreviation or special term	Explanation
NK	Natural killer
NOAEL	No-observed-adverse-effect level
NSCLC	Non-small cell lung cancer
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
pCR	Pathological Complete Response
cCR	Clinical Complete Response
PD	Progressive disease
PD-1	Programmed cell death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PR	Partial response
PRO	Patient-reported outcome
PVC	Polyvinyl chloride
Q2W	Every 2 weeks
Q3M	Every 3 months
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q12W	Every 12 weeks
QoL	Quality of life
QTc	Time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT	Radioterapy
SAE	Serious adverse event
SD	Stable disease
SID	Subject identification
sPD-L1	Soluble programmed cell death ligand 1
SOCS3	Suppressor of cytokine signaling 3
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half life
TEAE	Treatment-emergent adverse event
TIL	Tumor infiltrating lymphocyte
T_{max}	Time to peak concentration
$T_{max,ss}$	Time to peak concentration at steady state
TNF-α	Tumor necrosis factor alpha
TRG	Tumor Regression Grade

TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
USA	United States of America
WFI	Water for injection

Abbreviation or special term	Explanation
WHO	World Health Organization

1. INTRODUCTION

The standard treatment of locally advanced rectal cancer involves neoadjuvant chemoradiation therapy (CT/RT) followed by surgery and further adjuvant chemotherapy (AIOM 2017). The pathologic complete responses associated with neoadjuvant CT/RT are 10-20%. The prognosis of patients undergoing neoadjuvant CT/RT is associated to the extent of post-treatment tumor regression (Habr- Gama 2010).

In the PACIFIC trial in non-small lung cancer (NSCLC) the patients were treated with durvalumab (MEDI 4736) maintaining after CT/RT for locally advanced NSCLC. Treatment was administered 1 to 42 days after the patients had received chemo-radiotherapy without evidence of significant more toxicity than placebo arm (Antonia et al 2017).

Hence, the investigators hypothesize that the addition of durvalumab after to standard CT/RT for the treatment of locally advanced rectal cancer may improve the pathological response rate. This protocol describes an open-label single-arm phase 2 study designed to test this hypothesis. Moreover, this study will also identify genetic, serological, and pathological biomarkers that may be both prognostic and predictive of response and toxicity to treatment.

1.1 Disease background

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 et al. 2004).

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

PD-L1 is constitutively expressed by B-cells, dendritic cells, and macrophages (Qin et al

2016). Importantly, PD-L1 is commonly over-expressed on tumor cells or on non-transformed cells in the tumor microenvironment (Pardoll 2012). PD-L1 expressed on the tumor cells binds to PD-1 receptors on the activated T-cells leading to the inhibition of cytotoxic T cells. These deactivated

T cells remain inhibited in the tumor microenvironment. The PD-1/PD-L1 pathway represents an adaptive immune resistance mechanism that is exerted by tumor cells in response to endogenous anti-tumor activity.

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti–PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on 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.

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. 2015). In addition, high mutational burden (e.g., in bladder carcinoma [AIOM 2017 Linee guida AIOM 2017 Alexandrov et al. 2013]) may contribute to the responses seen with immune therapy.

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.

Pre-clinical data have 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. 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 US FDA 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, there are data from agents in the anti–PD-1/PD-L1class showing clinical activity in a wide range of tumor types.

1.1.2 Durvalumab background/non-clinical and clinical experience

The non-clinical and clinical experience is fully described in the most current version of the durvalumab Investigator's Brochure.

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). The proposed mechanism of action (MOA) for durvalumab is interference in the interaction of PD-L1 with PD-1 and CD80 (B7.1). Blockade of PD-L1/PD-1 and PD-L1/CD80 interactions releases the inhibition of immune responses, including those that may result in tumor elimination. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells resulting in the restored proliferation of IFN-γ (Stewart et al 2015). *In vivo* studies have shown that durvalumab inhibits tumor growth in xenograft models via a T-cell-dependent mechanism (Stewart et al

2015). Based on these data, durvalumab is expected to stimulate the patient's antitumor immune response by binding to PD-L1 and shifting the balance toward an antitumor response. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity.

To date durvalumab has been given to more than 6000 patients as part of ongoing studies either as monotherapy or in combination with other anti-cancer agents.

Details on the safety profile of durvalumab monotherapy are summarized in Section Durvalumab1.4.2.1. 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 Rectal cancer

The standard treatment for clinical stage 2-3 rectal adenocarcinoma is preoperative chemo-radiation therapy (CT/RT). The combination of capecitabine plus long course radiotherapy (RT) is accepted as standard therapy in locally advanced rectal cancer (AIOM 2017).

Surgery is usually performed after 6-8 weeks after the end of chemo-radiation therapy. The GRECCAR-6 study didn't demonstrate an increase of pathological complete response rate (pCR) after surgical resection waiting 11 weeks after CT/RT (Lefevre et al 2016). A time of 8-12 weeks is an adequate period from the end of CT/RT and surgery (Petrelli et 2016, Evans J et al 2016).

The pathologic complete responses associated with neoadjuvant CT/RT are 10-20%. The prognosis of patients undergoing neoadjuvant CT/RT is associated to the extent of post-treatment tumour regression, the final primary tumour stage and presence of involved lymph nodes in the surgical specimen. This data suggests that treatments that enhance the pathological response may result in improvements in survival. Pathologic Complete remission (pCR) can be considered as surrogate end point of efficacy of treatment in terms of disease free survival (DFS). Clinical complete remission (cCR) is an important endpoint for "wait and see" strategy (Habr-Gama 2010).

"Abscopal effect" is proposed as mediator of systemic effects after localized radiotherapy. Time to documented abscopal response ranged between less than one and 24months, with a median reported

time of 5months. Preclinical data points heavily toward a strong synergy between radiotherapy and immune treatments. Recent report already illustrate that such a systemic effect of radiotherapy is possible when enhanced by targeted immune treatments. However, several issues concerning dosage, timing, patient selection and toxicity need to be resolved before the abscopal effect can become clinically relevant (Ko 2018).

Deficient mismatch repair (dMMR) is a key biological factor for activity of immunotherapy. dMMR rectal cancer had excellent prognosis and pathologic response with current multimodality therapy including an individualized surgical treatment plan. However, a very few data are available about clinical implications of dMMR in rectal cancer.

1.2 Research hypothesis

This is a prospective phase II, open label, single arm, multi-centres study to evaluate activity of an innovative sequence of capecitabine plus concomitant radiation therapy followed by durvalumab in patients with operable rectal cancer.

The hypothesis is: durvalumab after CT/RT could improve pathological complete response (pCR) rate, which is a surrogate endpoint for DFS in patients with rectal cancer treated with standard neo-adjuvant chemotherapy with capecitabine and radiation followed by durvalumab and surgery.

1.3 Rationale for conducting this study

Preoperative 5FU based chemoradiotherapy is still the standard of treatment for locally advanced rectal cancer. About 15-20% of patients would achieve pathologic complete response after neoadjuvant CT/RT, and the survival outcome would be much better than non-pCR. However, distant metastasis would occur in about 30% of patients even after CT/RT (AIOM2017). To improve the survival of rectal cancer patients, we hope to improve the pCR rate through the use of durvalumab as a maintenance therapy after standard chemoradiation therapy before surgery. With more intensive neoadjuvant treatment, higher pCR rate might be observed.

Therefore, the objective of the study is to verify a greater effectiveness of these preoperative treatment through an increase of pCR, cCR and DSF. Moreover, safety of the treatment with durvalumab will be verified in this setting of patients.

1.3.1 Durvalumab monotherapy dose rationale

A durvalumab dose of 20 mg/kg Q4W is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002).

1.3.2 PK/Pharmacodynamic data

Based on available PK/pharmacodynamic data from ongoing Study 1108 with doses ranging from 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W, durvalumab exhibited non-linear (dose-dependent) PK consistent with target-mediated drug disposition. The PK approached linearity at ≥3 mg/kg Q2W, suggesting near complete target saturation (membrane-bound and sPD-L1), and further shows that the durvalumab dosing frequency can be adapted to a particular regimen given the linearity seen at doses higher than 3 mg/kg. The expected half-life with doses ≥3 mg/kg Q2W is approximately 21 days. A dose-dependent suppression in peripheral sPD-L1 was observed over the dose range studied, consistent with engagement of durvalumab with PD-L1. A low level of immunogenicity has been observed. No patients have experienced immune-complex disease following exposure to durvalumab (For further information on immunogenicity, please see the current IB).

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W) (Fairman et al. 2014). Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by AUC_{ss}

(4 weeks). Median $C_{max,ss}$ is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median $C_{trough,ss}$ is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of

20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

Given the similar area under the plasma drug concentration-time curve (AUC) and modest differences in median peak and trough levels at steady state, the observation that both regimens maintain complete sPD-L1 suppression at trough, and the available clinical data, the 20 mg/kg Q4W and 10 mg/kg Q2W regimens are expected to have similar efficacy and safety profiles, supporting further development with a dose of 20 mg/kg Q4W.

1.3.3 Clinical data

Refer to the current durvalumab Investigator's Brochure for a complete summary of clinical information including safety, efficacy and pharmacokinetics at the 20mg/kg Q4W regimen.

1.3.4 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.

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) is included in the current study.

1.4 Benefit/risk and ethical assessment

1.4.1 Potential benefits

The potential benefits of durvalumab treatment in patients with rectum cancer are not known at present and this study will assess the possible effectiveness of this treatment after standard neoadjuvant chemoradiotherapy prior to surgery.

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

1.4.3 Durvalumab

Risks with durvalumab include, but are not limited to, diarrhea/colitis and intestinal perforation, pneumonitis/ILD, endocrinopathies (hypo- and hyper-thyroidism, type I diabetes mellitus, hypophysitis and adrenal insufficiency) hepatitis/increases in transaminases, nephritis/increases in creatinine, pancreatitis/increases in amylase and lipase, rash/pruritus/dermatitis, myocarditis, myositis/polymyositis, other rare or less frequent inflammatory events including neurotoxicities, infusion-related reactions, hypersensitivity reactions and infections/serious infections.

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

Further information on these risks 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, asthenia, anemia, arthralgia, peripheral edema, headache, rash, and pruritus. Approximately 9% of patients experienced an AE that resulted in permanent discontinuation of durvalumab and approximately 6% of patients experienced an SAE that was considered to be 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 (Appendix 1).

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

1.4.4 Overall benefit-risk

In view of the potential benefit of treatment with durvalumab, after standard neoadjuvant chemoradiation therapy, in increasing pathological complete responses, as surrogate end point of efficacy of treatment in terms of disease free survival, and its few side effects and easy to manage with supportive therapies, the treatment proposed in this study is considered to have a favorable risk-benefit balance.

2. STUDY OBJECTIVES

2.1 Primary objective

Determine the pCR rate in patients with rectal cancer treated with standard neo-adjuvant chemotherapy with capecitabine and radiation followed by durvalumab and surgery. pCR can be considered as surrogate end point of efficacy of treatment in terms of disease free survival (DFS).

The primary endopoint is the percentage of patients achieving pCR.

2.2 Secondary objectives

Determine safety of treatment with durvalumab in patients with rectal cancer after treatment with standard neo-adjuvant chemotherapy with capecitabine and radiation, before surgery.

Determine clinical complete remission rate (cCR) after durvalumab treatment before surgery. Clinical complete remission (cCR) is an important endpoint for “wait and see” strategy.

Determine disease-free survival (DFS) as an indicator of the effectiveness of the proposed strategy.

2.3 Exploratory objective

Biological translational analysis. Tumor samples will be screened for actionable somatic mutational events in KRAS, NRAS, PI3KCA and BRAF genes. Mismatch repair proteins (MLH-1, MLH-2, MSH-6 and PMS2) will be analysed by immunoistochimistry. PD-L1, PD-1, CD3, CD4, CD8, CD68 and CD133 expression will be tested together with a panel of markers of inflammatory cells. Amplification of HER2 gene and its expression will be also investigated. Moreover, tumor mutational burden (TMB) will be evaluated.

3. STUDY DESIGN

3.1 Overview of study design

This is a prospective phase II, open label, single arm, multi-centre study.

The study will evaluate the efficacy and safety of an innovative sequence on capecitabine plus concomitant radiation therapy followed by durvalumab in patients with operable rectal cancer.

At baseline, patients should have histological diagnosis of adenocarcinoma of rectum, clinical stage II or III assessed by thorax abdomen pelvis with contrast Computed tomography (CT) scan, pelvi Magnetic resonance imaging (MRI) scan, pancolonscopy. The patient is at least 18 years of age and has adeguate hepatic and renal function. Patients should not have comorbidities that contraindicate use of immunotherapy.

Written informed consent will be obtained from each patient.

After careful staging, patients will be initiated to a standard concomitant chemoradiation therapy for 5 weeks (radiotherapy at dose of 45-50 Gy in 25-28 fractions combined with capecitabine 825 mg/mq PO twice daily 7 days/week). At the end of treatment patients will undergo a lesion biopsy. One week after the end of CT/RT patients will be treated with 1500 mg Q4W durvalumab for 3 administration. A fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

From week 9 to 10 after neoadjuvant therapy re-staging with CT and MRI scan will be performed. Surgery will be performed at week 10-12 from the end of CT/RT and the surgical piece will be analyzed both locally and centrally.

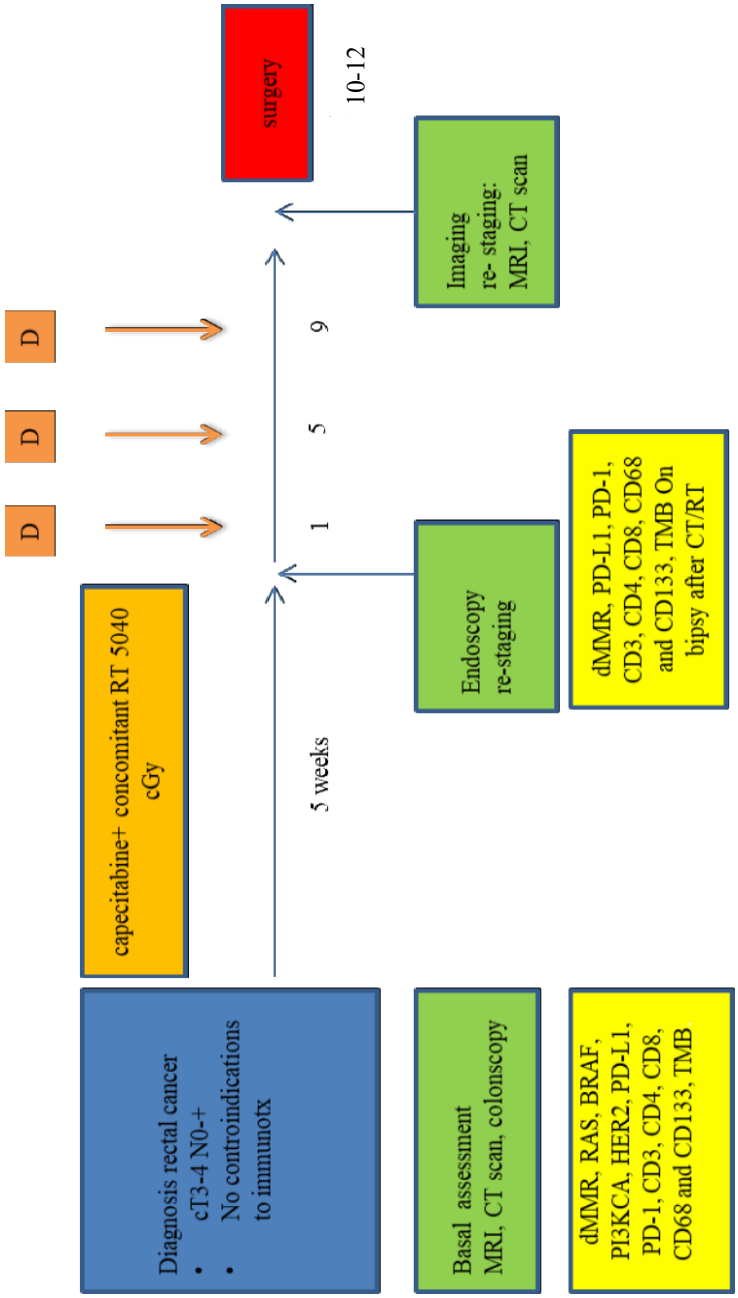
The study will be registered in www.clinicaltrials.gov.

60 patients are expected to be enrolled in 7 centres (8-9 patients per centre), for a total of 55 evaluable patients; the recruitment period will be of 24 months.

In the first stage of the study, 19 patients will be accrued, if there are 3 or fewer pCR in these 19 patients, the study will be stopped. The central assessment of response will be used for the analysis of primary objective.

3.2 Study schema

Figure 1. *Study Flow Chart*



3.3 Study oversight for safety evaluation

To evaluate the feasibility and the safety profile of the new treatment regimen, all patients will be strictly monitored. The trial will be terminated if the investigators consider it unsafe to continue with the trial. .

4. PATIENT SELECTION

The study will be conducted in a hospital outpatients clinical setting. Pts will be recruited from a population of pts previously evaluated at the participating institution or referred by others.

4.1 Inclusion criteria

For inclusion in the study patients must fulfill all of the following criteria:

1. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Written informed consent and Data Privacy Directive obtained from the patient/legal representative prior to performing any protocol-related procedures, including screening evaluations.
2. Age ≥ 18 years at time of study entry.
3. Eastern Cooperative Oncology Group (ECOG) 0 or 1.
4. Histological diagnosis of adenocarcinoma of rectum.
5. Clinical stage II-III rectal adenocarcinoma, assessed by thorax abdomen pelvis with contrast Computed tomography (CT) scan, pelvi Magnetic resonance imaging (MRI) scan, pancolonscopy.
6. Able to swallow oral medication.
7. Body weight >30kg.
8. Adequate normal organ and marrow function as defined below:
   - Haemoglobin ≥9.0 g/dL
   - Absolute neutrophil count (ANC) ≥ 1500 per mm^3
   - Platelet count ≥100,000 per mm^3
   - 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
   - Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976):

Males:

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

Females:

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

9. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre- menopausal patients. Women of childbearing potential or male patients with a female partner of childbearing potential must agree to use at least 1 highly effective method of contraception from the time of screening throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy) as detailed in section 7.1. Women will be considered post-menopausal if they have been amenorrhoeic 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 amenorrhoeic 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).
10. 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.
11. Must have a life expectancy of at least 12 weeks.

4.2 Exclusion criteria

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

1. Previous treatment for local advanced rectum cancer.
2. 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.
3. Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab
4. History of hypersensitivity to fluorouracil.
5. Know Dihydropyrimidine dehydrogenase (DPD) deficiency.
6. 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 study drug 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 e.g., cervical cancer in situ

7. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. The following are exceptions to this criterion:
   - Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)
   - Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
   - Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)
8. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
9. Major surgical procedure within 28 days prior to the first dose of therapy.
10. History of allogenic organ transplantation.
11. 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
12. 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
13. History of leptomeningeal carcinomatosis.

14. History of active primary immunodeficiency
15. 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.
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.
18. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients.
19. 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.
20. Patients unable to follow the Protocol procedures and to sign the informed consent. In the case of patients' incapable of giving informed consent, it must be provided and signed by guardians or legal representative. Patients incapable must also sign the agreement to the extent that they are able to do so.

4.3 Withdrawal of patients from study

4.3.1 Permanent discontinuation of study

An individual patient will not receive any further investigational product if any of the following occur in the patient in question:

1. An individual patient will not receive any further durvalumab monotherapy if their weight falls to 30kg or less.
2. Withdrawal of consent or lost to follow-up.
3. 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 the Dosing Modification and Toxicity Management Guidelines (Appendix 1).
4. 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.
5. Pregnancy or intent to become pregnant.

6. Any AE that meets criteria for discontinuation as defined in Section 6.3.
7. Grade ≥3 infusion reaction.
8. Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits.
9. Initiation of alternative anticancer therapy including another investigational agent.
10. Investigator determination that the patient is no longer benefiting from treatment with durvalumab.

Patients who are permanently discontinued from receiving investigational product will be followed for safety per Section 10.3.1, 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.

4.3.2 Withdrawal of consent

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

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

A patient who withdraws consent will always be checked for 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 PRODUCT

5.1 Durvalumab

5.1.1 Formulation/packaging/storage

Durvalumab (MEDI4736) will be supplied by AstraZeneca as a 500-mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab (MEDI4736), 26 mM

histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. 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.
Study drug will be labelled in accordance with regulatory requirements.

5.1.2 Durvalumab doses and treatment regimens

Patients will receive 1500 mg durvalumab (MEDI4736) via IV infusion q4w for 3 administrations before surgery or other treatment discontinuation criteria are met.

5.1.3 Study drug preparation

Patients will receive 1500mg durvalumab (MEDI4736) via IV infusion Q4W 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 removed from the study. Patients will receive 1500 mg durvalumab via IV infusion q4w.

5.1.4 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

Infusion solution must be allowed to equilibrate to room temperature prior to commencement of administration.

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 15 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) (ie, 1500mg of durvalumab [MEDI4736]) to the IV bag. The IV

bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Standard infusion time 1 hour. In the event that there are interruptions during infusion, the total allowed infusion time should not exceed 4 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.

5.1.5 Monitoring of dose administration

Patients will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment and in section 8.2.1. Patients will be monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

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

5.1.6 Accountability and dispensation

The local Investigator is responsible for ensuring that all study drug received at the site is inventoried and accounted for throughout the study. Study drug must be handled strictly in accordance with the protocol and the container label and will be stored in a limited access area or in a locked cabinet under appropriate environmental conditions.

Study drug should be dispensed under the supervision of the Investigator or a qualified member of the investigational staff, or by a hospital/clinic pharmacist. Study drug will be administered only to subjects participating in the study. All used vials of the product shall be destroyed. All unused or expired vials of the product shall be destroyed.

5.1.7 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

6. TREATMENT PLAN

6.1 Patient enrollment

This is a prospective phase II, open label, single arm, multi-centres study. The study will be conducted in a hospital outpatients clinical setting. Patients will be recruited from a population of patients previously evaluated at the participating institution or referred by others.

All patients that satisfy the inclusion and exclusion criteria and who have signed informed consent will be enrolled.

6.2 Dosage and administration

After enrollment, patients will be offered standard neoadjuvant chemoradiation therapy with 825 mg/m^2 twice daily capecitabine every day for 5 weeks and 5040 cGy radiotherapy for 5 days per week for 5 weeks. Capecitabine will be administered orally, the tablets should be swallowed with water within 30 minutes after a meal.

After one week from the end of the neoadjuvant standard treatment, patients will receive 1500 mg durvalumab (MEDI4736) via IV infusion q4w for 3 administrations before surgery or other treatment discontinuation criteria are met.

6.3 Toxicity management guidelines

6.3.1 Durvalumab

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non- immune-mediated reactions for durvalumab are provided in the durvalumab/tremelimumab Toxicity Management Guidelines (TMGs).

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

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Dosing Modification and Toxicity Management Guidelines in Appendix 1).

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

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

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

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:

- Female patients of childbearing potential who are not abstinent and intend to be 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 throughout the total duration of the drug treatment and the drug washout period (90 days after the last dose of durvalumab monotherapy). Non-sterilised male partners of a female patient of childbearing potential must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential:

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

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

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

Women will be considered post-menopausal if they have been amenorrhoeic 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 amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.

- Women ≥50 years of age would be considered post-menopausal if they have been amenorrhoeic 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.

Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 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/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone-based

[a] This is also considered a hormonal method

Blood donation

Patients should not donate blood while participating in this study or 90 days after receipt of the final dose of durvalumab.

7.2 Concomitant treatment(s)

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 or antiviral drugs for viral hepatitis B	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, radiotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment other than those under investigation in this study	Should not be given concomitantly whilst the patient is on study treatment. (Concurrent use of hormones for non-cancer-related conditions [e.g., insulin for diabetes and hormone replacement therapy] is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable [e.g., by local surgery or radiotherapy])

Prohibited medication/class of drug:	**Usage:**
Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and 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).
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
During Capecitabine therapy phenytoin, allopurinol, coumarin-derivative anticoagulants, sorivudine and chemically related analogues like brivudine	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 (pages 8-9).

- Tumor assessment dates are not affected by dose delays and remain as originally scheduled, as they are based on the date of randomization (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

- For durvalumab treatment: Dosing intervals of subsequent cycles may be shortened as clinically feasible in order to gradually align treatment cycles with the schedule of tumour efficacy (RECIST1.1). Subsequent time between 2 consecutive doses cannot be less than 22 days, based on the half-lives of durvalumab (see current Investigator Brochures for durvalumab).

8.1.1 Informed consent

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

Written and verbal versions of the participant information and Informed consent will be presented to the participants detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participants. The original signed form will be retained at the study site.

8.1.2 Screening phase

Screening procedures will be performed up to 4 weeks before Day 1 of standard neoadjuvant chemoradiotherapy with capecitabine, unless otherwise specified. All patients must first read, understand, and sign the IRB/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, such as chest abdomen pelvis with contrast Computed tomography (CT) scan, pelvi Magnetic resonance imaging (MRI) scan and pancolonscopy with biopsy, 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 respectively within 6 or 8 weeks from study entry .

The following procedures will be performed during the Screening Visit:

- Informed Consent
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam, with digital rectal examination
- ECOG Performance Status
- ECG
- Vitals signs (temperature, blood pressure, heart rate, respiratory rate, O_2 saturation on room air), weight and height
- Pancolonscopy with tumor biopsy, if not performed within 8 weeks from study entry
- Review of concomitant medications
- Imaging by chest abdomen pelvis CT scan with contrast, and pelvi MRI scan with contrast, if not performed within 6 weeks from study entry
- PRO measure EQ 5D 3L
- FFPE tissue sections shipment to central laboratory for translational analysis (see section 8.3).
- Clinical laboratory tests:
    - Hematology (see Table 4)
    - Clinical chemistry (see Table 5)
    - TSH
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Hepatitis serologies, if not performed within 28 days screening window end
    - HIV test, if not performed within 28 days screening window end
    - Urinalysis (see Table 6)
    - CEA

8.1.3 Patient Registration and Eligibility check

Patients will be registered into Electronic eCRF and all screening data will be recorded. Patient ID will be automatically assigned to each patient. The Eligibility criteria will be verified by the Biostatistics and Clinical Trial Unit of IRST (Coordinating Centre, CC).

Patients eligibility must be confirmed by the Coordinating Center prior to initiation of study therapy.

For any issue please contact:
Centro di Coordinamento Studi IRST
Unità di Biostatistica e Sperimentazioni Cliniche
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST)
c/o Ospedale S.Maria delle Croci
Viale Randi, 5 – 48121 RAVENNA (RA)
FAX 0544 285330
TEL 0544 28 5813 / 6223
cc.ubsc@irst.emr.it
all working days from Monday to Friday, from 9 AM to 16 PM

Further detailed information will be sent to participating centers and will also be included in the Investigator Site File.

8.1.4 Treatment phase

Standard concomitant chemoradiation therapy

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments.

Standard concomitant chemoradiation therapy with 825 mg/m2 twice daily capecitabine every day for 5 weeks and from 4500 to 5040 cGy radiotherapy for 5 days per week for 5 weeks will be performed (treatment over 6 weeks is allowed for organizational reasons, according to local practice). During neoadjuvant treatment visit will be carried out at the start of the treatment then after 1 week ±3 days, then every 2 weeks ±3 days (1st visit the first day of chemotherapy treatment, 2nd visit after 1 week ±3 days the beginning of CT/RT, 3rd visit after 3 weeks ±3 days the beginning of CT/RT, 4th visit after 5 weeks ±3 days the beginning of CT/RT) during visits will be carried out:

- Complete physical exam, with digital rectal examination
- ECOG Performance Status
- Recording of any changes in concomitant medications;
- Toxicity/AE assessment;
- Vitals signs (temperature, blood pressure, heart rate, respiratory rate, O2 saturation on room air, weight)
- Clinical laboratory tests for:
    - Hematology (see Table 4)
    - Clinical chemistry (see Table 5)
    - Creatinine Clearance
    - Laboratory testing performed as part of pre-treatment assessment within 7 days of start of therapy will be acceptable as 1st visit lab-work and not need to be repeated.

8.1.5 Endoscopy restaging

From the day after the end of CT/RT treatment within 1 week±3 days patients will undergo a rectoendoscopy with lesion biopsy. FFPE tissue sections will be shipped to central laboratory for translational analysis (see section 8.3).

8.1.6 Durvalumab treatment

One week±3 days after the end of CT/RT, patients will be treated with 1500 mg Q4W durvalumab for 3 administrations. The day before the drug administration a visit will be carried out:

- Complete physical exam, with digital rectal examination
- ECOG Performance Status
- Recording of any changes in concomitant medications;
- Toxicity/AE assessment;
- Vitals signs (temperature, blood pressure, heart rate, respiratory rate, O2 saturation on room air, weight)
- PRO measure EQ-5D-3L only before first administration of Durvalumab
- Clinical laboratory tests for:
    - Hematology (see Table 4)
    - Clinical chemistry (see Table 5)
    - TSH, If TSH is measured within 14 days prior to Day 1 (first infusion day of durvalumab), it does not need to be repeated at day 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
    - Creatinine Clearance
    - Urinalysis (see Table 6)

8.1.7 End of treatment

End of treatment is defined as the last planned durvalumab dosing visit.

Assessments for patients who have completed durvalumab treatment or have discontinued durvalumab due to toxicity are provided in Appendix1.

8.1.8 Re-staging

After the 3 dose of durvalumab, from week 9 to 10 ±3 days after neoadjuvant therapy will be performed re-staging with chest abdomen pelvis CT scan with contrast, pelvi MRI scan with contrast and PRO measure with EQ 5d 3L.

8.1.9 Surgery

Surgery will be performed at week 10-12±5 days from the end of CT/RT and the surgical piece will be analyzed both locally and centrally. A delay of 2 weeks in the surgical intervention is allowed in case of logistical/organizational problems due to COVID-19 emergency. For central assessment of response, FFPE tissue sections or blocks will be shipped as described in section 8.3.3.

8.1.10 Safety Follow-up of treatment with Durvalumab

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 durvalumab.

8.1.11 Follow-up after surgery

The follow-up period start from the surgery.

The follow-up visit will be carried out every 4 months after surgery for the first 2 years and then every 6 months for the next 3 years, during the visit will be carried out:

- Complete physical exam, with digital rectal examination
- ECOG Performance Status
- Vitals signs, weight
- Clinical laboratory tests for:
    - CEA

Imaging by thorax abdomen pelvis CT scan will be performed every 4 months after surgery for the first 2 years and then every 6 months for the next 3 years.

Sigmoidoscopy should be performed every 6 months after surgery for the first two years, the extension to a pancolonscopy should be performed 1 year after surgery, then 3 years and finally every 5 years in the presence of colon free of lesions.

8.2 Description of study procedures

8.2.1 Medical history and physical examination, 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.

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, digital rectal examination, and at screening only, height.

Resting 12-lead ECGs will be recorded at screening 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.

At Screening, a single ECG will be obtained on which QTcF must be <470 ms.

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

Situations in which ECG results should be reported as AEs are described in Section 10.1.1

Vital signs (temperature, blood pressure [BP], heart rate, respiratory rate, O_2 saturation on room air), will be evaluated according to the assessment schedules, body weight is also recorded at each visit along with vital signs.

8.2.2 First infusion of durvalumab

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

BP and pulse will be collected from patients in the I-O arms 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.

8.2.3 Subsequent infusions

BP, pulse and other vital signs should be measured, collected/recorded 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.

8.2.4 Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments):

Table 4. Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count

Mean corpuscular hemoglobin
Mean corpuscular hemoglobin concentration
Total white cell count

Table 5. Clinical Chemistry (Serum or Plasma) Laboratory Tests

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

[a] If total bilirubin is ≥2 × upper limit of normal (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

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

[c] Chloride, creatinine clearance, gamma glutamyltransferase, and magnesium testing are to be performed at baseline, on Day 0 (unless all screening laboratory clinical chemistry assessments are performed within 7 days prior to Day 1), and if clinically indicated.

[d] Creatinine Clearance will be calculated by data management using Cockcroft-Gault (using actual body weight).

[e] If TSH is measured within 7 days prior to Day 1 (first infusion day), it does not need to be repeated at day 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 6. Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

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

If a patient shows an AST or ALT ≥3xULN together with total bilirubin ≥2xULN, 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 durvalumab.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded. 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 Specimen collection for central assessment of response

Formalin-fixed paraffin embedded (FFPE) tumor tissue sections (about 10-15 sections x 5 micron) will be prepared for each patient, after surgical intervention. Samples will be shipped to central laboratory for assessment of pathological response (see section 8.3.4).

When it is not possible to ship FFPE tissue sections, the blocks should be shipped in order for sectioning to occur at the central laboratory. FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. Blocks should be shipped containing enough material to be provided to allow 10-15 sections to be cut.

8.3.2 Biomarker sampling and evaluation methods

Formalin-fixed paraffin embedded (FFPE) tumor tissue (about 15 unstained sections of 5 micron and 1 section stained with ematossilin-eosin) will be collected from each patient, at baseline (before the start of chemo-radiotharapy) and before the start of treatment with durvalumab (re-staging).

At baseline tumor samples will be screened for actionable somatic mutational events in KRAS, NRAS, PI3KCA, BRAF and other genes using Next Generation Sequencing (NGS) methodology.

In addition, at baseline amplification of HER2 gene and its expression will be also investigated using a fluorescence in situ hybridization (FISH) approach and immunohistochemistry (clone 4B5, Ventana/Roche), respectively.

At baseline (before the start of chemo-radiotharapy) and before the start of treatment with durvalumab, since microsatellite instability is considered a predictive marker of response to immunotherapy agents blocking the PD-1/PD-L1 checkpoint in colo-rectal cancer, mismatch repair proteins (MLH-1, MLH-2, MSH-6 and PMS2) will be analysed by immunoistochimistry using an automated immunostainer (ULTRA, Ventana Medical System, Tucson, AZ).

At baseline (before the start of chemo-radiotharapy) and before the start of treatment with durvalumab PD-L1 expression (clones 22C3 by Agilent and SP263 by Ventana/Roche, see section 8.3.2) will be tested together with a panel of markers of inflammatory cells in order to evaluate the immune microenvironment of tumor cells, including PD-1 (the PD-L1 ligand), CD3 (pan-T cell marker), CD4 (T-helper marker), CD8 (T- cytotoxic marker), CD68 (histiocytic marker) and CD133 (cancer stem cell population marker).

Genomic DNA will be extracted using specific kit. The tumor mutational burden (TMB) will be assessed on FFPE tumor samples collected at baseline and after chemo-radiotherapy treatment, by NGS. The mean number of nonsynonymous and synonymous exonic single nucleotide substitutions and the amount of transversion will be evaluated. The mutational load will be defined by the number of nonsynonymous and synonymous exonic single nucleotide substitutions within trinucleotide sequence context. A detailed report will be provided that includes the normalized mutation load (mutations/MB) and mutation signatures of the somatic variants, including percentage of mutations consistent with UV damage, tobacco smoke damage, de-amination, and specific substitutions.

8.3.3 PD-L1 testing

To ensure comparability of data across all studies of durvalumab 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

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 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

- Fixative

The following data will 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 for PD-L1 testing

Preparing Stored samples for testing

- Where samples already exist (provided they have been collected within the allowed window of 28 days before treatment start), they should be retrieved from the Pathology Archive . These blocks should undergo quality review, prior to evaluation, sectioning or shipment. Preferably, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) and shipped to IRST Bioscience Lab. If this is not possible, FFPE block may be shipped.

Preparing newly acquired samples for PD-L1 testing

- When patients undergo biopsy procedure, 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.
- When it is not possible to ship FFPE tissue sections, the blocks should be shipped in order for sectioning to occur at the central laboratory. Blocks should be shipped containing enough material to be provided to allow 12-15 sections to be cut (each 4-micron thick).

Sectioning instructions

- 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 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 Sample labelling and shipment

The biological samples will be labeled as described below and shipped to IRST Bioscience Laboratory by courier. The Shipment bill and the Shipper's account number for the Courier will be provided by IRST IRCCS.

The shipment of samples must be announced via fax (0543 739221) or via e-mail (paola.ulivi@irst.emr.it chiara.molinari@irst.emr.it) including date of shipment and shipping bill number.

Every slide with paraffin embedded tissue sections (please use special boxes) and/or blocks will be labelled with the following information: Study code PANDORA, site number, subject number, timing and date of collection, in order to maintain rigorous confidentiality standards.

The Promoter will provide labels to each participating site.

Sample labels:

PANDORA

Center ID	Subject No.	Timing	Date of collection (dd/mm/aaaa)
|__|__|	|__|__|__|__|	_____	|__|__|/|__|__|/|__|__|__|__|

The samples will be sent to Bioscience Laboratory of IRST IRCCS through internal procedures for IRST IRCCS Center and through courier for others Participating Centers (shipping paid by recipient), accompanied by the "Shipment Form" (see separated document), from Monday to Thursday to the following address:

Dr. Paola Ulivi/Dr. Chiara Molinari
c/o Laboratorio di Bioscienze,
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS,
Via Maroncelli 40,
47014 Meldola (FC).
E-mail: paola.ulivi@irst.emr.it
chiara.molinari@irst.emr.it
Phone: +39 0543 9228, Fax: +39 0543 9221

After receiving the samples, the IRST IRCCS laboratory staff will complete the "Sample Arrival Form" (see separated document), and will ship part of the samples to the Pathology Unit of S. Maria delle Croci Hospital of Ravenna. The biomolecular characterization of biological samples will be performed at the Bioscience Laboratory of IRST IRCCS. The PD-L1 immunohistochemistry analysis and the central analysis of pathological response will be performed at the Pathology Unit of of S. Maria delle Croci Hospital of Ravenna, AUSL Romagna.

Genetic information obtained from patient samples will remain confidential. All patients enrolled in the study will be assigned an identification code in order to maintain rigorous confidentiality standards. Samples will be destroyed after 15 years from the end of the study and all associated genetic data will be deleted from the study repository.

8.4 Study Procedures in case of COVID-19 emergency

In compliance with the provisions of the AIFA statement of 12/03/2020 concerning "Clinical trials' management in Italy during the COVID-19 (coronavirus disease 19) emergency" the Promoter authorizes the execution of laboratory tests and clinical assessments foreseen by the protocol (MRI, CT scan, endoscopy, physical examination) in health structures near the patient's home. All the assessments must be performed in public health structures; the use of private sites not recognized eligible pursuant to the Ministerial Decree of 19th March 1998 yet, will have to be carefully taken into consideration and chosen only in the case it represents the unique possibility for the patient's protection, as recommended by the AIFA press release mentioned above. In any case the use of private structures must be discussed with- and approved by the Promoter. The assessments reports must be appropriately sent to the experimental center.

9. DISEASE EVALUATION AND METHODS

9.1 Activity variable

Within 28 days before the screening of study, baseline tumour measurements will be performed on each patient. Computer tomography scan of Chest-abdomen-pelvi with contrast –enhanced (CT) and pelvi MRI with contrast should be performed at baseline.

Then after the 3 doses of durvalumab, from week 9 to 10 ±3 days after neoadjuvant therapy will be performed re-staging with chest abdomen pelvis CT scan with contrast, and pelvi MRI scan with contrast.

If intravenous CT contrast material is contraindicated because of hypersensitivity reaction Abdomen MRI plus Chest HRTC is required.

Radiological response will be evaluated with RECIST1.1 criteria.

Radiological assessments will be carried out at the radiology of each study center.

Complete clinical responses to treatment will be evaluated with clinical, endoscopic and radiological assessment to look

for evidence of residual disease.

Complete pathologic response is defined as as the lack of all signs of cancer cells in tissue samples. The pathological response will be assessed both locally (from the pathologist of each site) and centrally.

Central evaluation of response will be used for primary objective evaluation.

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.

Information related to all adverse events, both those reported spontaneously by the subject and those encountered by the Investigator as a result of specific questions or by physical examination of the patient, from laboratory investigations or otherwise, will be collected, recorded on the medical record and followed as appropriate.

10.1 Definitions

10.1.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a patient's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the patient has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the patient being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

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.

- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

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

10.1.3 Definition of adverse events of special interest (AESI)

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. An AESI may be serious or non-serious.

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 include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, adrenal insufficiency, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis / serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eye, skin, haematological and rheumatological events.

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

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochures. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (please 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 Appendix1) 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 medical record. 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.

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 v5.0.

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 10.1.2. 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.

10.3 Recording of adverse events and serious adverse events

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

During the course of the study, all AEs and SAEs should be proactively followed up for each patient for as long as the event is ongoing. Every effort should be made to obtain a resolution for all events, even if the events continue after the patient has discontinued study drug or the study has completed.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, but without further recording. Request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the drugs (yes or no)
- Action taken with regard to drugs
- 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 10.3.2
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

- 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).

During the course of 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.

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 treatment study 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.”

A guide to the interpretation of the causality question is found in Appendix1.

10.3.3 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 drug) 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 aetiology present in the patient’s medical record.

- Not protocol related: The event is related to an aetiology other than the procedure or intervention that was described in the protocol. The alternative aetiology 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. 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.

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 non-mandated 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 Appendix1. for further i nstruction 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 treatment study and have been identified after the patient's inclusion in this study.

10.3.9 Deaths

All deaths that occur during the study treatment period, or within the protocol-defined follow-up period after the administration of the last dose of study drug, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented. It 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 Study Monitor/Physician as an SAE within 24 hours. It should also be documented. The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented. A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to the Promoter who will report to Astra Zeneca Patient Safety within the usual timeframes.

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 Follow-up of unresolved adverse events

Any AEs that are unresolved at the patient's last visit in the study are followed up by the investigator for as long as medically indicated. After 90 days, only patients with ongoing investigational product- related SAEs will continue to be followed for safety.

The Promoter retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

10.3.11 Post-study events

After the patient has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study patients after the 90-day safety follow-up period for patients treated with durvalumab. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is

related to study treatment, the investigator should notify the Promoter who will report to AstraZeneca/MedImmune Drug Safety.

10.3.12 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 Experimental Promoter are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The Experimental Promoter of the trial shall ensure that all relevant information relating to Suspected Unexpected Series Adverse Reactions (SUSAR), which have killed or endangered the subject of the trial living are registered and notified to the Ministry of Health as soon as possible, and to the Ethics Committee(s) concerned, and in any case Within seven days of calendar (eg. emergency procedure) since when the sponsor of the trial has become aware of the case, and that subsequent information relevant are reported Within eight days from the first report.

All other SUSARs shall be notified to the Ministry of Health and the Committee(s) interested party as soon as possible and in any event Within 15 days since day on which the Promoter of the experimentation became aware of it for the first time.

The Experimental Promoter shall record all SUSARs of a medicinal product in the experimental phase brought to its attention. The Experimental Promoter of the trial shall also inform the other investigators.

Once a year throughout the clinical trial, the sponsor of the trial shall provide the Ministry of Health and Ethics Committees involved a list of all Series Adverse Reactions (SAR) suspects observed over the entire period and a report on the safety of the persons undergoing the clinical trial.

Send SAE report and accompanying cover page by way of email or fax to:

Dr. Francesco Pappalardo

e-mail: dirtecassfarmaceutica@auslromagna.it
cc: francesco.pappalardo@auslromagna.it

If a non-serious AE becomes serious, this and another relevant follow-up information must also be provided to the Promoter who will report to AstraZeneca/MedImmune Drug Safety.

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10.3.13 Reporting of deaths to the Promoter

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab safety follow-up period must be reported to the Promoter who will report to AstraZeneca 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 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 that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented, but will not be reported as an SAE. However, if an investigator learns of any SAEs, including death, at any time after the patient has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the Promoter who will report to AstraZeneca/MedImmune Drug Safety.

10.3.14 Other events requiring reporting

10.3.14.1 Overdose

An overdose is defined as a patient receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study patient with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the Promoter who will report to ***AstraZeneca.***

Send AE report and accompanying cover page to:

Dr. Francesco Pappalardo

e-mail: dirtecassfarmaceutica@auslromagna.it
cc: francesco.pappalardo@auslromagna.it

If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.3). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 10.1.2 and Section 10.3.2). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

10.3.14.2 Hepatic function abnormality

Hepatic function abnormality that fulfills the biochemical criteria of a potential Hy's Law case in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the Promoter who will report to ***AstraZeneca.***

Send AE report and accompanying cover page to:

Dr. Francesco Pappalardo

e-mail: dirtecassfarmaceutica@auslromagna.it
cc: francesco.pappalardo@auslromagna.it

unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed. The criteria for a potential Hy's Law case is Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

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

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the Promoter in agreement with AstraZeneca/MedImmune.

10.3.14.3 AESI grade ≥ 3

AESI enlisted in section 10.1.3 of grade ≥ 3 are required to be reported within 24 hours of knowledge of the event to the Promoter who will report to ***Astra Zeneca.***

Send AE report and accompanying cover page to:

Dr. Francesco Pappalardo

e-mail: dirtecassfarmaceutica@auslromagna.it
cc: francesco.pappalardo@auslromagna.it

10.3.14.4 Pregnancy

Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the drug 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 Promoter representatives within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

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

Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab, 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 90 days after the last dose of durvalumab, 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.

10.3.14.5 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
- Wrong drug administered to patient

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

- Patient accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Patient failed to return unused medication or empty packaging
- 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 Promoter within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it. The Promoter will report to AstraZeneca representatives

The designated Promoter 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

The objective of this study is to evaluate, in patients with rectal cancer treated with standard neo- adjuvant chemotherapy with capecitabine and radiation followed by durvalumab and then by surgery, activity with clinical and pathological complete response rate and tolerability.

11.1.1 Safety analysis set

The Safety Set includes all screening subjects who received at least one dose of study treatments.

11.1.2 Activity analysis set

The Activity Analysis Set includes all patients treated with at least 1 doses of Durvalumab.

11.2 Methods of statistical analyses

Before database lock, a SAP will be finalized, providing detailed methods for the analyses.

11.2.1 Safety analyses

All safety summaries and analyses will be based on the safety population defined as all screening patients who received at least one dose of study treatments, and include:

- Adverse events will be summarized with the number and the percentage of patients with every type of event classified from body system and Preferred Term (PT).
- The incidence and percentage of patients with at least 1 occurrence of a PT will be included, according to the most severe CTCAE grade.
- Causality (relationship to study drug), action taken, and outcome will be summarized separately. - Duration of AEs will be determined and included in the listings.

The safety assessment will be mainly based on the frequency of adverse events, including all serious adverse events. Adverse events will be summarized by presenting the number and percentage of patients who experienced any adverse event, an adverse event in a specific organism apparatus and a specific adverse event. Any other information collected (i.e. the severity or relationship to study drug) will be encoded as appropriate.

In addition, the following analytical lists will be produced, reporting detailed information concerning:

1. Patients who discontinued the study and the reasons therefore;
2. Patients who discontinued the study due to adverse events;
3. Patients who experienced serious adverse events;

The data of all participating centers in this study will be grouped together so that an adequate number of patients will be available for analysis.

- Study drug exposure will be summarized with following variables: number of infusion, number of cycles, duration of therapy, cumulative dose, dose intensity, and relative dose intensity.
- Laboratory results will be classified according to the NCI-CTCAE, Version 5.0. Incidence of laboratory abnormalities will be summarized.
- Hospitalizations due to AEs, transfusions, and vital signs will be summarized.

11.2.2 Activity analyses

The primary end point will be assessed by means of the proportion of patients having complete pathological response pCR after durvalumab treatment. Corresponding two-sided 95% confidence intervals (CIs) will be computed.

The same will be performed for cCR.

DFS, defined as the time since surgery until disease occurrence or death, whichever occur first, or last follow-up, will be estimated by using the Kaplan-Meier approach. Corresponding two-sided 95% CIs will be computed.

11.2.3 Exploratory analyses

For continuous measurement biomarker results, summary statistics (eg, the mean, standard deviation, median, and minimum/maximum levels) will be determined, as appropriate.
Data from biomarker assays may be analyzed using graphical methods and statistical tests. For regard to this last point, all results has to be considered purely exploratory and need to be further validate in an external independent set od data.

The detailed analyses of exploring associations between biomarkers and primary and secondary clinical endpoints such as, pCR, cCR and DFS will be provided in the SAP.

11.2.4 Interim analyses

No formal interim analysis will be performed.

11.3 Determination of sample size

Assuming a pCR rate of 15% with standard regimen, the study treatment proposed will be considered worthwhile in case of a pCR rate of 30% or greater. Assuming an $\alpha = 0.05$ and $\beta = 0.20$ (power = 0.80), in the first stage of the study, 19 patients will be accrued. If there are 3 or fewer pCR in these 19 patients, the study will be stopped for futility. Otherwise, if there are ≥ 4 responses, 36 additional patients will be accrued for a total of 55 evaluable patients. Assuming a 10% of dropout a total of 60 patients will be enrolled. The null hypothesis of pCR=15% will be rejected if ≥ 13 or more pCR are observed in 55 patients. Sample size has been computed using the optimal Simon's two-stage design (Simon R 1989).

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Patient data protection.

12.2 Ethics and regulatory review

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent forms, and other relevant documents, from the independent ethics committee (IEC). All correspondence with the IEC should be retained in the Investigator File. All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law.

12.3 Informed consent

The informed consent form must be in compliance with international committee harmonization good clinical practice (ICH GCP), local regulatory requirements, and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by the IEC. The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed on the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent form.

12.4 Changes to the protocol and informed consent form

No changes or amendments to this protocol may be made by the Investigators after the protocol has been agreed to and signed by both parties. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Chief Investigator and by the Principal Investigator and the signed amendment will be appended to this protocol.

Approval / advice of amendments by Ethical Committees or similar body is required prior to their implementation, unless there are overriding safety reasons.

If the change or deviation increases risk to the study population, or adversely affects the validity of the clinical investigation or the subject's rights, full approval / advice must be obtained prior to implementation. For changes that do not involve increased risk or affect the validity of the investigation or the subject's rights, approval / advice may be obtained by expedited review, where applicable.

In some instances, an amendment may require a change to a consent form. The Investigator must receive approval / advice of the revised consent form prior to implementation of the change.

12.5 Audits and inspections

Experimental Promoter or his delegate can control every center to verify that the study is conducted according to protocol and GCP. Regulatory Authority can require a control, in this case every investigator must immediately inform Experimental Promoter and the Ethics Committee.

By signing the protocol, each investigator agrees to audits by the Experimental Promoter (or his delegate) or by the Regulatory Authority.

13. STUDY MANAGEMENT

13.1 Training of study site personnel

Before the beginning of the study, the Experimental Promoter (or his delegate) will illustrate to the Investigator and his staff the operational details of the Protocol.

13.2 Monitoring of the study

13.2.1 Source data

During the study, the Experimental Promoter will be check the completeness of the patient's medical records, the accuracy of the compilation of the medical record, the adherence to the protocol and GCP and also to ensure that the study drug is properly stored, dispensed to patients and accounted for.

The investigator is responsible for filing and storage of essential documents of the study, before, during and after the completation or interruption of the study, according to the time provided by law and by GCP.

The investigator must keep the original data of the patient (eg. medical and demographic information, laboratory data, etc.). For some data can be established, before beginning the study, to be written directly on the medical record, which thus in this case will act as the original data.

13.2.2 Study monitoring

The Investigator(s) agree to(s) to perform the study in accordance with ICH Good Clinical Practice.

The Investigator is required to ensure his compliance to the procedures required by the protocol with respect to the investigational drug schedule and visit schedule. The Investigator agrees to provide all information requested in the Case Report Form in an accurate and legible manner according to the instructions provided.

The Investigator has responsibilities to the Health Authorities to take all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol adherence, integrity and validity of the data recorded on the case report forms.

13.2.2.1 Site Set-up and Initiation

All participating Investigators will be asked to sign the necessary agreements and supply a current CV to the coordinating centre or Sponsor/Promoter.

All members of the site research team will also be required to sign the “Site Signature and Delegation Log”.

Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, Adverse Event reporting, collection and reporting of data and record keeping.

Sites will be provided with an Investigator Site File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The coordinating centre or Sponsor/Promotermust be informed immediately of any change in the site research team.

13.2.2.2 On-site Monitoring

If a monitoring visit is required the coordinatingcentre, or Sponsor/Promoter will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the trial staff access to source documents as requested.

The main duty of the Trial Monitor is to help the Investigator and the StudyCoordinators to maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the study.

During each monitoring visit, the following points will be checked: subject informed consent, subject recruitment and follow-up, study drug allocation and labeling, subject compliance to the study treatment, study treatment accountability, Adverse Event documentation and reporting.

According to the guidelines on ICH Good Clinical Practice, the trial monitor will check the case report form entries against the source documents. This personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

13.2.2.3 Central Monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check data received for compliance with the protocol, data consistency, missing data and timing. Sites will be sent requests missing data or clarification of inconsistencies or discrepancies. For eCRFtrials these requests may be generated by automated data validation checks.

13.3 Study timetable and end of study

Experimental Promoter has the right to terminate the study in the event of medical, safety, regulatory, ethical, or other reasons consistent with applicable laws, regulations and GCP.

14. DATA MANAGEMENT

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor/Promoter (or designee), but will be identified by a site number, subject number.

14.1 Electronic Case Report Forms

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor/Promoter and should be handled in accordance with instructions from the Sponsor/Promoter. All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required

All data reported on medical recorder will derive from source documents and will be consistent with such documents. Any correction to recorder and source documents will be dated, signed and explained by the PI (or his delegate) and will not obscure the original entry. The PI will have ultimate responsibility for the accuracy, authenticity and timely collection and reporting of all clinical, safety, laboratory and molecular data. The PI (or his delegate) will also be responsible for retaining records (including the identity of all participating subjects), all original signed informed consent forms and source documents.

14.2 Study governance and oversight

Since the study is supported by Astra Zeneca, the safety of this clinical study will be closely monitored on an ongoing basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be addressed; for instance, this could involve amendments to the study protocol and letters to Investigators.

15. OWNERSHIP OF DATA AND USE OF THE STUDY RESULTS

The full ownership of the data generated in this study is retained by the Promoter.
Data deriving from this clinical trial are not intended for drug registration or for patent applications, but only for scientific and educational purposes, which include presentation at scientific meetings, congresses and symposia and/or publication in scientific journals.

16. PUBLICATION POLICY

Publications regarding the main study end-points will be prepared by the Chief Investigator. All the members of the steering committee and components of the CdC will be included in the authors list. Other area-specific publications will be prepared

by the coordinators of the single treatment modalities to increase the visibility of the study and investigators. However, the publication of secondary endpoints is discouraged before publication of the main endpoint and should be anyway discussed with the study and writing committee coordinators.

17. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

17.1 Identity of investigational product(s)

Table 7. List of Investigational Products for This Study

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

18. LIST OF REFERENCES

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Linee guida AIOM 2017

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Toxicity Management Guidelines (TMGs)

Drug Substance	Durvalumab and tremelimumab
TMG Version	17 Oct 2019, CTCAE v5.0

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 5.0

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 5.0.

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 v5.0)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications

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 v5.0.

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 toGrade ≤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.

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.

Toxicity Management

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).
- 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.

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 v5.0)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Note: For asymptomatic amylase or lipase levels of >2X 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).	– 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 5.0)	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 **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For Any Grade:** – 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; intervention not indicated)	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; limiting instrumental ADL) (Colitis: abdominal pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)	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 resumed after completion of steroid taper.	**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. – 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** Permanently discontinue study drug/study	**For Grade 3 or 4:**

(Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; limiting self care ADL; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, fever; ileus; peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: invasive intervention indicated; Grade 4 Perforation: life-threatening consequences; urgent intervention indicated)	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.	– 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 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 Grade**	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 **(**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 Grade 2.	– Continue LFT monitoring per protocol.
	Grade 2 (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 if baseline abnormal)	• Hold study drug/study regimen dose until resolution to Grade≤1. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade≤1, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – 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 ≤Grade 1 in 1 to 2 days, consider, as necessary, discussing with study physician. – 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]

Grade 3 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20× baseline if baseline abnormal; and/or TB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0× baseline if baseline abnormal) **Grade 4** (AST or ALT >20×ULN if baseline normal, >20×baseline if baseline abnormal; and/or TB >10×ULN if baseline normal, >10.0×baseline if baseline abnormal)	For elevations in transaminases ≤8×ULN, or elevations in TB ≤5×ULN: • Hold study drug/study regimen dose until resolution to Grade≤1 • Resume study drug/study regimen if elevations downgrade to Grade≤1 within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade≤1 within 14 days. For elevations in transaminases >8×ULN or elevations in bilirubin >5×ULN, 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]	**For Grade 3 or 4:** – 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 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 of 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 >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. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
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)	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.

	(Grade 4: serum creatinine >6.0×ULN)		– 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 5.0 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. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – 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 (or life-threatening):** – Consult Dermatology.

		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 (or life-threatening):** Permanently discontinue study drug/study regimen.	– 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 v5.0 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 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.	**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 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. 3. Doses of prednisone are ≤10 mg/day or equivalent.	**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. – 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 v5.0 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. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
	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. 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.	**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). – 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. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	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 (GB: moderate symptoms; limiting instrumental ADL)	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	**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

(MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)	respiratory insufficiency or autonomic instability.	– 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.
Grade 3 or 4 (Grade 3 GB: severe symptoms; limiting self care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant	**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 or autonomic instability.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician. – Recommend hospitalization. – Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They 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. o If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition

	but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	**For Grade 4:** Permanently discontinue study drug/study regimen.	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 or mild symptoms*; clinical or diagnostic observations only; intervention not indicated) *Treat myocarditis with mild symptoms as Grade 2.	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 moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support)) * Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.	- 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	Hold study drug/study regimen dose until resolution to Grade ≤1.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization.

weakness; pain limiting instrumental activities of daily living [ADLs])	- 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.	– 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 (Grade 3: pain associated with severe weakness; limiting self-care ADLs Grade 4: life-threatening consequences; urgent intervention indicated)	**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 5.0)	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 5.0)	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.