LUDWIG CANCER RESEARCH	**Study Protocol**	**LUD2015-005**	**US-IND #:** Not applicable **EudraCT #:** 2015-005298-19 **AstraZeneca Ref #:** ESR 15-10891
	Amendment 8	**Final**	**11-JAN-2022**

Protocol Title
Phase 1/2 Study of anti-PD-L1 in Combination with Chemo(radio)therapy for Oesophageal Cancer

Objectives and Synopsis

This is an open-label, Phase 1/2 study to evaluate the safety of durvalumab (MEDI4736) (and tremelimumab for certain cohorts as described in Section 3.1.7) in combination with chemo (radio) therapy according to the following cohorts:

- Cohorts A1, A2, and B: Oxaliplatin/capecitabine chemotherapy in metastatic/locally advanced oesophageal cancer (OC).
- Cohort C: Neoadjuvant oxaliplatin/capecitabine chemotherapy before surgery in operable OC.
- Cohort C-FLOT: Neoadjuvant 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel (FLOT) chemotherapy before surgery in operable OC. (Added per Amendment 6, See Section 2.2 for details):
- Cohort D: Neoadjuvant paclitaxel/carboplatin chemotherapy + radiotherapy before surgery in operable OC.

The immunotherapy will be given for a 4-week period before starting the standard chemo(radio)therapy, continuing durvalumab treatment once the chemotherapy starts for all cohorts except Cohort D. (Note: For a subset of Cohort D subjects (Cohort D2), durvalumab doses will continue during chemoradiotherapy, after the initial 4-week immunotherapy period. Upon approval of Amendment 7, enrollment will proceed to Cohort D2, unless there is a medical reason to enroll a specific subject to Cohort D.)

The study will include 2 phases, a safety run-in Phase 1 (Cohorts A1 and A2) and an expansion Phase 2 (Cohorts B, C/C-FLOT, and D/D2).

Phase 1 will evaluate the safety of durvalumab alone (Cohort A1) administered before chemotherapy (oxaliplatin + capecitabine) in subjects with metastatic or locally advanced OC. After completion of Cohort A1, Phase 2 in Cohorts C/C-FLOT, and D/D2 will begin, and a safety review will determine whether to explore the tremelimumab + durvalumab combination and dose-escalation for tremelimumab (Cohort A2).

Phase 2 includes the expansion into Cohorts B, C/C-FLOT, and D/D2. Once Cohort A1 is cleared, there will be concurrent enrollment into Phase 2 expansion for Cohorts C/C-FLOT and D/D2 (subjects with operable OC with neoadjuvant chemotherapy or chemoradiotherapy before surgery) and the dose-escalation phase for Cohort A2, if the safety review determines that Cohort A2 will be opened. Once Cohort A2 is completed, another safety review will determine whether to use the recommended combination dose (RCD) from Cohort A1 or A2 to start enrollment into the Cohort B (subjects with metastatic/locally advanced OC) expansion phase.

Subjects in Cohorts C/C-FLOT and D/D2 will undergo surgery after completing treatment, and they will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once

recovered from surgery, provided that this is within 3 months of surgery. Subjects in Cohort C-FLOT may receive durvalumab, FLOT, or durvalumab plus FLOT at the discretion of the investigator.

Primary objectives:

- Assess the Safety/Tolerability of durvalumab alone and tremelimumab + durvalumab in combination with oxaliplatin/capecitabine chemotherapy in metastatic/locally advanced OC (Endpoint: CTCAE version 4.03).
- Assess the Safety/Tolerability of durvalumab in combination with neoadjuvant chemo(radio)therapy (oxaliplatin/capecitabine, FLOT, and paclitaxel/carboplatin/radiotherapy) in operable OC. (Endpoint: CTCAE version 4.03).

Secondary objectives:

- Assess the Clinical Efficacy of durvalumab alone and tremelimumab + durvalumab in combination with oxaliplatin/capecitabine chemotherapy in metastatic or locally advanced OC. (Endpoints: Tumor Response by irRECIST, progression-free survival (PFS) and overall survival (OS))
- Assess the Clinical Efficacy of durvalumab in combination with neoadjuvant chemo(radio)therapy (oxaliplatin/capecitabine, FLOT, and paclitaxel/carboplatin/radiotherapy) in operable OC. (Endpoints: PFS after surgery, 1-year survival rate, OS, pathological and metabolic response rate)

Exploratory objectives:

- Evaluate the immunological effects of durvalumab and tremelimumab + durvalumab in tumor and peripheral blood samples.
- Relate the effects of immune modulation to allele variance, gene expression and host-pathogen relationships in the upper gastrointestinal tracts of OC subjects.
- Evaluate genomic differences between subjects who exhibit differential immune and therapeutic responses to durvalumab and tremelimumab + durvalumab therapy.

Per Amendment 8:

All subjects have completed treatment and On Study Follow-up. This amendment provides that the Post Study Follow-up for the collection of survival data will be discontinued as of 30 June 2022, and the study will be completed. As of 30 June 2022, all but up to 8 subjects will have completed the 3-year Post Study Follow-up, which would have occurred by December 2022 for the remaining subjects.

Sponsor: Ludwig Institute for Cancer Research Ltd., New York, NY **Local Sponsor**: Ludwig Institute for Cancer Research Ltd., Oxford, UK Sponsor Representative Signature and Date	**Study Chair/Chief Investigator:** [redacted] Department of Oncology, University of Oxford, UK Study Chair/Chief Investigator Signature and Date

Confidentiality Statement

The confidential and proprietary information in this document is owned by the Ludwig Institute for Cancer Research and provided to you as an Investigator, potential Investigator, or consultant, for review by you, your staff, and applicable institutional review board(s)/ethics committees. The information cannot be used, or divulged to any third party or published without the written consent of the Ludwig Institute for Cancer Research, except to the extent necessary to obtain informed consent from those persons to whom study medication may be administered. Any misappropriation of this information is prohibited by law.

Table of Contents

Table of Figures

1 Background

1.1 Oesophageal Cancer

Oesophageal adenocarcinoma (OAC) and oesophageal squamous cell carcinoma (OSCC) are the main types of oesophageal cancer (OC) and have an overall 5-year survival of less than 15%.[1] Oesophageal cancer is the sixth leading cause of cancer death world-wide. In western countries, its incidence has risen six fold in less than 40 years.[2] Despite large scale prospective studies of varying therapeutic regimes, mortality has remained closely related with OC incidence, indicating a failure to improve overall survival outcomes.[3] Treatment is broadly separated into endoscopic, for in-situ disease, surgical with neoadjuvant chemo(radio)therapy, and palliative approaches. Oesophageal cancer is often diagnosed late; hence only 23% of cases are suitable for curative surgery, complicated by a poor quality of life postoperatively and a 2-year recurrence rate of almost 50%.[4] Recent studies investigating novel chemotherapeutic regimes and targeted molecular inhibitors have been disappointing, conferring no overall survival advantages; therefore, new treatment strategies are urgently needed.

1.2 Oesophageal Cancer and Immunotherapy

Both OAC and OSCC have been characterized as promoting a strong immune response, in addition to their well-established inflammatory aetiologies.[5] Oesophageal adenocarcinoma occurs as a stepwise progression via Barrett's metaplasia in the distal oesophagus. The immune response to oesophageal inflammation is a key process driving the aberrant differentiation steps, which result in Barrett's metaplasia and subsequent adenocarcinogenesis. Specific cytokines related to Th2 response, and a range of gene mutations, are shown to drive columnar differentiation, predict subsequent carcinogenesis, and associate with prognosis.[6,7] Tumors, in general, have developed immune silencing abilities that can turn off the innate and effector elements of the immune system. Thus, subversion of key immune checkpoints has emerged as an exciting cancer therapeutic strategy directed at augmenting host-immune response to the tumor microenvironment. Oesophageal cancer is spontaneously targeted by the immune system and increased anti-tumor immune response has been associated with improved outcomes. This would suggest that emerging immunotherapy-based treatments could provide a desperately needed strategy for successful OC treatment.

Identifying specific tumor rejection antigens in OC has not yielded success, limiting efficacious molecular vaccine design. Current treatment relies on chemotherapy and targeted radiotherapy, relying on a direct tumoricidal effect rather than immune-mediated cell killing. Existing OC neoadjuvant strategies include chemotherapy alone with platinum and fluoropyrimidine agents, or chemoradiotherapeutic approaches also based on platinum agents. Radiotherapy can augment immune activation in the tumor microenvironment, via increased tumor production of IFN-β, which leads to T-cell priming and T-cell dependent tumor regression.[8]

1.3 CTLA-4

Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) is a member of the immunoglobulin family and locates on the T-cell surface following activation. Activation of CTLA-4 has been established as having a direct effect on T-cell attenuation and an inhibitor of this action formed the first FDA approved immune checkpoint blockade therapy.[9] Inhibition of CTLA-4 demonstrates frequent tumor rejection in immunocompetent mouse models of cancer; however, human trials in

melanoma have been less successful with anti-CTLA-4 monotherapy, as efficacy is largely dependent on tumor immunogenicity.[10] Activity in OC has to date been limited, with only 1 of 18 subjects treated with tremelimumab responding. More recent anti-CTLA-4 studies have involved combination therapeutic approaches with success in murine and melanoma models.[11]

1.4 PD-1 and PD-L1

The programmed cell death-1 (PD-1) pathway is expressed by activated T-cells, but not resting T-cells, and is regarded as a broadly negative T-cell regulator. Programmed cell death-1 is demonstrated to mostly restrain the immune response in chronic inflammation, infection, and cancer. Two ligands, PD-L1 and PD-L2, bind PD-1. PD-L1 is upregulated in many inflammatory cancers, and OCs, suggesting that PD-1 PD-L1/2 interaction is a key checkpoint employed by tumors to evade host-immune response. Expression of PD-L1, which is associated with increased chance of response to PD-1 and PD-L1 targeted agents in multiple tumor types, is evident in half of OCs.[12] Ligand expression is associated with a poorer prognosis after oesophageal resection.

The safety, tolerability, pharmacokinetics, and anti-tumor activity of MEDI4736 (durvalumab) is being evaluated in an ongoing multicenter, open-label, Phase 1/2 study in advanced solid tumors including gastroesophageal cancer (Study CD-ON-MEDI4736-1108). As of 21 August 2014, preliminary data were available for 41 gastroesophageal subjects treated with MEDI4736 10 mg/kg Q2W in the expansion phase of Study CD-ON-MEDI4736-1108.[13] In this population, MEDI4736 demonstrated an acceptable safety profile, which appeared to be consistent with the overall study population treated with MEDI4736 10 mg/kg Q2W. Among 41 gastroesophageal subjects, 35 (85%) experienced an adverse event (AE) of any grade, regardless of causality, while 22 (54%) experienced a treatment-related AE. Treatment-related Grade ≥ 3 AEs were reported in 7 (17%) of patients. No treatment-related AEs led to permanent discontinuation or death. As of this data cutoff, 28 subjects were evaluable for response with the potential for ≥ 12 weeks of follow up (including subjects with ≥1 follow up disease assessment or death or discontinuation to due disease progression prior to first assessment). Among the 28 evaluable subjects, 2 (7%) achieved an objective response and 5 (18%) maintained stable disease for ≥ 12 weeks. PD-L1 expression data were not available for subgroup analyses of response.

1.5 Combination Therapy

Targeting PD-1 and PD-L1 has yielded exciting and durable anti-tumor activity in some advanced solid organ cancers[14] and enabled fast tracking of durvalumab (MEDI4736), amongst other agents, directly to Phase 3 trials. Specific to OC, PD-1/PD-L1 immune targeted approaches demonstrate efficacy in immunocompetent mouse models of cancer and objective responses have been observed in the Phase 1 study of durvalumab. These clinical and preclinical findings indicate that PD-1/PD-L1 is an attractive therapeutic target in oesophageal cancer.[13] Accumulating evidence suggests that immune priming of the tumor microenvironment is specifically beneficial in immune therapy approaches. Chemotherapy mediated immune priming, either in combination or in sequence with anti-PD-L1, offers an exciting novel therapeutic strategy in operable OC.

Characterization of anti-CTLA-4/anti-PD-L1 effects in human studies has been mainly clinically based. The impact of anti-CTLA4 or anti-PD-L1 immune modulation on gene expression in OC has not been explored. A multidisciplinary clinical and scientific investigative team,

encompassing genomics, molecular biology, immunology, and oncology, provides a novel opportunity to holistically characterize anti PD-L1 and CTLA-4 therapeutic consequence in OC. The track record of this collaboration is validated with several high impact co-authored publications.[15,16]

Existing protocols for immune monitoring and clinical response provide important quantitative details of individual immune response, but cannot inform individual subject response to immune priming at a protein level, or whether a differential OC response is anticipated. Furthermore, relevant cytokine responses are linked to specific gastrointestinal microbiomic features that associate with oesophageal metaplasia,[17] a key target in cancer prevention strategies. Additionally, comparison between stratified response groups has not been reported at a genomic resolution to explore the determination and organisation of effective immune responses to cancer, in the context of new immunotherapeutic combinations. Combining immune monitoring and genomic data obtained before and during the proposed OC therapy regimen will provide greater understanding of the mechanistic effects of immunotherapy, and whether immune checkpoint blockade response in humans can be determined in a personalised fashion.

1.6 Study Drugs

The drugs used in this study are Investigational Medicinal Products (IMPs).

1.6.1 Capecitabine

Capecitabine is a non-cytotoxic fluoropyrimidine carbamate, which functions as an orally administered precursor of the cytotoxic moiety 5-fluorouracil (5-FU). Capecitabine is activated via several enzymatic steps. The enzyme involved in the final conversion to 5-FU, thymidine phosphorylase (ThyPase), is found in tumor tissues, but also in normal tissues, albeit usually at lower levels. Fluorouracil is further metabolized to 2 active metabolites, 5-fluoro-2-deoxyuridine monophosphate (FdUMP) and 5-fluorouridine triphosphate (FUTP), within normal and tumor cells. FdUMP inhibits DNA synthesis by reducing normal thymidine production, while FUTP inhibits RNA and protein synthesis by competing with uridine triphosphate.

1.6.2 Oxaliplatin

Oxaliplatin is an antineoplastic active substance belonging to a class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane (DACH) and with an oxalate ligand as a leaving group. After displacement of the labile oxalate ligand leaving group, active oxaliplatin derivatives, such as monoaquo and diaquo DACH platinum, alkylate macromolecules, forming both inter- and intra-strand platinum-DNA crosslinks, which result in inhibition of DNA replication and transcription and cell-cycle nonspecific cytotoxicity. Oxaliplatin exhibits a wide spectrum of both in vitro cytotoxicity and in vivo anti-tumor activity in a variety of tumor model systems including various cisplatin resistant models. A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both in vitro and in vivo.

1.6.3 Paclitaxel

Paclitaxel belongs to a class of chemotherapy drugs called plant alkaloids. The vinca alkaloids are made from the periwinkle plant, while taxanes are made from the bark of the Pacific Yew tree (taxus). The vinca alkaloids and taxanes are also known as antimicrotubule agents. Paclitaxel's

mechanism of action involves interference with the normal breakdown of microtubules during cell division. See Section 2.1 for additional information.

1.6.4 Carboplatin

Carboplatin is a platinum coordination complex and alkylating agent which is used as a chemotherapeutic agent for the treatment of various cancers. It is an alkylating agent and causes cross linking in DNA strands, which leads to inhibition of DNA and RNA and triggers cell death in rapidly dividing cells. See Section 2.1 for additional information.

1.6.5 Durvalumab (MEDI4736)

Durvalumab is briefly described in this section below. Refer to the current Investigator Brochure (IB) for complete and current information.

Durvalumab is a human immunoglobulin G1 kappa monoclonal antibody (mAb) directed against human PD-L1. Durvalumab is selective for recombinant PD-L1 and blocks the binding of recombinant PD-L1 to the PD-1 and cluster of differentiation (CD) 80 receptors.

As of the data cutoff dates in the IB (15Apr2015 to 12Jul2015), a total of 1,883 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored (6 monotherapy and 14 combination therapy) and 10 collaborative studies. Of the 1,883 subjects, 1,279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs, with the exception of patients with squamous cell carcinoma of the head and neck (SCCHN) where a higher incidence of bleeding has been reported. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy / neuromuscular toxicity, endocrinopathies such as hypo- and hyper-thyroidism, hypophysitis, adrenal insufficiency and type I diabetes mellitus, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

Partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00007) and 2 combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006). Clinical activity has been observed across the 4 studies.

According to MedImmune, the recommended dosing schedule for durvalumab is 20 mg/kg Q4W or 10mg/kg Q2W. The fixed dosing for durvalumab was selected based on pharmacokinetic (PK) models.

Using population PK models, simulations indicated that both body weight-based and fixed dosing regimens of durvalumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimens. A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given

expectation of similar PK exposure and variability, MedImmune considers it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 750 mg Q2W durvalumab is equivalent to 10 mg/kg Q2W, and 1500 mg Q4W durvalumab is equivalent to 20 mg/kg Q4W. This study will use a fixed dose of 750 mg Q2W for durvalumab.

1.6.6 Tremelimumab

Tremelimumab is briefly described in this section below. Refer to the current IB for complete and current information.

Tremelimumab (formerly CP-675,206) is a human immunoglobulin G2 (IgG2) mAb being investigated as a cancer immunotherapeutic agent. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins.

As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), 22 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these studies, 13 have been completed and 9 are ongoing. Tremelimumab has been administered as monotherapy to 973 subjects participating in 10 of the 22 clinical studies, 2 of which are ongoing. An additional 497 subjects have received tremelimumab or placebo in the ongoing double-blinded, Phase 2b mesothelioma study, D4880C00003(DETERMINE). Tremelimumab in combination with other anticancer agents has been administered to 208 subjects with a variety of tumor types in 12 of the 22 clinical studies, 7 of which are ongoing.

In clinical subjects, tremelimumab exhibits linear (dose-proportional) PK following intravenous (IV) infusion.

Across the clinical development program for tremelimumab, a pattern of efficacy has emerged, also observed for the related anti-CTLA-4 antibody, ipilimumab, which appears to be consistent across tumor types for this mechanism of action. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting several months even in subjects with aggressive tumors such as refractory metastatic melanoma. Some subjects may have what is perceived to be progression of their disease in advance of developing disease stabilization or a tumor response. Overall, the impact on conventionally-defined progression-free survival (PFS) can be small; however, the durable response or stable disease seen in a proportion of subjects can lead to significant prolongation of overall survival (OS).

The profile of adverse events (AEs) and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to subjects with melanoma). As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), AEs (all grades, regardless of causality) reported in > 10% of subjects in the completed and rollover tremelimumab monotherapy studies (N = 973, integrated data) were diarrhea (45.3%), fatigue (37.5%), nausea (32.5%), rash (28.8%), pruritus (27.3%), decreased appetite (22.8%), vomiting (22.5%), pyrexia (15.3%), cough (15.0%), constipation (14.4%), abdominal pain (13.9%), headache (13.8%), dyspnea (12.4%), and decreased weight (10.2%). Based on integrated data from completed studies of tremelimumab in combination with other agents (N = 116), AEs (all grades, regardless of causality) reported in > 15% of subjects were diarrhea (54.3%); nausea

(40.5%); fatigue (38.8%); rash (35.3%); pruritus, decreased appetite (30.2% each); vomiting (27.6%); pyrexia (26.7%); influenza like illness (20.7%); arthralgia (19.8%); constipation (19.0%); thrombocytopenia, injection site reaction (18.1% each); and increased aspartate aminotransferase (15.5%). Most of these events occurred at a higher rate with tremelimumab plus sunitinib than with other combinations. The events of diarrhea, rash, and pruritus are considered identified risks of tremelimumab. Acute renal failure was reported in subjects who received the combination of tremelimumab and sunitinib; however, acute renal failure has not been an expected AE for single-agent tremelimumab. The incidence and/or severity of many of the AEs observed following administration of tremelimumab can be reduced by following current guidelines for the management of immune-related toxicities.

According to MedImmune, the dose selection of 1 mg/kg Q4W for tremelimumab when combined with 20 mg/kg Q4W for durvalumab was based on the identification of an optimal dose of durvalumab that would "yield sustained target suppression, optimize synergy of the combination, while maintaining the balance of safety in combination with tremelimumab." This is consistent with the dosing regimen to be evaluated in the MedImmune program going forward.

The fixed dosing for tremelimumab is based on information from MedImmune, which indicates that the dose and schedule of 75 mg tremelimumab Q4W when combined with durvalumab was selected based on PK models as described below.

Using population PK models, simulations indicated that both body weight-based and fixed dosing regimens tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimens. A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, MedImmune considers it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 75 mg Q4W tremelimumab is equivalent to 1 mg/kg Q4W.

2 Study Rationale

While combination anti-CTLA-4/anti-PD-L1 therapy for OC is potentially interesting, its toxicity makes building this into existing treatment regimens difficult. In particular, the overlapping toxicity profiles of fluoropyrimidines and CTLA-4 antibodies present a challenge. The evidence is not yet sufficiently developed to justify anti-CTLA-4/anti-PD-L1 therapy use in place of chemo(radio)therapy. There is, however, preclinical work that supports the combination of anti-PD-L1 with radiotherapy [18] and oxaliplatin [19].

This study will focus on subjects with operable tumors so the tumor, microenvironment, and surrounding organ can be studied in detail. This also serves as a point of distinction from existing work in OC with durvalumab. As these subjects can potentially be cured, safety considerations, specifically ensuring that oesophagectomy is not compromised, are paramount.

In the United Kingdom (UK), the standard of care for operable OC is platinum and fluoropyrimidine chemotherapy for two 3-week cycles, followed by surgery, 6 to 8 weeks later. Pre-operative chemoradiation with the same drugs is the standard approach for middle and higher OCs, including squamous cell histologies.

In this study, the documented tolerability of existing durvalumab regimens will be combined with neoadjuvant chemotherapy, or it will be given prior to chemoradiotherapy (CRT) in subjects with operable OC.

2.1 Rationale for Amendment 2

For Amendment 2, the following key changes were implemented for Cohort D:

1. The oxaliplatin-capecitabine backbone of the CRT regimen was replaced with a paclitaxel/carboplatin regimen.
2. The Induction chemotherapy component of the neoadjuvant CRT regimen was eliminated
3. The radiotherapy (RT) dose was changed to 41.4 Gy in 23 fractions compared to the previous 45 Gy in 25 fractions).

2.1.1 Change from Oxaliplatin-Capecitabine CRT to Paclitaxel-Carboplatin

The fluoropyrimidine–platinum (traditionally 5Fu-cisplatin) based CRT regimen has long been a standard of care in the pre-operative management of oesophageal cancer. The use of this combination has been largely historic, with only one small positive phase trial, and several meta-analyses supporting its use over surgery alone.[20,21]

The oxaliplatin-capecitabine based CRT regimen was selected over the cisplatin-fluoropyrimidine regime prior to Amendment 2 based on several factors including: (1) maintaining the same chemotherapy backbone as proposed in the neoadjuvant chemotherapy arm of the trial; (2) a randomized Phase 2 study in definitive chemoradiation showing comparable efficacy and less toxicity of oxaliplatin-5FU combination in comparison to cisplatin-5FU combination[22]; (3) Emerging Phase 1b/2 data suggesting feasibility and activity of oxaliplatin-fluoropyrimidine based CRT regimens in the pre-operative setting[23-25]; and (4) use of this regimen in the NEOSCOPE trial, a randomized Phase 2 trial that was ongoing in the UK at the time when this protocol was being developed.[26]

However, over the last 2-3 years, there has been an increasing shift in international practice in favor of a neoadjuvant CRT regimen consisting of weekly paclitaxel and carboplatin as the chemotherapy backbone. This shift is based on the CROSS trial,[27] which is the largest trial to date in neoadjuvant CRT. For this trial, 368 subjects were randomized between surgery alone or pre-op CRT and showed a near doubling of median survival, with low level of Grade 3/4 hematological (7%) and non-hematological (13%) toxicity. The NEOSCOPE trial, a Phase 2 trial, randomized 85 subjects to oxaliplatin based CRT vs weekly paclitaxel/carboplatin based CRT.[28] The study demonstrated inferior outcome with the oxaliplatin/capecitabine arm (pathological complete response rate 14%) compared to paclitaxel/ carboplatin based CRT (pathological complete response rate 29%). Based on the low response rates in the oxaliplatin arm, it is unlikely to be pursued as the chemotherapy backbone in future CRT trials. Additionally, a retrospective study (n=165) comparing cisplatin-5FU based pre-operative CRT to paclitaxel/carboplatin based regimen has also suggested lower toxicity with the paclitaxel/carboplatin regimen with non-significant differences in response rates and long term survival.[29]

2.1.2 Elimination of the induction chemotherapy prior to neoadjuvant CRT

The CRT arm of the pre Amendment 2 protocol was adapted from the NEOSCOPE study and therefore included induction chemotherapy. In the past few years, there have been emerging data questioning the role of induction chemotherapy (ICT) prior to neoadjuvant CRT. Two randomized Phase 2 studies have failed to show benefit for ICT, and one of the studies has shown an increase risk of thrombocytopenia and reduction in dose intensity in the ICT arm.[30,31] In the NEOSCOPE trial there was an increase in Grade 3/4 hematological toxicity compared to CROSS; all 3 treatment-related deaths occurred during ICT and no deaths were seen during CRT. Thus, based on likely benefits and harm, ICT is no longer viewed as advisable in the neoadjuvant setting.

2.1.3 Reduction of the radiotherapy dose

Per Amendment 2, the RT dose will be reduced from 45 Gy/25 fractions (NEOSCOPE regimen) to 41.4 Gy/23 fractions (CROSS regimen). This decision was based on retrospective data suggesting that higher dose of RT may increase post-operative respiratory complications[32] and the positive outcome of the CROSS trial.

2.2 Rationale for Amendment 6

FLOT is a regimen combining 5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel.

Based on emerging data, a proposal was made to add Cohort C-FLOT to the study, in addition to Cohort C. The proposal for Cohort C-FLOT includes the following:

1. Replace Oxaliplatin and capecitabine as neo-adjuvant chemotherapy with the FLOT regimen to run concurrently with durvalumab treatment.
2. Introduce post-operative chemotherapy, also with FLOT. This will run concurrently with durvalumab immunotherapy.
3. Subjects allocated to oxaliplatin and capecitabine in Cohort C before the introduction of Cohort C-FLOT will not be replaced and will be included in the total 20 Subjects for Cohort C + Cohort C-FLOT.

Pre-operative fluoropyrimidine–platinum chemotherapy has long been a standard of care in the pre-operative management of oesophageal cancer. Opinions have differed as to the relative merits of continuing treatment post-operatively and of adding in an anthracycline (usually epirubicin). In metastatic disease taxane chemotherapy has established a role, either as a single agent or in combination with platinum and fluoropyrimidine therapy. However, the perceived potential for toxicity has limited taxane use in this often frail group of patients.

More recently the AIO, a German collaborative group, has advocated the use of FLOT (5-FU 2600 mg/m^2 (24-hr IV), leucovorin 200 mg/m^2 IV, oxaliplatin 85 mg/m^2 IV, and docetaxel 50 mg/m^2 IV, every two weeks, all on Day 1). The regimen has proved fairly well-tolerated in patients with metastatic disease, although the addition of the taxane did increase the rate of higher grade adverse events. In older patients, in the FLOT65+ trial, this increase was driven by higher rates of Grade 3 or 4 neutropaenia, leucopaenia and nausea. However, the rates of complicated neutropenia and of serious adverse events were not increased. As expected, alopecia was also significantly more common with the use of a taxane. Diarrhoea was also more common.

The results of the neo-adjuvant use of FLOT were presented at the ESMO 2017 Congress.[33] The data demonstrate increased progression-free and overall survival compared with fluoropyrimidine–platinum chemotherapy (in this case ECX or ECF). Median PFS improved to 30 months with FLOT (HR 0.75 vs ECX/ECF; 95% CI 0.62-0.91; p=0.004) and overall survival to 50 months (HR 0.77; 95% CI 0.63 - 0.94; p=0.012).

To date, detailed toxicity data have not been presented, but 97% of subjects proceeded to surgery (compared with 91% for neo-adjuvant CF in OE05, and 94% for ECF/ECX in FLOT4). SAE, post-operative complications and post-operative death rates were the same in both arms of the FLOT4 study, but more subjects started post-operative chemotherapy in the taxane arm (60% vs 52%).

Following these results, the FLOT regimen is being introduced in the UK and Europe as a standard of care for operable oesophageal cancer. As the goal of the LUD2015-005 study is to evaluate the addition of durvalumab and/or tremelimumab to standard treatments for this cancer, the use of this regimen for Cohort C-FLOT is proposed. The higher rates of neutropaenia and nausea are readily manageable and distinct from the side effect profile of checkpoint inhibitors. The increase in diarrhea incidence might pose questions of IMP attribution, but we are considering the use of FLOT only with durvalumab, as tremelimumab use is confined to the metastatic setting.

Regarding the need for prior evaluation of durvalumab combined with FLOT before use in the adjuvant setting, the safety of oxaliplatin, capecitabine and durvalumab has been established and there will be information from several subjects in the adjuvant setting before implementing the proposed change. Meanwhile, the safety of using anti-PD-1/PD-L1 agents with chemotherapies, including taxanes, has been established in multiple trials in neo-adjuvant and metastatic settings (e.g., Keynote-059 and -522). For these reasons it is proposed to implement FLOT in Cohort C-FLOT, without prior evaluation in subjects with more advanced disease, and to monitor safety closely.

Post-operative chemotherapy will become necessary in Cohort C-FLOT. This will not affect the plans for post-operative durvalumab, nor the duration of immunotherapy after surgery. The

decision as to the implementation of FLOT and durvalumab post-operatively will be delegated to the investigator, with the option of using one or other modality as well as the combination.

Enrollment to Cohort C and Cohort C-FLOT will be managed to ensure that each treatment will have at least 8 evaluable subjects.

2.3 Rationale for Amendment 7

Cohort D2:

For Cohort D of the study, subjects with operable OC receive 2 doses of durvalumab during a 4-week immunotherapy period, followed by neoadjuvant chemoradiotherapy (5 weekly doses of paclitaxel + carboplatin + radiotherapy) without concurrent durvalumab. Per Amendment 7, Cohort D2 is added. Cohort D2 is a subset of Cohort D subjects for whom durvalumab doses will continue during chemoradiotherapy, after the initial 4-week immunotherapy period. Upon approval of Amendment 7, enrollment will proceed to Cohort D2, unless there is a medical reason to enroll a specific subject to Cohort D. The rationale for the addition of Cohort D2 is as follows.

There is considerable interest in the potential for radiotherapy to augment the response to checkpoint blockade, with pre-clinical and mechanistic evidence for synergy. Until recently clinical data have been lacking, with the potential for overlapping toxicities of enteritis or pneumonitis a concern according to the site irradiated.

Trial reports now indicate that PD-1 inhibitors may be safely combined with thoracic irradiation at standard doses for the immunotherapies and radiation doses of up to 50 Gy. Maity et al. identified no Grade 3 or 4 toxicities in 24 subjects treated with pembrolizumab and radiotherapy up to 24Gy, and only 1 Grade 2 episode was reported.[34] Luke and colleagues in Chicago found up to 50 Gy irradiation well-tolerated with pembrolizumab in 62 subjects.[35] Six subjects experienced a Grade 3 treatment-related toxicity, but those in which radiotherapy was implicated were confined to the field treated. In a retrospective analysis, French oncologists found toxicity with nivolumab to be unaffected by the timing of treatment with respect to irradiation, including co-administration.[36]

The study at Perelman observed an expansion in PD-1+CTLA-4+CD8 cells after irradiation, a population associated with anti-tumour efficacy and exhaustion.[34] In the PACIFIC trial, where durvalumab administration after chemoradiotherapy for NSCLC improved survival over placebo, the effect was greatest in the sub-group treated soonest (<14 days) after chemoradiotherapy.[37]

These data provide impetus to explore extending durvalumab treatment to overlap with chemoradiotherapy and confidence that any additional toxicities will be manageable. We plan further mitigation by allowing overlapping treatment only where the study team (e.g., Investigator, Chief Investigator, and Sponsor Medical Monitor) have agreed that it is appropriate based on a review of the size of the radiation field as well as any potential impact on organ function.

Additional blood testing in long-term survivors:

Although deep and durable responses to immunotherapy have been observed in many tumour types, considerable uncertainty remains regarding their basis. Specifically, there is yet little

information on the specificity of the T cell populations thought to drive these responses. T cell clonal expansion is seen in subjects responding to date, and it is possible to track these over time and to look for common specificities in responding subjects. Data from TCR seq allow us to identify V beta and alpha chains, but there is considerable value in acquiring samples to purify and grow rare tumour-specific T cells from long term responders to better characterize their specificities.

Thus, per Amendment 7, the Investigator(s) will have the option to approach subjects with long-term survival (PFS > 1 year, still in remission) from the metastatic cohorts (A and B) of the trial to request blood (up to 300 mL) for additional testing.

3 Experimental Plan

3.1 Study Design

This is an open-label, Phase 1/2 study to evaluate the safety of durvalumab (and tremelimumab for certain cohorts as described in Section 3.1.7) in combination with chemo (radio) therapy according to the following cohorts:

- Cohorts A1, A2, and B: Oxaliplatin/capecitabine chemotherapy in metastatic/locally advanced oesophageal cancer (OC).
- Cohort C: Neoadjuvant oxaliplatin/capecitabine chemotherapy before surgery in operable OC.
- Cohort C-FLOT: Neoadjuvant FLOT chemotherapy before surgery in operable OC (adjuvant FLOT may also be used as described in Sections 3.1.7 and 3.1.12).
- Cohort D/D2: Neoadjuvant paclitaxel/carboplatin chemotherapy + radiotherapy before surgery in operable OC.

For Cohorts A1, A2, B and C, and C-FLOT, the immunotherapy will be given for a 4-week period before starting the chemotherapy, continuing durvalumab treatment once the chemotherapy starts. For Cohort D, the immunotherapy will be given for a 4-week period before starting chemoradiotherapy, but the durvalumab dosing will not continue during the chemoradiotherapy. A dose of durvalumab will be given following chemoradiotherapy on Day 64 (±3 days). If the subject has not completely recovered (per Investigator assessment) by Day 64 (±3 days), the durvalumab dose may be delayed until Day 71 (±3 days). For a subset of Cohort D subjects (Cohort D2), durvalumab doses will continue during chemoradiotherapy, after the initial 4-week immunotherapy period. For the chemoradiotherapy period of Cohort D2, durvalumab will be given on Cycle 1/Day 1, Cycle 1/Day 15, and Cycle 2/Day 8; durvalumab will not be given on Day 64 or 71. Note: Upon approval of Amendment 7, enrollment will proceed to Cohort D2, unless there is a medical reason to enroll a specific subject to Cohort D.

The study will include 2 phases, a safety run-in Phase 1 (Cohorts A1 and A2) and an expansion Phase 2 (Cohorts, B, C, C-FLOT, and D/D2).

3.1.1 Study Phase

Phase 1/2

3.1.2 Enrollment/Randomization

Subjects will be enrolled in a non-randomized manner. Subject enrollment and the safety of the combination regimen will be reviewed on an ongoing basis by an internal data safety monitoring panel (see Section 3.1.14).

Phase 1 will be a safety run-in for Cohort A1 and possibly Cohort A2, as described below. For Cohorts A1 and A2, the start of the study drug administration for the first and second subject will be separated by at least 24 hours. The safety data for subjects in Cohorts A1 and A2 will be reviewed for dose-limiting toxicities (DLTs); see Sections 3.1.7.1 and 3.1.9.

Enrollment will start in Cohort A1. Once this cohort is cleared, enrollment will begin in the Phase 2 expansion for Cohorts C, C-FLOT, and D/D2. A safety review will determine whether to open the dose-escalation phase for Cohort A2, which will explore the tremelimumab + durvalumab

combination with a dose-escalation for tremelimumab. Once Cohort A2 is completed, another safety review will determine whether to use the recommended combination dose (RCD) from Cohort A1 or A2 to start enrollment into the Cohort B expansion phase (see Section 3.1.7).

Note: Enrollment to Cohort C and Cohort C-FLOT will be managed to ensure that each treatment will have at least 8 evaluable subjects.

See note in Section 3.1 regarding enrollment to Cohort D2.

See notes in Section 3.1.7 (Cohort D), for information regarding safety assessment of subjects in Cohort D and prior to enrollment into Cohort D2.

3.1.3 Blinding/Unblinding

This is an open label study.

3.1.4 Subject Population

Subjects must have a histological diagnosis of oesophageal or gastrooesophageal cancer. See Section 5 for complete eligibility criteria.

Cohorts A (A1 and A2) and B will include subjects with metastatic/locally advanced OC, and Cohorts C, C-FLOT and D/D2 will include subjects with operable OC.

Subjects with operable disease will be allocated to Cohort C, C-FLOT or D/D2 based on the decision taken by the multidisciplinary team (MDT) on the standard treatment approach for any individual patient. The MDT will determine (1) operability and (2) whether neoadjuvant chemotherapy or chemoradiotherapy should be offered. These decisions will guide eligibility for enrollment to Cohorts C, C-FLOT, and D/D2. The radiotherapy offered in Cohort D/D2 will be provided per Section 6.13 for these subjects, as already determined by MDT.

3.1.5 No. of Sites/Subjects

Up to 4 sites; and 75 evaluable subjects are estimated for this study:

- Phase 1: 6-9 subjects for Cohort A1 and 6-12 subjects for Cohort A2.
- Phase 2: 54 subjects for Cohorts B (n = 14), C/C-FLOT (n = 20) and D/D2 (n = 20).

Note: Enrollment to Cohort C and Cohort C-FLOT will be managed to ensure that each treatment will have at least 8 evaluable subjects.

3.1.6 Sample Size and Statistical Considerations

Preceding standard chemo(radio)therapy with immunotherapy is not anticipated to yield significant additional toxicities; however, this needs to be verified. If dose limiting toxicities attributable to the addition of immunotherapy are found in only 0 or 1 of 6 evaluable subjects with metastatic disease, this would provide the necessary reassurance to proceed to treatment of potentially curable subjects. Allowing for replacement of inevaluable subjects (see Section 3.1.11) accounts for the projected sample size of Cohort A1 (n = 6-9 subjects) and Cohort A2 (n=6-12 subjects).

The sample sizes of Cohorts B (n = 14), C/C-FLOT (n = 20) and D/D2 (n = 20) are driven by the need to establish the safety profile of combination therapy as well as a preliminary assessment

of efficacy. The study is not designed to provide definitive information, but to deliver the basis for design of future trials and to allow interpretation of exploratory translational endpoints.

For example, in Cohort C/C-FLOT the study will allow us to estimate 6-month progression-free survival (PFS) and the R0 resection rate associated with combination therapy. The 6-month PFS rate taken from the time of surgery and R0 resection rate are surrogate markers for longer term clinical outcomes. If we observe a 6-month PFS of at least 78% in 20 subjects, we can be 95% confident that the true PFS at 6 months is at least 54.4% (lower 1-side 95% confidence limit=54.4%). Assuming an observed R0 resection rate of 80%, to reach alpha = 0.1 (1-side), if 20 subjects are recruited, we can be 80% confident that the true R0 rate is at least 64.0% (lower 1-side 80% confidence limit=64.0%). Achievement of these figures would suggest a regimen worthy of further study.

3.1.7 Treatment Arms and Treatment Schema

The study consists of 2 phases, a safety run-in Phase 1 (Cohorts A1 and A2) and an expansion Phase 2 (Cohorts, B, C/C-FLOT, and D/D2).

Subjects in all cohorts will have a **4-week period of immunotherapy** at the start of the study:

- Cohorts A1, C/C-FLOT, and D/D2 will receive durvalumab alone, 750 mg Q2W
- Cohort A2 will receive tremelimumab (37.5 mg or 75 mg) on Day 1 (see dose escalation, Section 3.1.7.1) + durvalumab (750 mg Q2W) combination.
- Cohort B will receive immunotherapy at RCD from Cohort A1 or A2.

Chemo(radio)therapy will follow the 4-week immunotherapy. For all cohorts except Cohort D, the 4-week immunotherapy period will be followed by a specific number of cycles for chemotherapy and durvalumab Q2W, depending on the cohort.

For Cohorts A1, A2, B and C, chemotherapy will start on the same day of the third durvalumab infusion (chemotherapy Cycle 1, Day 1; Study Day 29) and continue for up to six 3-week chemotherapy cycles (Cohorts A1, A2, and B) or two 3-week chemotherapy cycles (Cohort C), with durvalumab 750 mg administered Q2W. For these cohorts, chemotherapy will consist of oxaliplatin given at 130 mg/m^2 IV on Day 1 of each 3-week cycle and capecitabine 1250 mg/m^2/day, given orally in 2 divided doses continuously from Days 1 to 21 of each 3-week cycle.

For Cohort C-FLOT, chemotherapy will start after the 4-week durvalumab immunotherapy period, i.e., on Cycle 1, Day 1 (Study Week 5, Study Day 29). Durvalumab (750 mg Q2W) and chemotherapy will continue for two 4-week cycles. Chemotherapy will consist of FLOT (5-FU 2600 mg/m^2 (24-hr IV), leucovorin 200 mg/m^2 IV, oxaliplatin 85 mg/m^2 IV, and docetaxel 50 mg/m^2 IV) given on Days 1 and 15 of each of the two 4-week cycles.

See Section 2.2, regarding the rationale for not including a Phase 1 evaluation of durvalumab combined with FLOT.

For Cohort D, chemoradiotherapy will start after the 4-week durvalumab immunotherapy period, i.e., on Cycle 1, Day 1 (Study Week 5, Study Day 29). Subjects will receive 5 weekly doses of paclitaxel (50 mg/m^2) and carboplatin (AUC 2) concurrent with radiotherapy (41.4 Gy in 23 fractions), but without durvalumab. Radiotherapy will be given over 23 fractions over a period of 5 weeks. A dose of durvalumab will be given following chemoradiotherapy on Day 64 (±3

days). If the subject has not completely recovered (per Investigator assessment) by Day 64 (±3 days), the durvalumab dose may be delayed until Day 71 (±3 days). For a subset of Cohort D subjects (Cohort D2), durvalumab doses will continue during chemoradiotherapy, after the initial 4-week immunotherapy period. For the chemoradiotherapy period of Cohort D2, durvalumab will be given on Cycle 1/Day 1, Cycle 1/Day 15, and Cycle 2/Day 8; durvalumab will not be given on Day 64 or 71. Upon approval of Amendment 7, enrollment will proceed to Cohort D2, unless there is a medical reason to enroll a specific subject to Cohort D.

Note: For Cohort D, the durvalumab immunotherapy is not concurrent with chemoradiotherapy; therefore, a formal Phase 1 component is not proposed; however, safety for the first 6 subjects will be closely monitored.

Note: The Cohort D subset, Cohort D2, will start enrollment after several Cohort D subjects have been treated with the non-concurrent immunotherapy/ chemoradiotherapy schedules; ongoing safety review of those Cohort D subjects will inform enrollment into Cohort D2.

Subjects in Cohorts C/C-FLOT and D/D2 will undergo **surgery** 6 to 8 weeks after completing chemo(radio)therapy or according to institutional policies for surgery; they will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this is within 3 months of surgery. Subjects in Cohort C-FLOT may receive durvalumab, FLOT or durvalumab plus FLOT at the discretion of the Investigator.

Phase 1

Cohort A 1: The safety of durvalumab administered 4 weeks before and during chemotherapy (oxaliplatin + capecitabine) will be evaluated in subjects with metastatic or locally advanced OC.

Treatment Schedule for Cohort A1 (subjects with metastatic/locally advanced OC)				
Period	**Durvalumab 750 mg (IV)**	**Oxaliplatin 130 mg/m^2 (IV)**	**Capecitabine 1250 mg/m^2/day (oral)**	**Radiation**
Week 1-4	Days 1 and 15 of study	No	No	No
***Cycle 1-6**	First day of Cycle 1 (Day 29), then every 2 weeks	Day 1 of each cycle	Days 1 to 21 of each cycle	No

***3-week cycle**

After completion of Cohort A1, Phase 2 expansion into Cohorts C/C-FLOT and D/D2 will begin, and a safety review will determine whether to explore the tremelimumab + durvalumab combination with a dose-escalation for tremelimumab (Cohort A2). See Figure 1 and Section 3.1.7.1.

Once Cohort A1 is cleared, there will be concurrent enrollment into Phase 2 expansion for Cohorts C/C-FLOT and D/D2 (subjects with operable OC) and the dose-escalation phase for Cohort A2.

Cohort A2: If a decision is made to open Cohort A2, tremelimumab will be given once only on Day 1 of the study. These subjects will receive infusions of tremelimumab (dose escalation will

be determined according to Section 3.1.7.1) and durvalumab 750 mg on Day 1 of the study, with durvalumab repeated every 2 weeks (Q2W).

Treatment Schedule for Cohorts A2 (subjects with metastatic/locally advanced OC)					
Period	**Tremelimumab** 37.5 or 75 mg (IV)**	**Durvalumab 750 mg (IV)**	**Oxaliplatin 130 mg/m^2 (IV)**	**Capecitabine 1250 mg/m^2/day (oral)**	**Radiation**
Week 1-4	Day 1 of study	Days 1 and 15 of study	No	No	No
***Cycle 1-6**	No	First day of Cycle 1 (Day 29), then every 2 weeks	Day 1of each cycle	Days 1 to 21 of each cycle	No

***3-week cycle**

**Cohort A2 with a dose-escalation for tremelimumab will only be opened if a decision is made to explore the tremelimumab + durvalumab combination (see Section 3.1.7.1).

Phase 2 includes the expansion into Cohorts B, C, C-FLOT, and D/D2.

Cohort B: Once Cohort A2 is completed, another safety review will determine whether to use the RCD from Cohort A1 or A2 to start enrollment into the Cohort B (subjects with metastatic/locally advanced OC) expansion phase.

Cohort C: Following the 4-week immunotherapy, subjects will be treated with neoadjuvant chemotherapy (oxaliplatin + capecitabine) with ongoing durvalumab before surgery. Subjects will undergo surgery 6 to 8 weeks after completing treatment or according to institutional policies for surgery; they will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this is within 3 months of surgery.

Treatment Schedule for Cohort C (subjects with operable OC)				
Period	**Durvalumab 750 mg (IV)**	**Oxaliplatin 130 mg/m^2 (IV)**	**Capecitabine 1250 mg/m^2/day (oral)**	**Radiation**
Week 1-4	Days 1 and 15 of study	No	No	No
***Cycle 1-2**	First day of Cycle 1 (Day 29), then every 2 weeks	Day 1 of each cycle	Days 1 to 21 of each cycle	No

***3-week cycle**

Cohort C-FLOT: Following the 4-week immunotherapy, subjects will be treated with neoadjuvant FLOT chemotherapy with ongoing durvalumab for 2 cycles before surgery. Subjects will undergo surgery 6 to 8 weeks after completing treatment or according to institutional policies for surgery; they will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this is within 3 months of surgery. Subjects in Cohort C-FLOT may receive durvalumab, FLOT, or durvalumab plus FLOT at the discretion of the Investigator.

	Treatment Schedule for Cohort C-FLOT (subjects with operable OC)					
Period	**Durvalumab 750 mg (IV)**	**5-Fluorouracil 2600 mg/m^2 (24-hr IV)**	**Leucovorin 200 mg/m^2 (IV)**	**Oxaliplatin 85 mg/m^2 (IV)**	**Docetaxel 50 mg/m^2 (IV)**	**Radiation**
Week 1-4	Days 1 and 15 of study	No	No	No	No	No
***Cycle 1-2**	Days 1 and 15 of each cycle	Days 1 and 15 of each cycle	Days 1 and 15 of each cycle	Days 1 and 15 of each cycle	Days 1 and 15 of each cycle	No

*4-week cycles

Cohort D: Following the 4-week immunotherapy, subjects will be treated with neoadjuvant chemoradiotherapy (5 weekly doses of paclitaxel + carboplatin + radiotherapy) without concurrent durvalumab. A dose of durvalumab will be given following chemoradiotherapy on Day 64 (±3 days). If the subject has not completely recovered (per Investigator assessment) by Day 64 (±3 days), the durvalumab dose may be delayed until Day 71 (±3 days). Subjects in Cohort D will undergo surgery 6 to 8 weeks after completing treatment or according to institutional policies for surgery; they will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this is within 3 months of surgery.

Treatment Schedule for Cohort D (subjects with operable OC)				
Period	**Durvalumab 750 mg (IV)**	**Paclitaxel 50 mg/m^2 (IV)**	**Carboplatin AUC 2 (IV)**	**Radiation***
Weeks 1-4	Days 1 and 15 of study	No	No	No
Weeks 5-9	No	Day 1 of Study Weeks 5-9	Day 1 of Study Weeks 5-9	23 fractions over Study Weeks 5-9

***The 41.4 Gy radiotherapy is given over 23 fractions, Weeks 5-9.

Cohort D2: For a subset of Cohort D subjects, durvalumab doses will continue during chemoradiotherapy, after the initial 4-week immunotherapy period. Upon approval of Amendment 7, enrollment will proceed to Cohort D2, unless there is a medical reason to enroll a specific subject to Cohort D.

Treatment Schedule for Cohort D2 (subjects with operable OC)				
Period	**Durvalumab 750 mg (IV)**	**Paclitaxel 50 mg/m^2 (IV)**	**Carboplatin AUC 2 (IV)**	**Radiation***
Weeks 1-4	Days 1 and 15 of study	No	No	No
Weeks 5-9	Cycle 1/Day 1, Cycle 1/Day 15, and Cycle 2/Day 8	Day 1 of Study Weeks 5-9	Day 1 of Study Weeks 5-9	23 fractions over Study Weeks 5-9

***The 41.4 Gy radiotherapy is given over 23 fractions, Weeks 5-9.

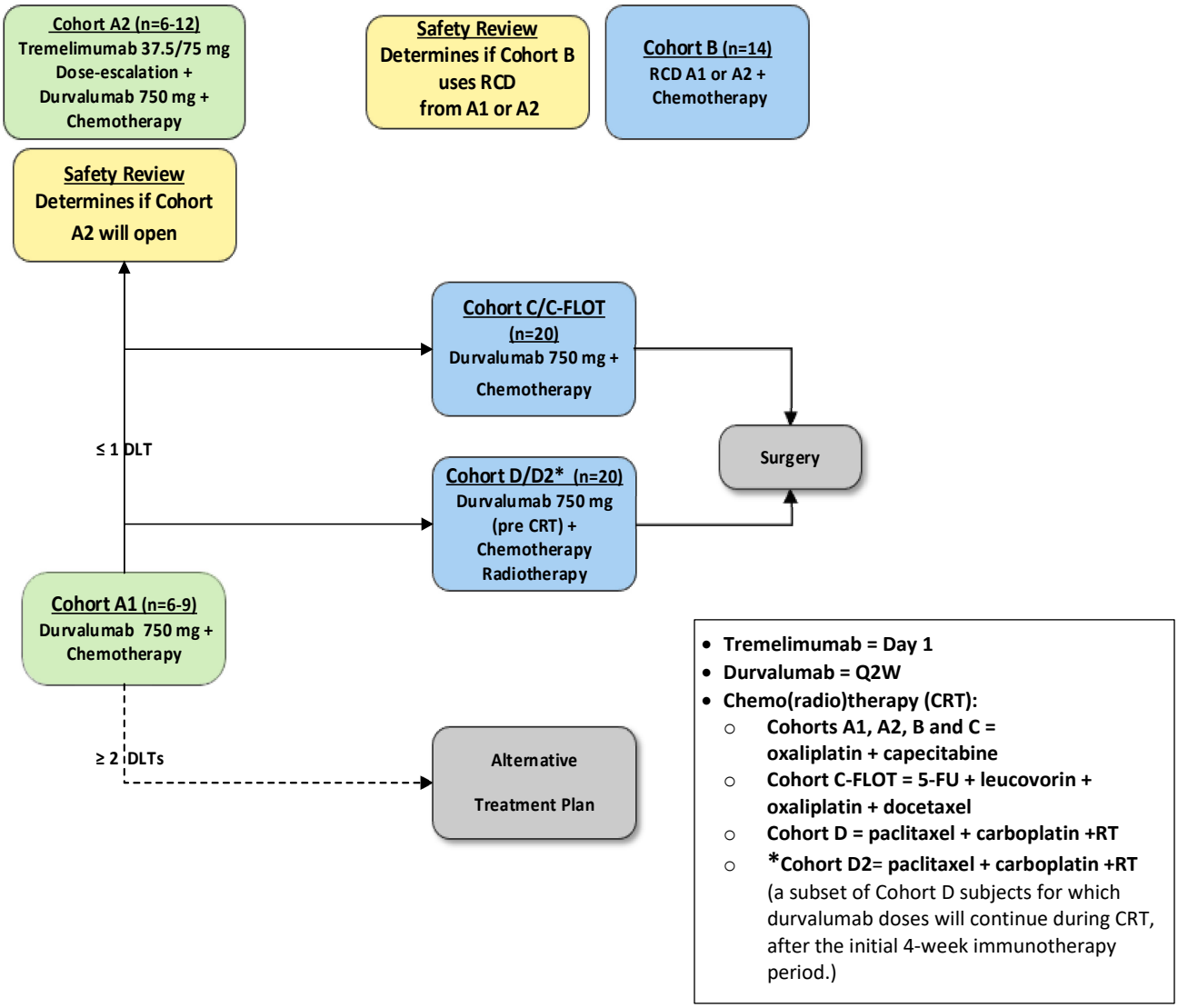

Figure 1: Treatment Schema

3.1.7.1 Phase 1 – Safety Run-in

For Cohorts A1 and A2, the start of the study drug administration for the first and second subject will be separated by at least 24 hours. See Section 3.1.9 for DLT evaluation for Cohorts A1 and A2.

If the decision is made to proceed with Cohort A2, a dose-escalation will be performed to determine the RCD for tremelimumab + durvalumab administered before chemotherapy

followed by durvalumab alone. The assessment for Cohort A2 will follow a standard 3 +3 dose-escalation for tremelimumab. Dose escalations for the determination of RCD will be performed based on the dose levels in the table below and the respective rules for a standard 3 + 3 dose escalation study design (see Figure 2).

Dose Level Table for Cohort A2 Escalations		
Dose level	***Durvalumab***	***Tremelimumab***
Starting	***750 mg Q2W***	***37.5 mg (Day 1)***
+1	750 mg Q2W	75mg (Day 1)

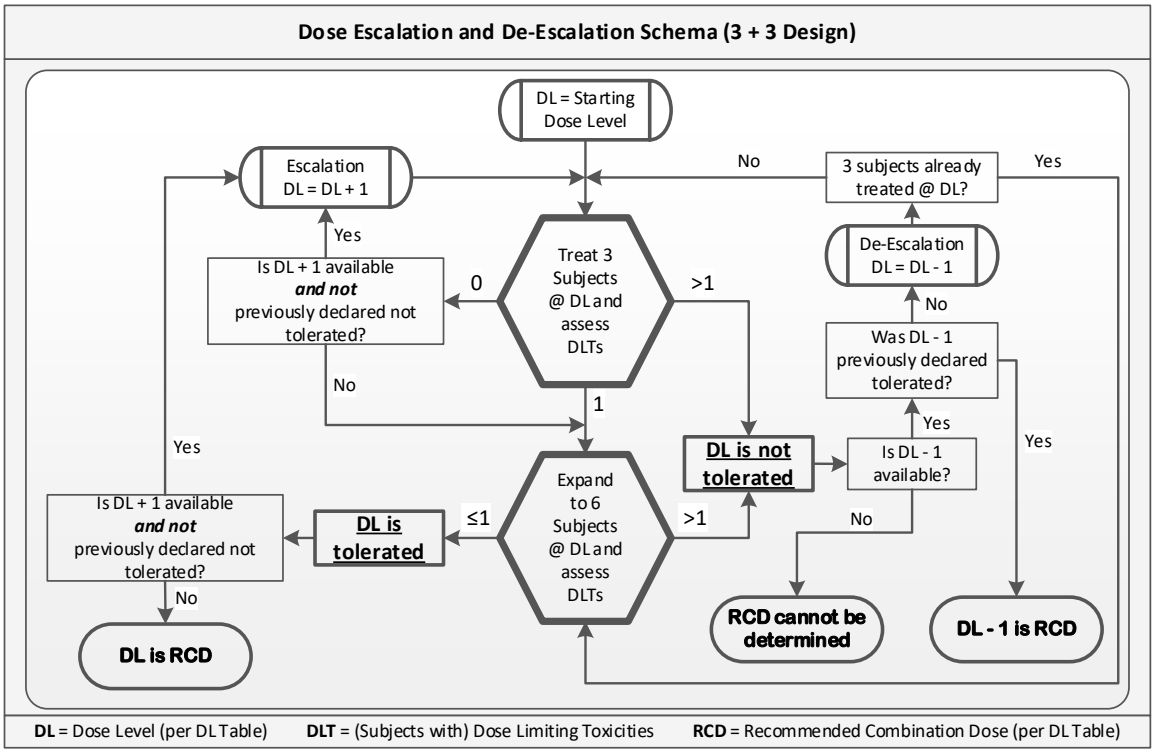

Figure 2: Dose Escalation Schema

Per Figure 2, the RCD for Cohort A2 is defined as the highest dose level at which no more than 1 of 6 subjects (i.e., < 33%) experience DLTs. The RCD cannot be determined if none of the predefined dose level cohorts fulfill that criterion.

3.1.7.2 Phase 2 – Expansion Phase

Once Cohort A1 is cleared, there will be concurrent enrollment into Phase 2 expansion for Cohorts C, C-FLOT, and D/D2 (operable OC with neoadjuvant chemotherapy or chemoradiotherapy before surgery) and the dose-escalation phase for Cohort A2 (see Section 3.1.7.1) if the safety review determines that Cohort A2 will be opened. Once Cohort A2 is completed, another safety review will determine whether to use the RCD from Cohort A1 or A2 to start enrollment into the Cohort B (subjects with metastatic/locally advanced OC) expansion phase.

3.1.8 Dosing Adjustments, Delays and Discontinuations

Dose adjustment and management guidelines for toxicity related to durvalumab and tremelimumab are outlined in Section 8.5; guidelines for oxaliplatin, capecitabine, and FLOT are provided in Section 8.6; guidelines for paclitaxel and carboplatin are provided in Section 8.7.

If a toxicity occurs that requires toxicity management and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

3.1.9 DLT

The aim of Phase 1 of the study (Cohorts A1 and A2) is to evaluate the feasibility/safety of administering durvalumab or tremelimumab + durvalumab pre-operatively to OC subjects. If the starting regimen in Cohort A1 is deemed unsuitable for pre-operative use, a switch to only consecutive treatment may be considered. If the decision is made to open Cohort A2 and the dose-escalation for tremelimumab is deemed unsuitable, tremelimumab will be omitted.

For Cohort A1, the safety of durvalumab alone administered before and with chemotherapy (oxaliplatin + capecitabine) in subjects with metastatic or locally advanced OC will be determined. The DLT evaluation period for the study will encompass the 4 weeks of immunotherapy (durvalumab alone) plus the subsequent first 6 weeks of chemotherapy, for a total of 10 weeks. If more than 1 of 6 subjects experience toxicity in the first 6 weeks of chemotherapy treatment that would in theory preclude oesophagectomy; then this dosing regimen will be deemed unsuitable for pre-operative administration in potentially curable subjects. This definition will extend beyond the usual concept of DLT and will be based on the evaluation of the internal data safety monitoring panel. If none of the 6 subjects in Cohort A1 experience such toxicity, Cohorts C/C-FLOT and D will be opened to enrollment as outlined in Section 3.1.7. If 1 subject in Cohort A1 experiences toxicity likely to interfere with surgery, the cohort will be expanded to 9 subjects, and the dosing regimen deemed tolerable only if none of the 3 additional subjects is similarly affected.

If the decision is made to open Cohort A2, DLTs will be observed over a period of 10 weeks, defined as the DLT Evaluation Period. The decisions for dose-escalation and RCD, as described in Section 3.1.7.1, will primarily be based on the number of subjects with DLTs occurring during the DLT Evaluation Period. DLTs occurring outside the DLT Evaluation Period will also be evaluated and may impact such decisions.

DLTs are defined as any adverse events that are possibly, probably, or definitely related to the administration of durvalumab or tremelimumab and durvalumab, in addition to chemotherapy, and fulfill any of the following criteria:

1. Any Grade ≥ 3 colitis, pneumonitis, neurological event, or uveitis
2. Any Grade 2 pneumonitis, neurological event, or uveitis with the *exception of those that* downgrade to Grade ≤ 1 within 3 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
3. Any *other* Grade ≥ 3 toxicity, with the *following exceptions*:
    - Grade ≥ 3 chemotherapy-related toxicities, manageable according to the dose modification instructions in the product information and Sections 8.6 and 8.7.

- Grade 3 irAEs that downgrade to Grade ≤ 2 within 3 days, or to Grade ≤ 1 or baseline within 14 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
- Grade 3 endocrinopathy that becomes asymptomatic when managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
- Grade 3 inflammatory reaction attributed to a local anti-tumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).
- Grade 3 fatigue for ≤ 7days.
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
- Liver transaminase elevation ≤ 8 times upper limit of normal (ULN) that downgrades to Grade ≤ 2 (≤ 5 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
- Total bilirubin ≤ 5 times ULN that downgrades to Grade ≤ 2 (≤ 3 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
- Grade ≥ 3 neutropenia that (1) is not associated with fever or systemic infection, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
- Grade 3 or Grade 4 lymphopenia.
- Grade 3 thrombocytopenia that (1) is not associated with clinically significant bleeding, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.
- Any pre-existing laboratory abnormality that deteriorates to Grade 3/4, but where the increment of deterioration is considered not clinically significant by both Investigator and Sponsor.
- Grade 3 or 4 asymptomatic increases in amylase or lipase levels for which appropriate evaluation shows no clinical evidence of pancreatitis.

Immune-related adverse events (irAEs) are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

While rules for adjudicating DLTs are specified above, an AE that is Grade < 3 or listed as exempt above may also be defined as DLT after consultation with the Sponsor and Investigators, based on the emerging safety profiles of durvalumab and tremelimumab in combination with chemoradiotherapy. Likewise, subjects who become not evaluable for DLT, because they discontinued or interrupted treatment due to toxicities other than DLTs, may be counted as DLT

subjects, if the toxicities cannot be managed in accordance with the dosing modifications described in Section 3.1.8.

Subjects who experience a DLT will be allowed to continue on study at a lower dose level only after discussion with the Chief Investigator and Sponsor. Otherwise subjects will be discontinued from study therapy and will enter the On Study Follow-up phase of the study (see Study Flowchart, Section 3.2).

The MTD will not be determined in this study.

3.1.10 Subject Withdrawal

A subject experiencing any of the following will be withdrawn from the relevant study treatment:

1. Withdrawal of consent for further treatment.
2. Pregnancy or intent to become pregnant.
3. Dose-limiting toxicity that precludes re-treatment at a lower dose (see Section 3.1.9 for definition of DLT and permitted continuation).
4. Grade ≥ 3 infusion reaction to durvalumab or durvalumab + tremelimumab
5. Confirmation of progressive disease requiring alternative treatment.
6. Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal.
7. Development of intercurrent, non-cancer related illnesses or complications that prevent either continuation of therapy or regular follow up.
8. Best medical interest of the subject (at the discretion of the Investigator)

Discontinuation from receiving study treatment does not mean that the subject is withdrawn from the study. Subjects who are withdrawn from the study treatment should enter the On Study Follow-up (see Section 3.1.16), if feasible. Subjects who begin other anti-cancer therapy should immediately be considered off-study and proceed to the Post Study Follow-up (Section 3.1.16).

A subject will be withdrawn from the study for the following reasons:

1. Best medical interest of the subject at the discretion of the Investigator
2. Initiation of alternative anticancer therapy (marketed or investigational)
3. Withdrawal of consent for all follow-up.
4. Lost to follow-up.
5. Death.

General subject withdrawal criteria are outlined in the Administrative, Legal and Ethical Requirements section of the Protocol (see Section 7). See also Sections 8.5 and 8.6 and 8.7 for treatment withdrawal due to necessary dosing interruptions or discontinuations.

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

3.1.10.1 Treatment Beyond Progression

Subjects in Cohorts A and B meeting criteria for progression (Section 8.8) will be allowed to continue on therapy until confirmation of progression as long as the following criteria are met at the discretion of the Investigator:

a. Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression;
b. No significant decline in ECOG performance status;
c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

See Section 8.8 for additional information regarding RECIST 1.1 and irRECIST.

3.1.11 Subject Replacements

In the *dose escalation phase*, subjects are fully evaluable for DLT if they fulfill the criteria for the Per-Protocol Population for DLT Assessment (as defined in Section 4.1.2).

In Cohorts A1 and A2, subjects who are not evaluable for DLT will be replaced.

Subjects who are not considered fully evaluable for the primary objective of overall safety and tolerability per Section 4.1.2 may be replaced.

3.1.12 Optional Study Treatment Extension

For Cohorts C/C-FLOT and D/D2, subjects will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this is within 3 months of surgery. Subjects in Cohort C-FLOT may receive durvalumab, FLOT, or durvalumab plus FLOT at the discretion of the Investigator.

3.1.13 Interim Analysis

No formal interim analyses will be performed, except for the cohort safety assessments for DLTs in Cohorts A1, and A2 (see Section 3.1.9).

3.1.14 Safety Monitoring and Study Stopping Rules

In accordance with the Administrative, Legal and Ethical Requirements section of the protocol (see Section 7), Safety Monitoring will be performed by an internal data safety monitoring panel, consisting of the Principal Investigators (and Co-investigators as needed), the sponsor Medical Monitor, and drug safety personnel from Medimmune, provider of the study drugs. Additional investigators and staff, or additional sponsor personnel and consultants, shall participate in reviews as indicated. An Independent Data Monitoring Board (IDMB) will not be utilized for this open label study.

For Cohorts C/C-FLOT and D/D2, subjects undergoing surgery will also be closely monitored for post-operative complications (compared with outcomes in the Oxford Oesophago-Gastric Surgical Database).

The study will be suspended or possibly stopped prematurely for any of the following reasons:

1. A death that is unexpected and at least probably related to durvalumab, tremelimumab, or to the combination of durvalumab or durvalumab and tremelimumab with chemo(radio)therapy.
2. Severe anaphylactic reaction (i.e., with respiratory and cardiovascular failure) to durvalumab or durvalumab and tremelimumab in any subject.
3. Any events that, in the judgment of the Medical Monitor, are deemed serious enough to warrant immediate review by the internal data safety monitoring panel. This may include any symptomatic and/or irreversible treatment-related Grade 4 pneumonitis, colitis, dermatitis, or hepatitis or any symptomatic treatment-related Grade ≥3 neurological toxicity or uveitis.
4. Any other safety finding assessed as related to durvalumab, durvalumab and tremelimumab, or chemo(radio)therapy that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.
5. Any interim findings that, in the opinion of the Investigators and the sponsor, suggest that the study treatment has no clinical benefit for the subjects.

If the study is suspended, dosing may not resume before obtaining approval of a substantial amendment from the Competent Regulatory Authority.

General criteria for premature trial termination are outlined in the Administrative, Legal and Ethical Requirements section of the protocol.

3.1.15 Duration of Study

Recruitment will take 6 months for Cohort A1, 6 months for Cohort A2, increasing by a further 6 months if alternative doses need to be explored, and 1 year for Cohorts B and C/C-FLOT. Cohort D/D2 will require 15 months to recruit. Treatment duration will be approximately 6 months (not accounting for maintenance durvalumab given post-operatively) and follow-up is likely to require a further 1 to 2 years depending upon efficacy. Total study duration (to LPLV) is therefore predicted to be 4 to 5 years, although useful data will emerge within 12-15 months.

Duration of Treatment:	Up to 6 months for individual subjects (plus a further 6 months if on maintenance durvalumab)
Enrollment Period:	30 months
Length of Study:	5 years NOTE: Per Amendment 8, all post study follow-up for the collection of survival data will be discontinued as of 30 June 2022 (see rationale in Section 8.1, Amendment 8 on Page 96).

3.1.16 On Study and Post Study Follow-up

All subjects, whether they complete the study as planned, discontinue treatment, or prematurely withdraw from the study per Sections 3.1.10 and 7.2.7, will be followed per institutional guidelines in accordance with the usual standard of care principles.

For all subjects who complete study treatment or who discontinue treatment prematurely according to Section 3.1.10, there will be an On Study Follow-up period for 110 days after the last study drug treatment, which will include collection of AE data.

NOTE: For each of the cohorts, additional details regarding the On Study Follow-up period are provided in Section 7.1.5.

See Section 7.1.5 for information on recording AEs during the On Study Follow-up.

If the determination is made to remove a subject from treatment at a visit that coincides with the first On Study Follow-up visit (which is 14 days after the last dose of study treatment), any assessments required in the first On Study Follow-up visit that are not covered as part of the last on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the last on-treatment visit and the first On Study Follow-up visit should not be repeated.

Refer to Flowchart in Section 3.2 for post treatment biopsies. If the subject discontinues from treatment early, the biopsy specimen should be collected at the last study visit or the first On Study Follow-up visit.

Following the On Study Follow-up, there will be a Post Study Follow-up, where, clinical outcomes data (dates of progression/relapse and survival) will be collected at least every 6 months for up to 3 years from the initiation of the treatment.

The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 110 days since the last administration of study drug.

For subjects who do not continue Post Study Follow-up at one of the study sites after the end of study, the Principal Investigators or the clinical team, under the supervision of the Principal Investigator, will obtain this data through review of outside records or communication with the subject or his/her physician.

NOTE: Per Amendment 8, all post study follow-up for the collection of survival data will be discontinued as of 30 June 2022 (see rationale in Section 8.1, Amendment 8 on Page 96).

3.1.16.1 End of Study Visit

If a subject is **withdrawn from study** according to the criteria defined in Section 3.1.10, an End of Study visit must be conducted at the time of withdrawal. For subjects not yet in On Study Follow-up, this End of Study visit will be the first planned visit of the On Study Follow-up. For subjects already in On Study Follow-up, this End of Study visit will be the next planned visit of the On Study Follow-up. However, any procedures/assessments that were done within 7 days of the End of Study visit need not be repeated. All subjects of childbearing potential who withdraw from study must have a serum pregnancy test done at the End of Study visit, unless it was done within 7 days prior to the End of Study Visit.

After the End of Study Visit, the subject will proceed into Post Study Follow-up as described above, unless otherwise unable to do so (e.g., subject withdraws consent for all follow-up).

3.2 Study Flowcharts

3.2.1 Study Flowchart for All Cohorts Except Cohort C-FLOT and Cohort D2

LUD2015-005 Study Flowchart for all Cohorts except C-FLOT and D2 Part 1	Screening / Baseline	Treatment												
		Immunotherapy Only Period (4 weeks)				Cycle 1 (3 weeks)			Cycle 2 (3 weeks)			Cycle 3 (3 weeks)		
Cycle week		1	2	3	4	1	2	3	1	2	3	1	2	3
Visit Day per Cycle		1	8(±3)	15(±3)	22(±3)	1(±3)	8(±3)	15(±3)	1(±3)	8(±3)	15(±3)	1(±3)	8(±3)	15(±3)
Cumulative Study Week		1	2	3	4	5	6	7	8	9	10	11	12	13
Cumulative Study Day	-28 to -1	1	8	15	22	29	36	43	50	57	64	71	78	85
Treatment for Cohort A1/Cohort B[J]														
Durvalumab		X		X		X		X		X		X		X
Oxaliplatin						X			X			X		
Capecitabine						Daily			Daily			Daily		
Treatment for Cohort A2/Cohort B[J]														
Durvalumab		X		X		X		X		X		X		X
Tremelimumab		X												
Oxaliplatin						X			X			X		
Capecitabine						Daily			Daily			Daily		
Treatment for Cohort C - see separate flowchart for Cohort C-FLOT														
Durvalumab		X		X		X		X		X				
Oxaliplatin						X			X					
Capecitabine						Daily			Daily					
Surgery - 6 to 8 weeks after completion of therapy or according to institutional policies for surgery[p]														
Treatment for Cohort D - see separate flowchart for Cohort D2														
Durvalumab for Cohort D[L]		X		X							X[L]			
Paclitaxel						X	X	X	X	X				
Carboplatin						X	X	X	X	X				
Radiotherapy (41.4 Gy over 23 fractions)								X						
Surgery - 6 to 8 weeks after completion of therapy or according to institutional policies for surgery[p]														
Tumour & Disease Assessments														
CT for Cohorts A1, A2, and B[o]	X						X						X	
PET/CT for Cohorts C and D[n,o]	X											X		
Study Procedures and Examinations														
Eligibility Assessment and Informed Consent (IC)[K]	X													
Demographics (incl. DoB; sex; height; race; ethnicity)	X													
Medical history	X													
Physical Exam (incl weight and ECOG Perf Status)[b]	X	X		X		X	X	X	X	X	X[L]	X		X
ECG (and as clinically indicated after Day 1)[m]	X	X												
Vital Signs (T, HR, BP, RR)[e]	X	X		X		X	X	X	X	X	X[L]	X		X
Concomitant Medication /Procedure[g, p]	X	X	X	X	X	X	X	X	X	X	X[L]	X	X	X
Adverse Events (starting or worsening after IC)[d,g,p]	X	X	X	X	X	X	X	X	X	X	X[L]	X	X	X
Routine Lab Specimens														
Blood Hematology (complete blood count, differential, platelets)[a]	X	X		X		X	X	X	X	X	X[L]	X		X
Chemistry (gluc., BUN, creat., Na, K, Cl, CO_2, Ca, PO_4, Mg, prot., alb., TBili., AST, ALT, ALP, GGT, LDH, Free T_3, Free T_4, TSH)[a]	X	X		X		X	Coh D only	X	Coh D only	X	X[L]	X		X
Chemistry cont. (amylase and lipase)[a]	X	X		X		X		X		X	X[L]	X		X
Urinalysis[a]	X	X		X		X		X		X	X[L]	X		X
Coagulation parameters[f]	X													
Serum pregnancy test[a]	-7 to -1 days													
Urine pregnancy test[a]		X				X				X	X[L]			X
Blood for Correlative Immune Monitoring														
Total Lymph, CD4/5/8 T-cell counts; Phenotyping of T-cell/B-cell/NK cell subsets, flow cytometry; Activated T-cell expression markers, % Tregs, Treg to effector cell ratio; Myeloid derived suppressor cells; serum cytokine profiling[r]	X			X[a]				X[a]						
Tumour Biopsy Sample Collections														
Tumour infiltrating lymphocytes; PD-1 expressing lymphocytes; measurement of tumour/stromal cell PD-L1 expression	X				X									
Genomic investigations	X				X									
Saliva samples and photographs[q]	X				X									

LUD2015-005 Study Flowchart for all Cohorts except C-FLOT and D2 Part 2	Treatment												On Study Follow-up[d, p]				Post Study Follow-up[s]
	Cycle 4 (3 weeks)			Cycle 5 (3 weeks)			Cycle 6 (4weeks)				Post Surgery Durvalumab[c] (4 week cycle)						
Cycle week	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**4**	**1**	**3**	Last Study Drug Dose +14(±4) days	Last Study Drug Dose +42 (±7) days	Last Study Drug Dose +91(±7) days	Last Study Drug Dose +110(±7) days	Every 6 months for up to 3 years post initiation of treatment(see footnote "s"). Telephone contact or medical record review to include clinical outcomes data (dates of progression/relapse and survival).
Visit Day per Cycle	1(±3)	8(±3)	15(±3)	1(±3)	8(±3)	15(±3)	1(±3)	8(±3)	15(±3)	22(±3)	1(±3)	15(±3)					
Cumulative Study Week	14	15	16	17	18	19	20	21	22	23							
Cumulative Study Day	92	99	106	113	120	127	134	141	148	155							
Treatment for Cohort A1/Cohort B[J]																	
Durvalumab		X		X		X		X									
Oxaliplatin	X			X			X										
Capecitabine	Daily			Daily			Daily										
Treatment for Cohort A2/Cohort B[J]																	
Durvalumab		X		X		X		X									
Tremelimumab																	
Oxaliplatin	X			X			X										
Capecitabine	Daily			Daily			Daily										
Treatment for Cohort C - see separate flowchart for Cohort C-FLOT																	
Durvalumab											X[c]	X[c]					
Oxaliplatin																	
Capecitabine																	
Surgery - 6 to 8 weeks after completion of therapy or according to institutional policies for surgery[p]			X														
Treatment for Cohort D - see separate flowchart for Cohort D2																	
Durvalumab for Cohort D[L]											X[c]	X[c]					
Paclitaxel																	
Carboplatin																	
Radiotherapy (41.4 Gy over 23 fractions)																	
Surgery - 6 to 8 weeks after completion of therapy or according to institutional policies for surgery[p]			X														
Tumour & Disease Assessments																	
CT for Cohorts A1, A2, and B[o]					X					X[h]							
PET/CT for Cohorts C and D[n,o]											X		X				
Study Procedures and Examinations																	
Eligibility Assessment and Informed Consent (IC)[K]																	
Demographics (incl. DoB; sex; height; race; ethnicity)																	
Medical history																	
Physical Exam (incl weight and ECOG Perf Status)[b]	X	X		X		X	X	X			X[c]	X[c]	X	X	X	X	
ECG (and as clinically indicated after Day 1)[m]													X				
Vital Signs (T, HR, BP, RR)[e]	X	X		X		X	X	X			X[c]	X[c]	X	X	X	X	
Concomitant Medication /Procedure[g, p]	X	X	X	X	X	X	X	X	X	X	X[c]	X[c]	X	X	X	X	
Adverse Events (starting or worsening after IC)[d,g,p]	X	X	X	X	X	X	X	X	X	X	X[c]	X[c]	X	X	X	X	
Routine Lab Specimens																	
Blood Hematology (complete blood count, differential, platelets)[a]	X	X		X		X	X	X			X[a,c]	X[a,c]	X	X	X	X	
Chemistry (gluc., BUN, creat., Na, K, Cl, CO_2, Ca, PO_4, Mg, prot., alb., TBili., AST, ALT, ALP, GGT, LDH, Free T_3, Free T_4, TSH)[a]		X		X		X		X			X[a,c]	X[a,c]	X	X	X	X	
Chemistry cont. (amylase and lipase)[a]		X		X		X		X			X[a,c]	X[a,c]	X	X	X	X	
Urinalysis[a]		X		X		X		X			X[a,c]	X[a,c]	X	X	X	X	
Coagulation parameters[f]																	
Serum pregnancy test[a]																	
Urine pregnancy test[a]				X				X			X[a,c]		X	X	X	X	
Blood for Correlative Immune Monitoring																	
Total Lymph, CD4/5/8 T-cell counts; Phenotyping of T-cell/B-cell/NK cell subsets, flow cytometry; Activated T-cell expression markers, % Tregs, Treg to effector cell ratio; Myeloid derived suppressor cells; serum cytokine profiling[r]				X[i]						X[h]						X[r]	
Tumour Biopsy Sample Collections																	
Tumour infiltrating lymphocytes; PD-1 expressing lymphocytes; measurement of tumour/stromal cell PD-L1 expression				X[i]						X[h]							
Genomic investigations				X[i]						X[h]							
Saliva samples and photographs[q]				X[i]						X[h]							

Flowchart Footnotes for all Cohorts except C-FLOT and D2:
a- Pre-dose; record times as well as dates. If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Day 1 lab assessments may be performed within 3 days prior to Day 1. Results for safety blood tests (chem, hematology, and pregnancy [when applicable]) must be available and reviewed before commencing an infusion. GGT tested at Screening, Day 1 and as clinically indicated. For each on-treatment cohort, hematology, chem, urine & pregnancy safety assessments should coincide with drug administration study visits. With the exception of On Study Follow-up, Lab assessments are not applicable if there is no drug administration visit for a particular cohort. End of study pregnancy test for women of child-bearing potential must be done on serum.
b- Full physical examination (including neurological exam) at baseline; targeted physical examination (including neurological exam) at other time points For each on-treatment cohort, physical exams should coincide with drug administration study visits. With the exception of On Study Follow-up, physical exams are not applicable if there is no drug administration visit for a particular cohort.
c- Cohorts C and D will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided this is within 3 months of surgery.
d- See Section 7.1.5 for details on collection of AEs during On Study Follow-up
e- For each on-treatment cohort, vital signs assessments should coincide with drug administration study visits. With the exception of On Study Follow-up, vital sign assessments are not applicable if there is no drug administration visit for a particular cohort. For durva and treme, vital signs are measured before, during and after infusions according to Section 6.11.
f - Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated; record times as well as dates.
g - Concomitant med and AE information may be collected by telephone if there is no study drug administration/lab test/scan/procedure visit scheduled.
h - Post treatment for Coh A and B (a window of -7 to +14 days is allowed). If subject discontinues from treatment early, include at last study visit or first On Study follow-up
i - On day of surgery for Cohorts C and D (blood draw must be pre-surgery and may be up 3 days before). If subject discontinues from treatment early, include at last study visit or first On Study follow-up.
J- Once Cohort A1 is cleared, a safety review / decision will be made whether to start Cohort A2; A safety review will also determine whether the RCD of Cohort A1 or A2 will be used for Cohort B.
K- A screening log must be kept of all subjects considered for the study including any that are subsequently excluded; reason for exclusion must be recorded on this form. A copy of the screening log should be sent to the trial office on request, but without subject identifiers. The original must be retained on site, Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart
L- Cohort D: Subjects will discontinue durvalumab after Week 3; a dose of durvalumab will be given following chemoradiotherapy on Day 64 (±3 days). If the subject has not completely recovered (per Investigator assessment) by Day 64 (±3 days), the durvalumab dose may be delayed until Day 71 (±3 days). Lab assessments, pregnancy test and safety assessments should be done on the day (64 or 71) the durvalumab dose is given.
m - 12 Lead ECG - baseline and abnormal ECG at any time will be done in triplicate (2-5 minutes apart); others may be single measurements.
n - PET/CT scan for Cohorts C and D: Scan scheduled after completion of therapy/before surgery may be combined as part of the surgery workup or per local institutional standards. Post surgery scan may be done at first post surgery treatment visit. PET scan at the post-surgery and On-Study Follow-Up timepoints may be replaced with a CT scan.
o -Scans should be done per local institutional standards and reported per irRECIST/RECIST 1.1 guidance. See Sections 4.2.1 and 8.8 and eCRF. Scanning protocols and modalities should remain consistent throughout the study.
p -For subjects in Cohorts C and D: 1. All AEs will be collected for 110 days after the last dose of pre-surgery durva, with the exception of those AEs that are related to the protocol-defined surgical procedure(s). If the decision is made that a subject will not receive continued durva, the subject must start On Study Follow-up and have at least one On Study Follow-up visit at 110 days (+30 days) after last dose of durva or at the point of the decision (+30 days), whichever is later. 2. If any subjects in Cohorts C and D continue durva treatment after the planned surgical procedure, they will follow the On Study Follow-up period according to the Flowchart, and all AEs will be collected for 110 days after the last dose of durva. See Section 7.1.5 for details on Cohorts A and B
q - Saliva samples may be collected at each biopsy collection time point; photographs at endoscopy may be taken.
r - The Investigator(s) have the option to approach subjects with long-term survival (PFS > 1 year, still in remission) from the metastatic cohorts (A and B) to request blood (up to 300 mL) for additional testing as described in Section 2.3.
s - Per Amendment 8, all post study follow-up for the collection of survival data will be discontinued as of 30Jun2022 (see Section 8.1, Amendment 8).

3.2.2 Study Flowchart for Cohort C-FLOT

LUD2015-005 Study Flowchart for Cohort C-FLOT Part 1	Screening / Baseline	Treatment							
		Immunotherapy Only Period (4 weeks)				Cycle 1 (4 weeks)		Cycle 2 (4 weeks)	
Cycle week		**1**	**2**	**3**	**4**	**1**	**3**	**1**	**3**
Visit Day per Cycle		1	8(±3)	15(±3)	22(±3)	1(±3)	15(±3)	1(±3)	15(±3)
Cumulative Study Week		1	2	3	4	5	7	9	11
Cumulative Study Day	-28 to -1	1	8	15	22	29	43	57	71
Treatment for Cohort C-FLOT									
Durvalumab		X		X		X	X	X	X
5-Fluorouracil						X	X	X	X
Leucovorin						X	X	X	X
Oxaliplatin						X	X	X	X
Docetaxel						X	X	X	X
Surgery - 6 to 8 weeks after completion of therapy or according to institutional policies for surgery[K]									
Tumour & Disease Assessments									
PET/CT scan[L]	X								
Study Procedures and Examinations									
Eligibility Assessment and Informed Consent (IC)[J]	X								
Demographics (incl. DoB; sex; height; race; ethnicity)	X								
Medical history	X								
Physical Exam (incl weight and ECOG Perf Status)[b]	X	X		X		X	X	X	X
ECG (and as clinically indicated after Day 1)[h]	X	X							
Vital Signs (T, HR, BP, RR)[e]	X	X		X		X	X	X	X
Concomitant Medication /Procedure[g, K]	X	X	X	X	X	X	X	X	X
Adverse Events (starting or worsening after IC)[d,g,K]	X	X	X	X	X	X	X	X	X
Routine Lab Specimens									
Blood Hematology (complete blood count, differential, platelets)[a]	X	X		X		X	X	X	X
Chemistry (gluc., BUN, creat., Na, K, Cl, CO_2, Ca, PO_4, Mg, prot., alb., TBili., AST, ALT, ALP, GGT, LDH, Free T_3, Free T_4, TSH)[a]	X	X		X		X	X	X	X
Chemistry cont. (amylase and lipase)[a]	X	X		X		X	X	X	X
Urinalysis[a]	X	X		X		X	X	X	X
Coagulation parameters[f]	X								
Serum pregnancy test[a]	-7 to -1 days								
Urine pregnancy test[a]		X				X		X	
Blood for Correlative Immune Monitoring									
Total Lymph, CD4/5/8 T-cell counts; Phenotyping of T-cell/B-cell/NK cell subsets, flow cytometry; Activated T-cell expression markers, % Tregs, Treg to effector cell ratio; Myeloid derived suppressor cells; serum cytokine profiling	X			X[a]			X[a]		
Tumour Biopsy Sample Collections									
Tumour infiltrating lymphocytes; PD-1 expressing lymphocytes; measurement of tumour/stromal cell PD-L1 expression	X				X				
Genomic investigations	X				X				
Saliva samples and photographs[m]	X				X				

LUD2015-005 Study Flowchart for Cohort C-FLOT Part 2	Treatment			On Study Follow-up[d,K]				Post Study Follow-up[n]
	Surgery	Post Surgery treatment[c] (4 week cycle)						
Cycle week		1	3	Last Study Drug Dose +14(±4) days[K-3]	Last Study Drug Dose +42 (±7) days	Last Study Drug Dose +91(±7) days	Last Study Drug Dose +110(±7) days	Every 6 months for up to 3 years post initiation of treatment. (See footnote "n") Telephone contact or medical record review to include clinical outcomes data (dates of progression/relapse and survival).
Visit Day per Cycle		1(±3)	15(±3)					
Cumulative Study Week								
Cumulative Study Day								
Treatment for Cohort C-FLOT								
Durvalumab		X[c]	X[c]					
5-Fluorouracil		X[c]	X[c]					
Leucovorin		X[c]	X[c]					
Oxaliplatin		X[c]	X[c]					
Docetaxel		X[c]	X[c]					
Surgery - 6 to 8 weeks after completion of therapy or according to institutional policies for surgery[K]	X							
Tumour & Disease Assessments								
PET/CT scan[L]	X	X		X				
Study Procedures and Examinations								
Eligibility Assessment and Informed Consent (IC)[J]								
Demographics (incl. DoB; sex; height; race; ethnicity)								
Medical history								
Physical Exam (incl weight and ECOG Perf Status)[b]		X[c]	X[c]	X	X	X	X	
ECG (and as clinically indicated after Day 1)[h]				X				
Vital Signs (T, HR, BP, RR)[e]		X[c]	X[c]	X	X	X	X	
Concomitant Medication /Procedure[g, K]	X	X[c]	X[c]	X	X	X	X	
Adverse Events (starting or worsening after IC)[d,g,K]	X	X[c]	X[c]	X	X	X	X	
Routine Lab Specimens								
Blood Hematology (complete blood count, differential, platelets)[a]		X[a,c]	X[a,c]	X	X	X	X	
Chemistry (gluc., BUN, creat., Na, K, Cl, CO_2, Ca, PO_4, Mg, prot., alb., TBili., AST, ALT, ALP, GGT, LDH, Free T_3, Free T_4, TSH)[a]		X[a,c]	X[a,c]	X	X	X	X	
Chemistry cont. (amylase and lipase)[a]		X[a,c]	X[a,c]	X	X	X	X	
Urinalysis[a]		X[a,c]	X[a,c]	X	X	X	X	
Coagulation parameters[f]								
Serum pregnancy test[a]								
Urine pregnancy test[a]		X[a,c]		X	X	X	X	
Blood for Correlative Immune Monitoring								
Total Lymph, CD4/5/8 T-cell counts; Phenotyping of T-cell/B-cell/NK cell subsets, flow cytometry; Activated T-cell expression markers, % Tregs, Treg to effector cell ratio; Myeloid derived suppressor cells; serum cytokine profiling	X[i]							
Tumour Biopsy Sample Collections								
Tumour infiltrating lymphocytes; PD-1 expressing lymphocytes; measurement of tumour/stromal cell PD-L1 expression	X[i]							
Genomic investigations	X[i]							
Saliva samples and photographs[m]	X[i]							

Flowchart Footnotes for Cohort C-FLOT:
a- Pre-dose; record times as well as dates. If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety blood tests (chem, hematology, and pregnancy [when applicable]) must be available and reviewed before commencing an infusion. GGT tested at Screening, Day 1 and as clinically indicated. For each on-treatment cohort, hematology, chem, urine & pregnancy safety assessments should coincide with drug administration study visits. With the exception of On Study Follow-up, Lab assessments are not applicable if there is no drug administration visit for a particular cohort. End of study pregnancy test for women of child-bearing potential must be done on serum.
b- Full physical examination (including neurological exam) at baseline; targeted physical examination (including neurological exam) at other time points For each on-treatment cohort, physical exams should coincide with drug administration study visits. With the exception of On Study Follow-up, physical exams are not applicable if there is no drug administration visit for a particular cohort.
c- Cohort C-FLOT will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided this is within 3 months of surgery. Subjects in Cohort C-FLOT may receive durvalumab, FLOT, or durvalumab plus FLOT at the discretion of the investigator.
d- See Section 7.1.5 for details on collection of AEs during On Study Follow-up
e- Vital signs assessments should coincide with drug administration study visits. With the exception of On Study Follow-up, vital sign assessments are not applicable if there is no drug administration visit. For durvalumab, vital signs are measured before, during and after infusions according to Section 6.11.
f - Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated; record times as well as dates.
g - Concomitant med and AE information may be collected by telephone if there is no study drug administration/lab test/scan/procedure visit scheduled.
h - 12 Lead ECG - baseline and abnormal ECG at any time will be done in triplicate (2-5 minutes apart); others may be single measurements.
i - On day of surgery (blood draw must be pre-surgery and may be up to 3 days before). If subject discontinues from treatment early, include at last study visit or first On Study follow-up.
J- A screening log must be kept of all subjects considered for the study including any that are subsequently excluded; reason for exclusion must be recorded on this form. A copy of the screening log should be sent to the trial office on request, but without subject identifiers. The original must be retained on site, Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart
K -For subjects in Cohort C-FLOT: 1. All AEs will be collected for 110 days after the last dose of pre-surgery durvalumab, with the exception of those AEs that are related to the protocol-defined surgical procedure(s). If the decision is made that a subject will not receive continued durvalumab, the subject must start On Study Follow-up and have at least one On Study Follow-up visit at 110 days (+30 days) after last dose of durvalumab or at the point of the decision (+30 days), whichever is later. 2. If any subjects in Cohort C-FLOT continue durvalumab treatment after the planned surgical procedure, they will follow the On Study Follow-up period according to the Flowchart, and all AEs will be collected for 110 days after the last dose of durvalumab. 3. If any subjects continue FLOT treatment alone (no durva) after the planned surgical procedure, they will complete the first On Study Follow-up at Day 28 (+14 days) post last dose of FLOT. All AEs will be collected for at least 28 (+14) days after the last dose of FLOT; however, point #1 must still be followed for a visit post last dose of durvalumab.
L - PET/CT scan for Cohort C-FLOT: Scan scheduled after completion of therapy/before surgery may be combined as part of the surgery workup or per local institutional standards. Post surgery scan may be done at first post surgery-treatment-visit. PET scan at the post-surgery and On-Study Follow-Up timepoints may be replaced with a CT scan. Scans should be done per local institutional standards and reported per irRECIST/RECIST 1.1 guidance. See Sections 4.2.1 and 8.8 and eCRF. Scanning protocols and modalities should remain consistent throughout the study.
m - Saliva samples may be collected at each biopsy collection time point; photographs at endoscopy may be taken.
n - Per Amendment 8, all post study follow-up for the collection of survival data will be discontinued as of 30Jun2022 (see Section 8.1, Amendment 8).

3.2.3 Study Flowchart for Cohort D2

LUD2015-005 Study Flowchart for Cohort D2 Part 1	Screening / Baseline	Treatment								
		Immunotherapy Only Period (4 weeks)				Cycle 1 (3 weeks)			Cycle 2 (2 weeks)	
Cycle week		**1**	**2**	**3**	**4**	**1**	**2**	**3**	**1**	**2**
Visit Day per Cycle		1	8(±3)	15(±3)	22(±3)	1(±3)	8(±3)	15(±3)	1(±3)	8(±3)
Cumulative Study Week		1	2	3	4	5	6	7	8	9
Cumulative Study Day	-28 to -1	1	8	15	22	29	36	43	50	57
Treatment for Cohort D2										
Durvalumab for Cohort D2		X		X		X		X		X
Paclitaxel						X	X	X	X	X
Carboplatin						X	X	X	X	X
Radiotherapy (41.4 Gy over 23 fractions)								X		
Surgery: 6 to 8 weeks after completion of therapy or according to institutional policies for surgery[k]										
Tumour & Disease Assessments										
PET/CT for Cohort D2[L]	X									
Study Procedures and Examinations										
Eligibility Assessment and Informed Consent (IC)[J]	X									
Demographics (incl. DoB; sex; height; race; ethnicity)	X									
Medical history	X									
Physical Exam (incl weight and ECOG Perf Status)[b]	X	X		X		X	X	X	X	X
ECG (and as clinically indicated after Day 1)[h]	X	X								
Vital Signs (T, HR, BP, RR)[e]	X	X		X		X	X	X	X	X
Concomitant Medication /Procedure[g, k]	X	X	X[g]	X	X	X	X	X	X	X
Adverse Events (starting or worsening after IC)[d,g,k]	X	X	X[g]	X	X	X	X	X	X	X
Routine Lab Specimens										
Blood Hematology (complete blood count, differential, platelets)[a]	X	X		X		X	X	X	X	X
Chemistry (gluc., BUN, creat., Na, K, Cl, CO_2, Ca, PO_4, Mg, prot., alb., TBili., AST, ALT, ALP, GGT, LDH, Free T_3, Free T_4, TSH)[a]	X	X		X		X	X	X	X	X
Chemistry cont. (amylase and lipase)[a]	X	X		X		X		X		X
Urinalysis[a]	X	X		X		X		X		X
Coagulation parameters[f]	X									
Serum pregnancy test[a]	-7 to -1 days									
Urine pregnancy test[a]		X				X				X
Blood for Correlative Immune Monitoring										
Total Lymph, CD4/5/8 T-cell counts; Phenotyping of T-cell/B-cell/NK cell subsets, flow cytometry; Activated T-cell expression markers, % Tregs, Treg to effector cell ratio; Myeloid derived suppressor cells; serum cytokine profiling	X			X[a]				X[a]		
Tumour Biopsy Sample Collections										
Tumour infiltrating lymphocytes; PD-1 expressing lymphocytes; measurement of tumour/stromal cell PD-L1 expression	X				X					
Genomic investigations	X				X					
Saliva samples and photographs[m]	X				X					

LUD2015-005 Study Flowchart for Cohort D2 Part 2	Treatment					On Study Follow-up[d, k]				Post Study Follow-up[o]
	Post Treatment Safety Assessments[n]		Surgery	Post Surgery Durvalumab[c] (4 week cycle)						
Cycle week	4 (±1) weeks post last dose	up to 2 weeks pre surgery		1	3	Last Study Drug Dose +14(±4) days	Last Study Drug Dose +42 (±7) days	Last Study Drug Dose +91(±7) days	Last Study Drug Dose +110(±7) days	Every 6 months for up to 3 years post initiation of treatment. (see footnote "o") Telephone contact or medical record review to include clinical outcomes data (dates of progression/relapse and survival).
Visit Day per Cycle				1(±3)	15(±3)					
Cumulative Study Week										
Cumulative Study Day										
Treatment for Cohort D2										
Durvalumab for Cohort D2				x[c]	x[c]					
Paclitaxel										
Carboplatin										
Radiotherapy (41.4 Gy over 23 fractions)										
Surgery: 6 to 8 weeks after completion of therapy or according to institutional policies for surgery[k]			x							
Tumour & Disease Assessments										
PET/CT for Cohort D2[L]			x	x		x				
Study Procedures and Examinations										
Eligibility Assessment and Informed Consent (IC)[J]										
Demographics (incl. DoB; sex; height; race; ethnicity)										
Medical history										
Physical Exam (incl weight and ECOG Perf Status)[b]	x	x		x[c]	x[c]	x	x	x	x	
ECG (and as clinically indicated after Day 1)[h]						x				
Vital Signs (T, HR, BP, RR)[e]	x	x		x[c]	x[c]	x	x	x	x	
Concomitant Medication /Procedure[g, k]	x	x	x	x[c]	x[c]	x	x	x	x	
Adverse Events (starting or worsening after IC)[d,g,k]	x	x	x	x[c]	x[c]	x	x	x	x	
Routine Lab Specimens										
Blood Hematology (complete blood count, differential, platelets)[a]	x	x		x[a,c]	x[a,c]	x	x	x	x	
Chemistry (gluc., BUN, creat., Na, K, Cl, CO_2, Ca, PO_4, Mg, prot., alb., TBili., AST, ALT, ALP, GGT, LDH, Free T_3, Free T_4, TSH)[a]	x	x		x[a,c]	x[a,c]	x	x	x	x	
Chemistry cont. (amylase and lipase)[a]	x	x		x[a,c]	x[a,c]	x	x	x	x	
Urinalysis[a]	x	x		x[a,c]	x[a,c]	x	x	x	x	
Coagulation parameters[f]										
Serum pregnancy test[a]										
Urine pregnancy test[a]	x	x		x[a,c]		x	x	x	x	
Blood for Correlative Immune Monitoring										
Total Lymph, CD4/5/8 T-cell counts; Phenotyping of T-cell/B-cell/NK cell subsets, flow cytometry; Activated T-cell expression markers, % Tregs, Treg to effector cell ratio; Myeloid derived suppressor cells; serum cytokine profiling			x[i]							
Tumour Biopsy Sample Collections										
Tumour infiltrating lymphocytes; PD-1 expressing lymphocytes; measurement of tumour/stromal cell PD-L1 expression			x[i]							
Genomic investigations			x[i]							
Saliva samples and photographs[m]			x[i]							

Flowchart Footnotes for Cohort D2:
a- Pre-dose; record times as well as dates. If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Day 1 lab assessments may be performed within 3 days prior to Day 1. Results for safety blood tests (chem, hematology, and pregnancy [when applicable]) must be available and reviewed before commencing an infusion. GGT tested at Screening, Day 1 and as clinically indicated. End of study pregnancy test for women of child-bearing potential must be done on serum.
b- Full physical examination (including neurological exam) at baseline; targeted physical examination (including neurological exam) at other time points
c- Cohort D2 subjects will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided this is within 3 months of surgery.
d- See Section 7.1.5 for details on collection of AEs during On Study Follow-up
e- For durvalumab, vital signs are measured before, during and after infusions according to Section 6.11.
f - Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated; record times as well as dates.
g - Concomitant med and AE information may be collected by telephone if there is no study drug administration/lab test/scan/procedure visit scheduled.
h - 12 Lead ECG - baseline and abnormal ECG at any time will be done in triplicate (2-5 minutes apart); others may be single measurements.
i - Collected on day of surgery for Cohort D2 (blood draw must be pre-surgery and may be up 3 days before). If subject discontinues from treatment early, include at last study visit or first On Study follow-up.
J- A screening log must be kept of all subjects considered for the study including any that are subsequently excluded; reason for exclusion must be recorded on this form. A copy of the screening log should be sent to the trial office on request, but without subject identifiers. The original must be retained on site, Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart
K -For subjects in Cohort D2: 1. All AEs will be collected for 110 days after the last dose of pre-surgery durvalumab, with the exception of those AEs that are related to the protocol-defined surgical procedure(s). If the decision is made that a subject will not receive continued durva, the subject must start On Study Follow-up and have at least one On Study Follow-up visit at 110 days (+30 days) after last dose of durvalumab or at the point of the decision (+30 days), whichever is later. 2. If any subjects in Cohort D2 continue durvalumab treatment after the planned surgical procedure, they will follow the On Study Follow-up period according to the Flowchart, and all AEs will be collected for 110 days after the last dose of durvalumab (durva).
L - PET/CT scan for Cohort D2: Scan scheduled after completion of therapy/before surgery may be combined as part of the surgery workup or per local institutional standards. Post surgery scan may be done at first post surgery treatment visit. PET scan at the post-surgery and On-Study Follow-Up timepoints may be replaced with a CT scan. Scans should be done per local institutional standards and reported per irRECIST/RECIST 1.1 guidance. See Sections 4.2.1 and 8.8 and eCRF. Scanning protocols and modalities should remain consistent throughout the study.
m - Saliva samples may be collected at each biopsy collection time point; photographs at endoscopy may be taken.
n - For Cohort D2, the following additional visits are required during which all safety assessments are done and a safety review is conducted: 1. A visit that occurs 4 weeks (± 1 week) after the completion of chemoradiotherapy + durvalumab 2. A pre-surgery visit, up to 2 weeks before surgery Note: During post surgery, there is regular contact between the PI and the surgical staff to assess status and whether post surgery durvalumab will be initiated.
o - Per Amendment 8, all post study follow-up for the collection of survival data will be discontinued as of 30Jun2022 (see Section 8.1, Amendment 8).

4 Study Objectives & Endpoints

Primary Objectives	• Assess the Safety/Tolerability of durvalumab alone and tremelimumab + durvalumab in combination with oxaliplatin / capecitabine chemotherapy in metastatic/locally advanced OC. • Assess the Safety/Tolerability of durvalumab in combination with neoadjuvant chemo(radio)therapy (oxaliplatin/capecitabine, FLOT, and paclitaxel/carboplatin/radiotherapy) before surgery in operable OC. (Endpoint: CTCAE version 4.03)
Secondary Objectives	• Assess the Clinical Efficacy of durvalumab alone and tremelimumab + durvalumab in combination with oxaliplatin/capecitabine chemotherapy in metastatic or locally advanced OC. (Endpoints: Tumor Response by irRECIST, progression-free survival (PFS) and overall survival (OS)) • Assess the Clinical Efficacy of durvalumab in combination with neoadjuvant chemo(radio)therapy (oxaliplatin/capecitabine, FLOT, and paclitaxel/carboplatin/radiotherapy) in operable OC. (Endpoints: PFS after surgery, 1-year survival rate, OS, pathological and metabolic response rate)
Exploratory objective	• Evaluate the immunological effects of durvalumab and tremelimumab + durvalumab in tumor and peripheral blood samples. • Relate the effects of immune modulation to allele variance, gene expression and host-pathogen relationships in the upper gastrointestinal tracts of OC subjects. • Evaluate genomic differences between subjects who exhibit differential immune and therapeutic responses to durvalumab and tremelimumab + durvalumab therapy.

In order to be fully evaluable (per protocol) for the primary endpoint, major protocol violations that interfere with the assessment of the primary endpoint must be absent.

4.1 Safety and Tolerability

The assessment of safety and tolerability will be performed by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls with the investigators.

4.1.1 Endpoints & Assessment Methods

Standard safety evaluation and reporting for early phase trials will be used for Cohorts B, C/C-FLOT, and D/D2. In addition, for Cohorts C/C-FLOT and D/D2, subjects undergoing surgery will be closely monitored for post-operative complications (compared with outcomes in the Oxford Oesophago-Gastric Surgical Database) to evaluate the possibility of an impact.

Laboratory tests, vital sign measurements, physical exams (including neurological exams) and subject interviews will be performed to detect new abnormalities and deteriorations of any pre-existing conditions. The investigator will evaluate any laboratory abnormalities for clinical significance, and clinically significant abnormalities will be recorded as adverse events. All clinically significant abnormalities and deteriorations from time of signing of informed consent to the end of study visit should be recorded in the Case Report Forms as adverse events and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

4.1.2 Subject Evaluation & Statistics

The ***Per-Protocol (PP) Population for DLT Assessment*** is defined as:

- All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9) and
- All subjects with no DLT who received at least 75% of the scheduled doses of durvalumab and chemotherapy or tremelimumab, durvalumab and chemotherapy as well as, respective safety assessments without major protocol violations over the entire DLT Evaluation Period (as defined in Section 3.1.9).

Refer to Section 3.1.11 for subject replacement.

The **Safety Population** is defined as all subjects who receive at least one dose of durvalumab or tremelimumab.

In Phase 1, for the primary endpoint of determining DLTs and the RCD, the analysis of safety and tolerability will be based on the **PP Population for DLT Assessment.**

In both phases, the overall analysis of safety and tolerability will be based on the **Safety Population.**

Appropriate summaries of AEs, laboratory data and vital sign data will be presented. Adverse events will be coded using the MedDRA dictionary. Incidences of treatment-emergent adverse events (TEAE, those events that started after dosing or worsened in severity after dosing) will be presented overall and by maximum severity (according to CTCAE version 4.03) and relationship to study medication.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented by treatment arm for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. Additionally, for each continuous hematology and chemistry parameter, descriptive statistics will be presented by treatment arm for the changes from baseline to each post-treatment assessment time point. Descriptive statistics will be presented by cohort for the changes in vital signs from baseline to each post-treatment assessment time point.

4.2 Clinical Efficacy

Clinical efficacy evaluation will include tumor response assessed by irRECIST, Progression-free Survival (PFS), Overall Survival (OS), and Objective Response Rate (ORR). In addition, metabolic response on PET scanning and histological response in resection specimens will be assessed in Cohorts C/C-FLOT and D/D2.

4.2.1 Endpoints & Assessment Methods

Clinical Efficacy is determined by measuring the PFS, response (objective, metabolic and histologic), and OS. Every attempt should be made to use whichever imaging technique(s) and test(s) are used initially for repeat evaluations throughout the study, whereby the last tumor assessment will be at least 4 weeks from the prior assessment.

The study will provide a preliminary assessment of the efficacy of durvalumab alone or tremelimumab+ durvalumab therapy with chemotherapy in metastatic or locally advanced OC. Endpoints will include tumor response rate according to irRECIST, PFS, and OS. In addition, there will be a preliminary assessment of the efficacy of durvalumab therapy and neoadjuvant chemo(radio)therapy in operable OC. Progression-free survival after surgery, 1-year survival rate, and OS will be evaluated, along with metabolic response on PET scanning and histological response in resection specimens. Histologic response will record resection status (R0, R1, R2), Mandard grade and complete pathological response (present/absent).

Evaluation according to irRECIST using CT scanning will be performed every 6 weeks for Cohorts A and B. Subjects in Cohorts C/C-FLOT and D/D2, will undergo PET/CT scanning before and after treatment per the Study Flowchart in Section 3.2. The scans should be carried out according to local institutional standards and reported according to irRECIST and RECIST1.1 (see the guidelines in Section 8.8). The information to be captured at each scan is outlined in the eCRF. Scanning protocols and modalities should remain consistent throughout the study. Metabolic response will be assessed according to PERCIST.[38]

4.2.1.1 Tumor Response Assessment by irRECIST

Tumor Response will be assessed by irRECIST (see Section 8.8).

4.2.1.2 Progression-free Survival Rate

Progression-free Survival will be determined for each subject with time origin at the start of the treatment (Day 1) until the first occurrence of confirmed progression by irRECIST or date of death if the subject dies from any causes before progression. For subjects in Cohorts C/C-FLOT and D/D2 undergoing successful surgery, post-operative PFS will also be monitored with time origin at the day of surgery until the first occurrence of confirmed progression by irRECIST or date of death if the subject dies from any causes before progression. The 6-month PFS rate taken from the time of surgery and R0 resection rate are surrogate markers for longer term clinical outcomes. Every effort will be made to follow subjects for progression after they discontinue the study.

4.2.1.3 Objective Response Rate

Objective Response Rate is defined as the percentage of subjects meeting criteria of irCR or irPR over a period of at least 4 weeks.

4.2.1.4 Overall Survival

Overall survival (OS) will be measured for each subject with time origin at the start of the treatment (Day 1) until recorded date of death. Every effort will be made to follow subjects for overall survival after they discontinue the study.

NOTE: Per Amendment 8, all post study follow-up for the collection of survival data will be discontinued as of 30 June 2022 (see rationale in Section 8.1, Amendment 8 on Page 96).

4.2.2 Subject Evaluation & Statistics

All subjects who received at least one dose of durvalumab and/or tremelimumab, as well as baseline and at least one post-baseline disease assessments, will be evaluated for clinical efficacy. Tumor Responses by irRECIST, PFS, and OS will be summarized and analyzed descriptively.

4.3 Immune Monitoring

Samples for exploratory assessment of correlative immune monitoring will be collected according to the Study Flowchart in Section 3.2.

Note: Per Amendment 7, the Investigator(s) will have the option to approach subjects with long-term survival (PFS > 1 year, still in remission) from the metastatic cohorts (A and B) of the trial to request blood (up to 300 mL) for additional testing as described in Section 2.3.

All subjects will be assessed for immunological biomarkers in peripheral blood collected prior to their first durvalumab or tremelimumab + durvalumab infusion and in the 3rd week of immunotherapy as well as on Cycle 1, Day 15. Samples will also be collected on the day of surgery (blood may be collected up to 3 days before surgery) for Cohorts C/C-FLOT and D/D2 and post completion of treatment for Cohorts A and B.

Pre-treatment biopsies, on treatment biopsies and post-operative resectional tissue (or post completion of treatment for Cohorts A and B) will be collected. On treatment research biopsies will be taken during the 4th week of immunotherapy, i.e. prior to the start of chemotherapy. Longitudinal comparison of pre and post immunotherapy effects can thus be evaluated in OC tissue and provide critical measures of treatment impact on immune checkpoint inhibition.

4.3.1 Endpoints & Assessment Methods

Subjects who received at least one dose of tremelimumab or durvalumab, and provide baseline and at least one post-treatment sample, will be evaluated. Peripheral blood samples will be assessed for:

1. Total lymphocyte count and CD4/5/8 T-cell counts
2. Phenotyping of T-cell/B-cell/NK cell subsets via antibody labelling and flow cytometry or mass cytometry. This will include assessment of activated T-cell expression markers, percentage of regulatory T-cells (Tregs) and Treg to effector cell ratio, determination of activation of immune cells based on inducible costimulatory expression and quantification of myeloid derived suppressor cells.
3. Serum cytokine profiling using ELISAs.

Pre-treatment biopsies, on treatment biopsies and post-operative resectional tissue will be evaluated retrospectively for the following:

1. Tumor infiltrating lymphocytes, as above, by flow and/or mass cytometry, including assessment of PD-1 expressing lymphocytes
2. Measurement of tumor/stromal cell PD-L1 expression by immunohistochemistry.

Please refer to the Laboratory Manual for this study for additional information on lab specimen handling and logistics.

4.3.2 Subject Evaluation & Statistics

Results from the correlative studies will be summarized descriptively and evaluated in relation to outcome.

4.4 Genomic Investigation

The study will determine genomic profiles that predict durvalumab and tremelimumab + durvalumab treatment response in OC subjects. It will evaluate the effects of durvalumab and tremelimumab + durvalumab on allele variance, gene expression and pathogenicity in the upper gastrointestinal tract, and how this relates to subject outcomes, immune monitoring and disease characteristics.

Pre-treatment biopsies and post-operative resectional tissue or post treatment biopsies will be RNA and DNA sequenced under existing ethical agreement and collection protocols. Allele variants and gene expression profiles will be examined from OC tissue and multiple control sites in the upper gastrointestinal tract before and during immune modulation. Relationships between high-throughput sequencing data, subject outcome measures, immune monitoring results and disease characteristics will be examined enabling novel study of the effects of immune modulation on the transcriptome in subjects with OC. Application of these findings with an established pipeline for identification of non-human DNA in oesophageal disease also enables thorough interrogation of the host-pathogen relationship in oesophageal cancer, and how this is influenced by anti CTLA-4/PD-L1 immune therapy.

5 Subject Eligibility

5.1 Inclusion Criteria

Note: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.

A screening log must be kept of all subjects considered for the study including any that are subsequently excluded; the reason for exclusion must be recorded on this form. A copy of the screening log should be sent to the trial office on request, but without subject identifiers. The original must be retained on site.

*Eligible subjects **must fulfill** all of the following criteria:*

1.	Histological diagnosis of oesophageal or gastrooesophageal cancer. Have not received full dose systemic chemotherapy. • Cohorts A and B - metastatic/locally advanced cancer • Cohorts C, C-FLOT and D/D2 - deemed suitable for surgery with curative intent Subjects with operable disease will be allocated to Cohort C/C-FLOT or D/D2 based on the decision taken by the multidisciplinary team (MDT) on the standard treatment approach for any individual patient. The MDT will determine (1) operability and (2) whether neoadjuvant chemotherapy or chemoradiotherapy should be offered. These decisions will guide eligibility for enrollment to Cohorts C/C-FLOT and D/D2. The radiotherapy offered in Cohort D/D2 will be standard of care for these subjects, as already determined by MDT.
2.	Recovered from prior therapy (Grade 1 persistent AEs acceptable)
3.	Anticipated lifespan greater than 4 months
4.	ECOG performance status of 0 or 1.
5.	At the time of day 1 of the study, subjects with brain metastases must be asymptomatic for at least 4 weeks and: • at least 8 weeks without tumor progression after any whole brain radiotherapy • at least 4 weeks since craniotomy and resection or stereotactic radiosurgery • at least 3 weeks without new brain metastases as evidenced by MRI/CT

<table>
<tr><td>6.</td><td>Adequate normal organ and marrow function as defined below.
Laboratory parameters for vital functions should be in the normal range. Laboratory abnormalities that are not clinically significant are generally permitted, except for the following laboratory parameters, which must be within the ranges specified, regardless of clinical significance:
<table>
<tr><td>Hemoglobin</td><td>≥ 9 g/dL</td></tr>
<tr><td>Neutrophil count</td><td>≥ 1.5 x 10^9/L</td></tr>
<tr><td>Platelet count</td><td>≥ 100,000/mm^3</td></tr>
<tr><td>Serum creatinine, or Creatinine Clearance</td><td>≤ 1.5x Institutional Upper Limit of Normal (ULN), or ≥ 40 mL/min (by Cockcroft-Gault formula)</td></tr>
<tr><td>AST/ALT</td><td>AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal</td></tr>
<tr><td>Alkaline phosphatase</td><td>≤ 2.5 x ULN</td></tr>
<tr><td>Serum bilirubin</td><td>≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects 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.</td></tr>
</table></td></tr>
<tr><td>7.</td><td>Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.</td></tr>
<tr><td>8.</td><td>Age ≥18 years.</td></tr>
<tr><td>9.</td><td>Have been informed of other treatment options</td></tr>
<tr><td>10.</td><td>Willing and able to comply with the protocol for the duration of the study including undergoing treatment, scheduled visits, examinations, biopsies and follow up</td></tr>
</table>

5.2 Exclusion Criteria

*Subjects **<u>may not</u>** enter the study if they fulfill any of the following criteria:*

1.	Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). Previous enrollment in the present study.
2.	Prior treatment in another clinical study with an investigational product within 4 weeks prior to Day 1 of the study; resolution of respective adverse event to Grade 1 or lower should have occurred. Note: all prior AEs, regardless of subject’s inclusion in a clinical trial, must have resolved to Grade 1 or lower.
3.	Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia’s Correction
4.	Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave’s disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded

5.	Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
6.	History of allogeneic organ transplant
7.	Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B, hepatitis C, known immunodeficiency or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
8.	Known history of previous clinical diagnosis of tuberculosis
9.	Prior exposure to tremelimumab / durvalumab or checkpoint inhibitors, such as anti-CTLA4 and anti-PD1/anti-PD-L1 antibodies.
10.	History of severe allergic reactions to any unknown allergens or any components of the study drugs.
11.	Known dihydropyrimidine dehydrogenase (DPD) deficiency
12.	Treatment with sorivudine or its chemically related analogues, such as brivudine
13.	Peripheral sensitive neuropathy with functional impairment.
14.	History of sarcoidosis syndrome.
15.	Metastatic disease to the central nervous system for which other therapeutic options, including radiotherapy, may be available.
16.	History of pneumonitis or interstitial lung disease.
17.	Major surgical procedure (as defined by the Investigator) within 30 days prior to Day 1 or still recovering from prior surgery.
18.	Women who are breast feeding or pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG). **Female subjects of childbearing potential** who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception (see table below) from the time of screening, and must agree to continue using such precautions for 90 days after the last dose of durvalumab or for 6 months after the last dose of durvalumab + tremelimumab (whichever is longer). Nonsterilized male partners of a female subject must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female subjects should refrain from breastfeeding throughout the period described above. Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal. Females will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

	• Females <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy). • Females ≥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. **Nonsterilized male subjects** who are sexually active with a female partner of childbearing potential must use male condoms plus spermicide from screening through 90 days after last dose of durvalumab or through 6 months after the last dose of durvalumab + tremelimumab (whichever is longer). Female partners (of childbearing potential) of a male subject must use a highly effective method of contraception (see table below) throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout the period described above. Highly effective methods of contraception are described in the table below. A highly effective method of contraception is defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. 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). Acceptable highly effective methods of contraception are described in the following table:

	Highly Effective[a] Methods of Contraception **Barrier/Intrauterine Methods** / **Hormonal Methods** • Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[b] • • "Implants": Etonogestrel-releasing implants: e.g., Implanon® or Norplan® • "Intravaginal Devices": 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® • "Minipill[c]": Progesterone based oral contraceptive pill using desogestrel: e.g., Cerazette® a - Highly effective (i.e. failure rate of <1% per year) b - This is also considered a hormonal method c - Cerazette® is currently the only highly effective progesterone based pill **NOTE: additional requirements for carboplatin, paclitaxel, or FLOT treatment.** Women of childbearing potential should avoid becoming pregnant while taking carboplatin, paclitaxel, or FLOT; they should notify the treating physician immediately if pregnancy occurs. Female and male subjects of fertile age and/or their partners should use effective contraceptives during and for at least 6 months after treatment with these drugs. Male subjects should also avoid sperm donation during and for at least 6 months after treatment with these drugs. Breastfeeding should be discontinued for the duration of treatment with these drugs. Male subjects should be advised regarding cryoconservation of sperm prior to treatment because of the possibility of irreversible infertility due to the treatment.
19.	Any condition that, in the clinical judgment of the treating physician, is likely to interfere with evaluation of study treatment, interpretation of subject safety or study results, prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.
20.	Subjects should not donate blood while participating in this study or for at least 90 days following the last infusion of durvalumab, 6 months following the last infusion of tremelimumab, or until the time specified in the prescribing information of oxaliplatin, capecitabine, paclitaxel, carboplatin, or FLOT (5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel), whichever is longest
21.	For oxaliplatin, capecitabine, paclitaxel, carboplatin, and FLOT (5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel): refer to prescribing information for additional information

5.3 Restrictions on Concomitant Therapies

5.3.1 Non-Permitted Concomitant Therapies

*Subject **may not** receive the following concomitant therapies during the study:*

1.	Systemic treatment with high dose corticosteroids (greater than Prednisone 10 mg daily or equivalent) or other immunosuppressive treatments (e.g. methotrexate, chloroquine, azathioprine). See Section 5.3.2 for exceptions. Wash-out period: 2 weeks prior to Day 1
2.	Other cancer therapy (e.g., drug, radiation (see Section 5.3.2) or immunotherapy). Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Day 1; 6 weeks for nitrosoureas).
3.	Live/attenuated vaccines 1 month prior to Day 1 and for at least 6 months after the last dose of treatment.
4.	Sunitinib within 3 months after the last dose of tremelimumab.
5.	Immunosuppressive doses of steroids or other immunosuppressive medication through 90 days post last dose of tremelimumab. Note however, that inhaled and topical steroids when medically indicated as treatment for an acute illness or as pretreatment before CT scans (for contrast allergies) are allowed. The investigator is permitted to use corticosteroids as treatment for infusion reactions.
6.	Drugs with laxative properties and herbal or natural remedies for constipation should be avoided through 90 days post last dose of tremelimumab because of the potential for exacerbation of diarrhea.
The wash-out period prior to Day 1 of the study for all non-permitted drugs should be at least 1 week, unless stated otherwise above.	

For **oxaliplatin, capecitabine, paclitaxel, carboplatin,** and **FLOT (5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel)** refer to the prescribing information and the additional information below:

Warfarin: INR (International normalised ratio) control may be affected by capecitabine. If a subject requiring coumarin-derived anticoagulants such as warfarin is taking capecitabine, more frequent INR monitoring is required. The use of low molecular weight heparin instead of warfarin is at the discretion of the Investigator.

Phenytoin: Blood phenytoin levels may increase with capecitabine or 5-fluorouracil. If a subject is taking phenytoin concomitantly with these drugs, they should be monitored regularly for increased phenytoin plasma concentrations and associated clinical symptoms.

Other anti-epileptic substances: Leucovorin may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed).

Allopurinol: Interactions with allopurinol have been observed for 5-fluorouracil; with possible decreased efficacy of 5-fluorouracil. Concomitant use of allopurinol with capecitabine or 5-fluorouracil should be avoided.

Antivirals: Brivudine and sorivudine must not be prescribed with capecitabine as they may produce a life-threatening interaction.

Brivudin, sorivudin and analogues: 5-fluorouracil must not be given in combination with brivudin, sorivudin and analogues. Brivudin, sorivudin and analogues are potent inhibitors of the 5-fluorouracil metabolising enzyme dihydropyrimidine dehydrogenase (DPD).

5-Fluorouracil must not be given to subjects known to be homozygotic for dihydropyrimidine dehydrogenase (DPD).

Vaccination with a live vaccine should be avoided in subjects receiving 5-fluorouracil due to the potential for serious or fatal infections. Contact should be avoided with people who have recently been treated with polio virus vaccine.

Photosensitivity: It is not advisable to have prolonged exposure to sunlight because of the risk of photosensitivity with 5-fluorouracil.

Nephrotoxic/ototoxic drugs: Auditory defects have been reported during carboplatin therapy. Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics is not recommended as they may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance.

CYP2C8 or CYP3A4 inhibitors/inducers: Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.
The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided.

Cytochrome P450-3A: The metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as ciclosporine, ketoconazole and erythromycin.

5.3.2 Permitted Concomitant Therapies

*Subject **may** receive the following concomitant therapies during the study:*

1.	Prophylactic anti-emetic treatment, consisting of a 5-HT3 antagonist, steroids and other anti-emetics are to be administered in conjunction with chemotherapy as per local practice guidelines. For example: • Dexamethasone 4 mg b.d. x 1 day • Granisetron or ondansetron for 1-2 days od • Domperidone or metoclopramide prn Note: For subjects at high risk of steroid side effects (e.g. diabetics) or for those who develop toxicity attributable to steroids (e.g. dyspepsia, dysphoria), the oral steroid should be carefully monitored or omitted.
2.	Intranasal or inhaled steroids for treating mild to moderate asthma or allergies, physiological steroid replacement, intra-articular steroids, or topical steroids for localized dermatitis (<5% of body surface area).
3.	NSAIDs, acetylsalicylic acid and specific COX-2 inhibitors.
4.	Antihistamines and other non-steroidal anti-allergy medication.
5.	Hormone replacement therapy.
6.	At the discretion of the investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, including high dose corticosteroids or anti-TNF agents (e.g. infliximab) to treat immune-mediated adverse reactions. Subjects should receive full supportive care, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheal, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.
7.	Subjects may receive localized palliative radiotherapy on study if clinically indicated after discussion with the LICR medical monitor.
All prescription and nonprescription drugs must be recorded in the concomitant medications section of the case report form, listing generic (preferably) or brand name, indication, dose, route and dates of administration. All non-drug therapies must be recorded in the respective sections of the case report form.	
For oxaliplatin, capecitabine, paclitaxel, carboplatin, and FLOT (5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel), refer to prescribing information for additional information.	

6 Study Drug Preparation and Administration and Radiotherapy Delivery

On days with concurrent tremelimumab and durvalumab dosing, durvalumab administration will start at least 60 minutes after the end of the tremelimumab infusion.

On days with concurrent durvalumab and oxaliplatin dosing, oxaliplatin administration will start at least 60 minutes after the end of the durvalumab infusion. The morning dose of capecitabine is taken after the oxaliplatin infusion.

On days with concurrent paclitaxel and carboplatin dosing, paclitaxel will be infused over 1 hour followed by carboplatin infusion over 1 hour according to local standards.

On days with concurrent durvalumab and FLOT dosing, the cytotoxic chemotherapy drugs should be administered at least 60 minutes after the end of the durvalumab infusion. Local standard procedures for the administration of 5-fluorouracil, leucovorin, oxaliplatin and docetaxel will apply. Note that leucovorin should not be mixed in the same infusion as 5-fluorouracil because a precipitate may form.

For chemotherapy, banded doses may be used according to institutional guidelines.

6.1 Oxaliplatin

Refer to the prescribing information for oxaliplatin.

Oxaliplatin should always be administered before fluoropyrimidines.

6.2 Capecitabine

Refer to the prescribing information for capecitabine.

6.3 Paclitaxel

Refer to the prescribing information for paclitaxel.

6.4 Carboplatin

Refer to the prescribing information for carboplatin.

6.5 5-Fluorouracil

Refer to the prescribing information for 5-fluorouracil.

6.6 Leucovorin

Refer to the prescribing information for leucovorin.

6.7 Docetaxel

Refer to the prescribing information for docetaxel.

6.8 Tremelimumab

6.8.1 Tremelimumab Study Drug Information

Manufacturer	MedImmune		
Expiration/Retest Date	*Expiration/retest dates are documented in the QA Disposition of IMP Report.*		
Container Description	*Type:* Single use vial	*Material:* clear glass	*Size:* 20 mL
Formulation	Liquid solution containing 400 mg tremelimumab per vial. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5		
Active Ingredient Content	*Mass/Weight:* 400 mg/vial	*Volume:* 20 mL	*Concentration:* 20 mg/mL
Storage Conditions	2°C to 8°C (36°F to 46°F) Do not freeze		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.8.2 Tremelimumab Investigational Product Inspection

Each vial of tremelimumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator and Sponsor should be notified immediately.

6.8.3 Tremelimumab Preparation

The dose of tremelimumab for administration must be prepared by the IP manager or designated personnel using aseptic technique. No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed. However, administration sets containing cellulose-based filters should not be used with tremelimumab.

Dose Calculation:
Subjects will receive a fixed dose of tremelimumab. The starting dose is 37.5 mg with dose escalation to 75 mg (see Section 3.1.7.1). Tremelimumab is given only on Day 1 for certain cohorts (See Section 3.1.7).

The volume of tremelimumab required for 75 mg is 3.75 mL; the volume for 37.5 mg is 1.875 mL (see calculation below).

Tremelimumab Dose (mL)	=	dose level (mg)	÷	Tremelimumab concentration (20 mg/mL)

The corresponding volume of investigational product should be rounded according to institutional practice.

Dose Preparation:
Tremelimumab will be administered using a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. The calculated volume of tremelimumab is added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Example: The volume of tremelimumab required for 75 mg dose is 3.75 mL. The corresponding volume of investigational product should be rounded according to institutional practice. For example, (for a 75 mg dose of tremelimumab), if the institutional practice is to round the volume to the nearest tenth mL, 3.75 mL would be rounded to 3.8 mL, which would be the volume of tremelimumab added to the bag; the bag is then mixed by gentle inversion.

Tremelimumab does not contain preservatives and any unused portion must be discarded.

6.8.4 Tremelimumab Administration

Following preparation of the dose, tremelimumab will be administered according to the following guidelines:

- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available.
- Prior to the start of the infusion, the IV bag contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- Tremelimumab must not be administered via IV push or bolus but as an IV infusion.
- Tremelimumab must be administered at room temperature by controlled infusion into a peripheral vein or central line.
- Tremelimumab solution should not be infused with other solutions or medications.
- The entire contents of the IV bag should be administered by IV infusion over approximately 60 (±5) minutes, using a 0.2, or 0.22-µm in-line filter. **An infusion of less than 55 minutes is considered a deviation.**
- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.
- The total time from needle puncture of the tremelimumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.
- The date, start time, interruption, and completion time of tremelimumab administration must be recorded in the source documents.
- Subjects will be monitored before, during and after infusion with assessment of vital signs according to Section 6.11
- See Section 8.5.1 for guidelines for infusion-related reactions.

6.9 Durvalumab (MEDI4736)

6.9.1 Durvalumab (MEDI4736) Study Drug Information

Manufacturer	MedImmune		
Expiration/Retest Date	*Expiration/retest dates are documented in the QA Disposition of Investigational Medicinal Product (IMP) Report.*		
Container Description	*Type:* Single use vial	*Material:* glass	*Size:* 10 mL
Formulation	Liquid solution containing 500 mg durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, at pH 6.0.		
Active Ingredient Content	*Mass/Weight:* 500 mg	*Volume:* 10mL	*Concentration:* 50 mg/mL
Storage Conditions	2°C–8°C (36°F to 46°F) Do not freeze		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.9.2 Durvalumab Investigational Product Inspection

Each vial of durvalumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator and Sponsor should be notified immediately.

6.9.3 Durvalumab Preparation

Preparation of durvalumab and preparation of the intravenous (IV) bag are to be performed by the IP Manager or designated personnel using aseptic technique. No incompatibilities between durvalumab and polyvinylchloride or polyolefin copolymers have been observed.

Dose Calculation:
Subjects will receive a fixed dose of durvalumab: 750 mg Q2W.

The volume of durvalumab (in mL) to add to the IV bag is calculated as follows:

Volume of Durvalumab (mL)	=	Dose level (mg)	÷	Durvalumab Concentration (nominal 50 mg/mL)

Dose Preparation:
Durvalumab will be administered using a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose and delivered through an IV administration set with a 0.2 or 0.22 µm in-line filter. A volume of diluent equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab. The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Example: For a 750 mg dose, 15 mL of durvalumab is to be diluted in a 250 mL IV bag. First, 15.0 mL of diluent is removed from the IV bag, and then 15.0 mL of durvalumab is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Durvalumab does not contain preservatives, and any unused portion must be discarded.

6.9.4 Durvalumab Administration

Following preparation of the dose, durvalumab will be administered according to the following guidelines:

- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational products. Fully functional resuscitation facilities should be available.
- Prior to the start of the infusion, the IV bag contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures
- Durvalumab must not be administered via IV push or bolus but as an IV infusion.
- Durvalumab solution should not be infused with other solutions or medications.
- Durvalumab must be administered at room temperature by controlled infusion into a peripheral vein or central line.
- The entire contents of the IV bag should be administered as an IV infusion **over approximately 60 (± 5) minutes**, using a 0.2- or 0.22-µm in-line filter. **An infusion of less than 55 minutes is considered a deviation.**
- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.
- The total time between needle puncture of the durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.
- The date, start time, interruption, and completion time of durvalumab administration must be recorded in the source documents.
- Subjects will be monitored before, during and after infusion with assessment of vital signs according to Section 6.11.
- See Section 8.5.1 for guidelines for infusion-related reactions.

6.10 Estimated Study Drug Requirements

Drug	Required Quantity
Oxaliplatin	Sourced locally by sites
Capecitabine	Sourced locally by sites
Paclitaxel	Sourced locally by sites
Carboplatin	Sourced locally by sites
5-fluorouracil (5-FU)	Sourced locally by sites
leucovorin	Sourced locally by sites
docetaxel	Sourced locally by sites
Tremelimumab	35 x 400 mg vials
Durvalumab	2400 x 500 mg vials

6.11 Monitoring of Tremelimumab and Durvalumab Administration

Subjects will be monitored before, during and after infusion of tremelimumab and durvalumab with assessment of vital signs according to the table below:

Vital Signs Assessment on Study Drug Administration Days					
Drug	**Pre Dose**	**During Infusion**	**End of Infusion (± 5 minutes)**	**30 (± 5) Minutes Post Infusion**	**60 (± 5) Minutes Post Infusion**
Tremelimumab	X	every 30 (± 5) minutes	X		
Durvalumab	X	every 15 (± 5) minutes	X	X	X

Note: When durvalumab and tremelimumab are to be administered on the same day, durvalumab infusion will start at least 60 minutes after the end of tremelimumab infusion even though vital signs assessment is not required during the entire 60-minute period post tremelimumab.

If a subject tolerates treatment well for the first 4 doses of durvalumab (i.e., no infusion reactions), subsequent infusions for that subject can be monitored according to the table below. A longer duration of observation after the end of infusion can be used if the Investigator deems it clinically necessary.

Vital Signs Assessment on Study Drug Administration Days (after first 4 doses)				
Drug	**Pre Dose**	**During Infusion**	**End of Infusion (± 5 minutes)**	**15 (± 5) Minutes Post Infusion**
Durvalumab	X	Every 30 (± 5) minutes	X	X

6.12 Drug Overdose Management

6.12.1 Capecitabine, Oxaliplatin, Paclitaxel, Carboplatin, and FLOT (5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel)

Any overdose with these drugs should be managed according to the respective prescribing information.

6.12.2 Durvalumab and Tremelimumab

Any overdoses with tremelimumab and durvalumab should be managed symptomatically. There are no known antidotes available for these drugs. An overdose is defined as a subject receiving any dose in excess of that specified in this protocol by > 10%. All such overdoses must be reported, with or without associated AEs/SAEs, according to Section 7.1.2.2.

6.13 Radiotherapy Delivery

Radiotherapy will be delivered per current best practice. Investigators are advised to refer to separate Radiotherapy and Planning document for guidance.

7 Administrative, Legal & Ethical Requirements

7.1 Documentation and Reporting of Adverse Events

7.1.1 General AE/SAE Definitions per ICH Guidelines

An **Adverse Event (AE)** is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with the 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 (investigational) product, whether or not related to the medicinal (investigational) product.

N.B.: The definition above, provided for in the GCP-ICH Guideline E6, is being extended for the purpose of LICR studies to include any events, intercurrent diseases and accidents observed while the subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre- and post-treatment periods, under placebo or in a reference group receiving drug or non-drug therapy or no treatment.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that:

1. Results in death,
2. Is life-threatening[A],
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly / birth defect or
6. Is another medically important condition[B].

[A] The term "life-threatening" in the definition of "serious" refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

[B] Medically important conditions that may not result in death, be immediately life-threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

N.B.: The term "severe" is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, e.g., pain). The event itself may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on subject/event outcome or action criteria usually associated with events that pose a threat to subject's life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

NOTE: If a subject is hospitalized for a planned standard of care procedure that is not related to an AE, the hospitalization does not require an SAE report. However, if there is an additional AE or

complication during the hospitalization, or if the hospitalization is prolonged, the SAE procedures described in Section 7.1 must be followed.

7.1.2 Additional Expedited Reporting Requirements for this Study

For the purpose of this study, the following events must be reported by phone or email to the Sponsor within 24 hours of knowledge of the event (See Section 7.1.6 for Sponsor contact information) **and may result in submission of an SAE based on certain criteria outlined below**:

1. Pregnancy
2. Overdose (as defined in Section 6.12)
3. Hepatic function abnormality (as defined in Section 7.1.8).

7.1.2.1 Pregnancy

7.1.2.1.1 Maternal exposure

Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer).

If a subject becomes pregnant during the course of the study, the study drugs 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 (see Section 7.1.6). 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 subject 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 Sponsor (see Section 7.1.6 for Sponsor contact information) within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

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

The same timelines apply when outcome information is available.

7.1.2.1.2 Paternal exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer).

Pregnancy of the subject'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 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 subject's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

7.1.2.2 Overdose

Any overdose (as defined in Section 6.12) of a study subject with durvalumab + tremelimumab, with or without associated AEs/SAEs, is required to be reported **within 24 hours of knowledge of the event** to the Sponsor (see Section 7.1.6 for Sponsor contact information). If the overdose results in an AE, the AE must also be recorded as an AE according to Section 7.1.5. 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 according to Section 7.1.6. There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab. The investigator will use clinical judgment to treat any overdose. See Section 6.12 for additional details.

7.1.2.3 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 7.1.8) in a study subject, 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 Sponsor, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed (see Section 7.1.6 for Sponsor contact information).

- 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 subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject 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 Sponsor and AstraZeneca/MedImmune.

7.1.3 Severity of an Adverse Event

The severity of all serious and non-serious adverse events should be assessed according to the National Cancer Institute CTCAE Scale (Version 4.03).

7.1.4 Relationship of Adverse Events to Study Drug

The relationship of all serious and non-serious adverse events to the investigational agent(s) will be determined by the Investigator on the basis of their clinical judgment, using one of the following terms (in accordance with NCI Guideline "Expedited Adverse Event Reporting Requirements for NCI Investigational Agents", NCI Cancer Therapy Evaluation Program, January 2001):

Definitely related (The AE is *clearly related* to the investigational agent)
Probably related (The AE is *likely related* to the investigational agent)

Possibly related (The AE *may be related* to the investigational agent)
Unlikely related (The AE is *doubtfully related* to the investigational agent)
Unrelated (The AE is *clearly not related* to the investigational agent)

N.B.: When making the assessment on causality, it should be taken into consideration that immune-therapeutic agents have the potential to cause very late and/or permanent effects on the immune system, i.e., a causal relationship could exist despite a lack of apparent temporal relationship. Information provided in the IB and/or in Section 1 of this protocol may support these evaluations.

7.1.5 General Reporting Requirements

All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4 This documentation is required for all AEs that occur:

a. from the date of signing the informed consent, and
b. until the off-study date or 110 days after the last administration of study drug, whichever is longer, or until a new treatment is initiated (see Section 3.1.10 for subjects who begin other anti-cancer treatment).

Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 110 days after the last dose of the last study treatment (regardless of initiation of another therapy).

NOTE: For subjects in Cohorts A and B:

1. If durvalumab is discontinued early, subjects will follow the On Study Follow-up period according to the Flowchart in Section 3.2, and all AEs will be collected for 110 days after the last dose of durvalumab.
2. If any subjects continue chemotherapy treatment alone (no durvalumab), they will complete the first On Study Follow-up at Day 28 (+14 days) post last dose of chemotherapy. All AEs will be collected for at least 28 (+14) days after the last dose of chemotherapy; however, per point #1, subjects must still be followed for On Study Follow-up post last dose of durvalumab for 110 days.

NOTE: For subjects in Cohorts C/C-FLOT and D/D2, the On Study Follow-up period is defined as follows:

1. All AEs will be collected for 110 days after the last dose of pre-surgery durvalumab, with the exception of those AEs that are related to the protocol-defined surgical procedure(s). If the decision is made that a subject will not receive continued durvalumab, the subject must start On Study Follow-up and have at least one On Study Follow-up visit at 110 days (+30 days) after last dose of durvalumab or at the point of the decision (+30 days), whichever is later. See Flowchart in Section 3.2 for details.

2. If any subjects in Cohorts C/C-FLOT and D/D2 continue durvalumab treatment after the planned surgical procedure, they will follow the On Study Follow-up period according to the Flowchart in Section 3.2, and all AEs will be collected for 110 days after the last dose of durvalumab.
3. If any subjects in Cohort C-FLOT continue FLOT treatment alone (no durvalumab) after the planned surgical procedure, they will complete the first On Study Follow-up at Day 28 (+14 days) post last dose of FLOT. All AEs will be collected for at least 28 (+14) days after the last dose of FLOT; however, point #1 must still be followed for an On Study Follow-up visit post last dose of durvalumab.

See Section 8.7.3 for Reference Safety Information (RSI) on radiotherapy; see Sections 8.6.3 and 8.7.4 for RSI on surgery.

7.1.6 Expedited Serious Adverse Event (SAE) Reporting Requirements

In addition to the General Reporting Requirements specified in Section 7.1.5, all events meeting the criteria for an SAE as per Section 7.1.1, irrespective of suspected causation, must be reported by the Investigator to the Sponsor's Drug Safety Contact (primarily) or, alternatively, to the Primary Sponsor Contact, within 24 hours of becoming aware of the event. This should be done using the "Initial Serious Adverse Event Report Form," provided by the Sponsor, or, if Medidata RAVE data capture is utilized, using the respective Adverse Event and Safety Case Summary eCRFs. This includes any deaths that occur after the off-study date, but within 30 days of last study drug administration. Note: If an SAE cannot be reported through the "Initial Serious Adverse Event Report Form" or through Medidata RAVE within 24 hours of becoming aware of the event, the Sponsor's Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact, must be contacted by phone or email within 24 hours of becoming aware of the event. In this case, the phone or email notification can then be followed up by an "Initial Serious Adverse Event Report Form" or through Medidata RAVE within one working day of the event.

The expedited reports should be directed by fax or e-mail to the Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact. Studies utilizing the Medidata "Safety Gateway", built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to "Safety Gateway" procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact (see table below).

In urgent cases, pre-notification via phone or informal e-mail should be considered.

Drug Safety Contact:	*Primary Sponsor Contact:*
[redacted] Senior Manager, Drug Safety Clinical Trials Management Ludwig Institute for Cancer Research 600 3rd Ave 32nd Floor New York, New York 10016 [redacted]	[redacted] Senior Director, Clinical Project Management Clinical Trials Management Ludwig Institute for Cancer Research 600 3rd Ave 32nd Floor New York, New York 10016 [redacted]

Serious adverse events must also be reported by the Principal Investigator to the respective the appropriate Research Ethics Committee or Institutional Research Governance Committee in accordance with local rules and guidelines after being assigned a serious adverse event tracking number by the Sponsor. Research Ethics Committee/Institutional Research Governance Committee may have specific rules on which Adverse Events need to be reported expeditiously, as well as, the time frames for such reporting.

SAE Reports will be evaluated by the Sponsor's Medical Monitor. Regulatory authorities and other investigators, as well as institutional and corporate partners, will be informed by the Sponsor as required by ICH guidelines, laws and regulations in the countries where the investigational agent is being administered. In particular, SAEs that are unexpected and for which a causal relationship with the study drug(s) cannot be ruled out, will be reported by the Sponsor within 15 calendar days; if they are life-threatening or fatal, they will be reported within 7 Calendar days.

Serious adverse event reporting to AstraZeneca/Medimmune is described in a separate agreement.

7.1.7 Serious Adverse Event (SAE) Follow-up Requirements

Subjects experiencing SAEs should be followed closely until the condition resolves or stabilizes, and every effort should be made to clarify the underlying cause. Follow-up information related to SAEs must be submitted to the Sponsor as soon as relevant data are available, using the "SAE Follow-up Report form", provided by the Sponsor or, if Medidata RAVE data capture is utilized, using the respective Adverse Event and Safety Case Summary eCRFs.

7.1.8 Adverse Events of Special Interest (AESIs)

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the investigational products and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. The rapid recording of all AEs, including AESIs, allows ongoing surveillance of these events in order to characterize and understand them in association with the use of the investigational products.

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

If the Investigator has any questions in regards to an AE being an irAE, the Investigator should promptly contact the Medical Monitor.

If an AESI also meets SAE criteria, the event will be reported as an SAE per Section 7.1.6.

AESIs observed with durvalumab and tremelimumab and those considered AESIs for the purpose of this study are listed below. Further information on these AESIs (e.g. presenting symptoms) can be found in the current versions of the durvalumab and tremelimumab Investigator Brochures. Guidelines for the management of subjects experiencing these toxicities can be found in Section 8.5 and in the following Medimmune guideline: ***"Medimmune's Dosing Modification and Toxicity Management Guidelines for Immune- mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 (durvalumab) Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)."***

- **Diarrhea/Colitis and intestinal perforation**
  Diarrhea and colitis are the most commonly observed treatment-emergent AEs following dosing with study medications. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome, if not properly managed.

- **Pneumonitis/Interstitial lung disease (ILD)**
  Adverse events of pneumonitis have been observed with anti-PD-1, and anti-PD-L1 antibodies.[39,40] Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Typically, pulmonary consultation is required.

- **Hepatic Function Abnormality (Hepatitis/transaminase increases)**
  Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies.[39] Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin. Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a concurrent or pre-existing disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Cases where a subject shows an AST **or** ALT ≥ 3 x ULN **or** total bilirubin ≥ 2 x ULN may need to be reported as SAEs. 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.

- **Neurotoxicity (Neuropathy/Neuromuscular toxicity)**
  Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis.

- **Endocrine Disorders**
  Immune-mediated endocrinopathies include hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism, and Type 1 diabetes mellitus.
  Type 1 diabetes mellitus: For subjects with suspected diabetes mellitus, Investigators

should obtain an endocrinology consult and institute appropriate management which may include the administration of insulin.

- **Dermatitis/Rash**
  Prompt treatment with steroids (topical or systemic based on severity) is important as per current established toxicity management guidelines.

- **Nephritis and increases in serum creatinine**
  A consult with a Nephrologist should be done as well as monitoring 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, proteinuria, etc.). Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, etc.). 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.

- **Pancreatic Disorders**
  Immune-mediated pancreatitis includes autoimmune pancreatitis (or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase).

- **Myocarditis**
  Myocarditis, a rare but severe immune-mediated adverse event, presents with signs/symptoms such as decreased ejection fraction, arrhythmias, in particular occurrences of atrioventricular block. For subjects with suspected myocarditis, investigators should obtain a cardiology consult and institute full diagnostic work-up (that includes exclusion of other alternate causes such as infection).

- **Myositis / Polymyositis**
  Myositis or polymyositis should be suspected in subjects who present with proximal muscle weakness and the evaluation should include an examination of the skin, muscle enzyme measurement, antibody testing, any systemic disease manifestations and exclusion of other diseases including drug-induced myopathy. Cases of myositis have been reported with myocarditis in which immune infiltration has been described in skeletal and cardiac muscle (see IB).

- **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, hematological and rheumatological events.

- **Hypersensitivity and Infusion Reactions**
  Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy.[39] As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies (MAbs) can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema,

hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

7.2 Administrative Sponsor Requirements

7.2.1 Pre-Study Requirements

The following are required before study drug can be shipped to the study site:

- Satisfactory Site Validation (conducted by Sponsor or a suitable delegate)
- Signed Statement of Investigator
- Regulatory Approval
- Research Ethics Committee approval of Protocol and Informed Consent Form
- NHS R and D Approval for the study site
- Executed Clinical Trial Agreement (if applicable)

7.2.2 Study Master Files

The Investigator must retain a Sponsor-specified comprehensive and centralized filing system (Study Master File) of all trial-related documentation that is suitable for inspection by the Sponsor and regulatory authorities. Upon completion of the trial, the Investigator is required to submit a summary report to the Sponsor.

The Investigator must arrange for the retention of the Study Master File for a period of time determined by the Sponsor. No part of the Study Master File shall be destroyed or relocated without prior written agreement between the Sponsor and the Investigator.

A screening log must be kept of all subjects considered for the study including any that are subsequently excluded; the reason for exclusion must be recorded on this form. A copy of the screening log should be sent to the trial office on request, but without subject identifiers. The original must be retained on site.

7.2.3 Case Report Form Data Collection

Electronic Case Report Forms (eCRF) will be completed in accordance with respective guidance and after training provided by the Sponsor. The use of eCRFs encompasses electronic data entry, query management and sign-off. Systems used for electronic data capture will be compliant with FDA regulations 21 CFR Part 11 and within the constraints of the applicable local regulatory agency guidelines (whichever provides the greatest protection to the integrity of the data).

All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF.

The Investigators electronic signature indicates a thorough inspection of the data in the CRF and will certify its content.

7.2.4 Language

The protocol is written in English. All correspondence between the study site and the Sponsor should be maintained in English. Case Report Forms must be completed in English. All written material to be used by subjects and para-clinical staff must use vocabulary that is clearly understood, and be in the language appropriate for the trial site.

7.2.5 Monitoring

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site validation, site initiation, routine monitoring and site close-out. Clinical Monitors and/or other sponsor staff will meet with the investigator staff and require direct access to source data/documents. Such access may also be required for Research Ethics Committee review, regulatory inspection and sponsor audits. Direct access is defined as permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study. All reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information will be exercised.

It is the Clinical Monitor's responsibility to inspect the case report forms at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to Good Clinical Practice guidelines. The Clinical Monitor should have access to subject charts, laboratory reports and other subject records needed to verify the entries on the case report forms ("source data verification").

7.2.6 Protocol Amendments

Protocol amendments may be implemented only after approval by the Investigator, Sponsor, Research Ethics Committee and, if required, the regulatory authorities. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to such approvals. However, in this case, approval must be obtained as soon as possible after implementation. Implementation of administrative amendments (or non-substantial amendments in the UK) that do not affect the safety of the subjects do usually not require prior Research Ethics Committee approval, just notification.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to subjects, the Investigator will contact the Sponsor if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documentation.

7.2.7 Premature Subject Withdrawal

A subject may withdraw from treatment or from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the study site. Likewise, the Investigator and/or Sponsor have the right to withdraw subjects from treatment or from the study. Specific subject withdrawal reasons are listed in Section 3.1.10. Should a subject (or a subject's legally authorized representative) decide to withdraw, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

A complete final evaluation should be made at the time of the subject's withdrawal, the appropriate form in the Case Report Form should be completed with an explanation of why the subject is withdrawing, and an attempt should be made to perform a follow-up evaluation.

7.2.8 Early Trial Termination

"End of study" is defined as the last visit of the last subject. Sponsor and Investigator have the right to terminate the study early. Specific study stopping rules are listed in Section 3.1.14. In such case, one party must notify the other in advance in writing about the intent of and the reasons for the termination. The investigator must also notify the appropriate Research Ethics Committee or Institutional Research Governance Committee in accordance with local rules and guidelines.

7.2.9 Study Drug Shipments & Accountability

Study drug shipments will be addressed to the Principal Investigator's authorized designee, preferably the site's pharmacy. The recipient will verify the amount and condition of the drug and will return a signed Acknowledgment of Receipt to the shipper.

A drug dispensing log (inventory) will be kept by the study site, containing at least the following:

- the subject's identification (subject number and code)
- date and quantity of drug dispensed
- date and quantity of drug returned to the investigator/pharmacy (if applicable)
- date and quantity of accidental loss of drug (if any)

These inventories must be made available for inspection by the Clinical Monitor. The Investigator is responsible for the accounting of all used and unused trial supplies. At the end of the study, the Clinical Monitor will also collect the original study drug dispensing records.

At the end of the study or as directed by the Sponsor, all used and unused supplies, including partially used or empty containers, will be disposed of or transferred as instructed by the Sponsor, and in accordance with local written procedures, if applicable. Any disposal or transfer of investigational agent shall be noted on the investigational drug disposition log and signed-off by a second person. At the end of the study, the Clinical Monitor will collect the original drug disposition logs.

7.3 Regulatory, Legal & Ethical Requirements

7.3.1 Good Clinical Practice (GCP), Laws and Regulations

The investigator must ensure that he/she and all authorized personnel for the study are familiar with the principles of Good Clinical Practice (GCP) and that the study is conducted in full conformity with the current revision of the Declaration of Helsinki, ICH Guidelines and applicable local laws and regulations, with the understanding that local laws and regulations take precedence over respective sections in the Declaration of Helsinki and/or the ICH Guidelines.

7.3.2 Informed Consent

The investigator must obtain witnessed (if applicable) written informed consent from the subject or the subject's legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study-specific procedures are performed. The subject should be given a copy of the informed consent documentation. The original signed and dated informed consent form must be retained in the study records at the study site, and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

7.3.3 Research Ethics Committee

The investigator must obtain written approval from the appropriate Research Ethics Committee for the protocol and informed consent, and all amendments thereof, prior to recruitment of subjects and prior to shipment of investigational agents.

The investigator must report Serious Adverse Events (SAEs) to the appropriate Research Ethics Committee or Institutional Research Governance Committee in accordance with local rules and guidelines (see also Section 7.1).

The investigator must assure that continuing review (at least once per year) of the study is performed by the Research Ethics Committee throughout the duration of the study, by providing annual and other reports required.

All correspondence with, and reports to, the Research Ethics Committee or Institutional Research Governance Committee must be maintained in the study files at the study site and copies must be sent to the Sponsor.

7.3.4 Subject Confidentiality

The investigator must ensure that the subject's privacy is maintained. A subject should only be identified by their initials, date of birth and subject number on the case report forms or other documents submitted to the Sponsor. Documents that are not submitted to the Sponsor (e.g., signed informed consent form) should be kept in a strictly confidential section of the study file by the Investigator.

The investigator shall permit the Sponsor and authorized representatives of regulatory agencies to review the portion of the subject's medical record that is directly related to the study. As part of the informed consent process, the subject must have given written consent that his/her records will be reviewed in this manner.

8 Appendices

8.1 Protocol Version History

Original Issue
Issue date: 11-NOV-2015
Summary of Changes: n/a

Amendment 001
Issue date: 25-FEB-2016
Summary of Changes:

- Sections 3.1.4 and 5.1: Added the following clarification: "Subjects with operable disease will be allocated to Cohort C or D based on the decision taken by the multidisciplinary team (MDT) on the standard treatment approach for any individual patient. The MDT will determine (1) operability and (2) whether neoadjuvant chemotherapy or chemoradiotherapy should be offered. These decisions will guide eligibility for enrollment to Cohorts C and D. The radiotherapy offered in Cohort D will be standard of care for these subjects, as already determined by MDT."
- Section 3.1.14: The following clarification was added: "If the study is suspended, dosing may not resume before obtaining approval of a substantial amendment from the Competent Regulatory Authority."
- Sections 3.1.16 and 7.1.5: On Study Follow-up was changed from 90 to 110 days; an additional follow-up visit at 110 days was added to the flowchart (Section 3.2).
- Section 3.2 (Study flowchart):
  - Amylase and lipase assessments were added
  - Footnote b: neurological examination was added to physical examination.
- Section 4.1.1: clarification was added to indicate that physical exam includes neurological exam.
- Section 5.3.1: the following points were added to Non-permitted Concomitant Therapies:
  - "Immunosuppressive doses of steroids or other immunosuppressive medication through 90 days post last dose of tremelimumab. Note however, that inhaled and topical steroids when medically indicated as treatment for an acute illness or as pretreatment before CT scans (for contrast allergies) are allowed. The investigator is permitted to use corticosteroids as treatment for infusion reactions."
  - "Drugs with laxative properties and herbal or natural remedies for constipation should be avoided through 90 days post last dose of tremelimumab because of the potential for exacerbation of diarrhea."
- Administrative changes:
  - EudraCT # and AstraZeneca Ref # were added to the header of the Title Page.
  - Section 8.10: MDT (multidisciplinary team) was added to abbreviations list.

Amendment 1.1 (Administrative Change)
Issue date: 06-MAY-2016
Summary of Changes:

- Section 3.2, Flowchart: For Cohorts A1 and A2, oxaliplatin administration was deleted from Cycle 5/Day 15 and Cycle 6/Day 8; oxaliplatin administration was added to Cycle 6/Day1.

Amendment 2
Issue date: 23-JAN -2017
Summary of Changes:

- **Synopsis:** Chemoradiotherapy for Cohort D was changed as described in Section 2.1. Changes related to Cohort D were added as follow**s:**
  - Paragraph 1 (changes in bold): This is an open-label, Phase 1/2 study to evaluate the safety of durvalumab (MEDI4736) **(and tremelimumab for certain cohorts as described in Section 3.1.7)** in combination **with chemo (radio) therapy according to the following cohorts:**
    - **Cohorts A1, A2, and B: Oxaliplatin/capecitabine chemotherapy in metastatic/locally advanced oesophageal cancer (OC).**
    - **Cohort C: Neoadjuvant oxaliplatin/capecitabine chemotherapy before surgery in operable OC.**
    - **Cohort D: Neoadjuvant paclitaxel/carboplatin chemotherapy + radiotherapy before surgery in operable OC.**

    ~~**oxaliplatin/capecitabine chemotherapy in metastatic/locally advanced oesophageal cancer (OC) and with neoadjuvant chemo(radio)therapy before surgery in operable OC**~~
    The immunotherapy will be given for a 4-week period before starting the standard chemo(radio)therapy, continuing durvalumab treatment once the chemotherapy starts **for all cohorts except Cohort D**. The study will include 2 phases, a safety run-in Phase 1 (Cohorts A1 and A2) and an expansion Phase 2 (Cohorts B, C, and D).
  - Primary and Secondary Objectives (changes in bold)
    Primary objective #2: Assess the Safety/Tolerability of durvalumab in combination with neoadjuvant chemo(radio)therapy **(oxaliplatin/capecitabine and paclitaxel/carboplatin/radiotherapy)** in operable OC. (Endpoint: CTCAE version 4.03).
    Secondary objective #2**:** Assess the Clinical Efficacy of durvalumab in combination with neoadjuvant chemo(radio)therapy **(oxaliplatin/capecitabine and paclitaxel/carboplatin/radiotherapy)** in operable OC. (Endpoints: PFS after surgery, 1-year survival rate, OS, pathological and metabolic response rate)
- Sections 1.6.3 and 1.6.4 (Paclitaxel and Carboplatin) were added.
- Section 1.6.5 (durvalumab): the following changes were made for paragraph 4 (changes in bold): "The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs, **with the exception of patients with squamous cell carcinaoma of the head and neck (SCCHN) where a higher incidence of bleeding has been reported**. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy / neuromuscular toxicity, ~~**endocrinopathy**~~ **endocrinopathies such as hypo- and hyper-**

thyroidism, hypophysitis, adrenal insufficiency and type I diabetes mellitus, dermatitis, and nephritis."

- Section 1.6.5 (Durvalumab): Paragraph 7 was changed **FROM**: "The fixed dosing for durvalumab is based on information from MedImmune, which indicates that the dose and schedule of 1500 mg durvalumab Q4W was selected based on PK models as described below." **TO: "**The fixed dosing for durvalumab was selected based on pharmacokinetic (PK) models."
- Section 1.6.5 (Durvalumab): The following sentence was added after the last paragraph: "This study will use a fixed dose of 750 mg Q2W for durvalumab."
- Section 1.6.6 (Tremelimumab): For Paragraph 3, the phrase "data remain blinded" was removed from the DETERMINE study, as this is no longer applicable.
- Section 2.1 (Rationale for Amendment 2) was added, and the key changes to Cohort D were described.
- Section 3.1 (Study Design) Changes in bold:
  This is an open-label, Phase 1/2 study to evaluate the safety of durvalumab (**and tremelimumab for certain cohorts as described in Section 3.1.7)** in combination with **chemo (radio) therapy according to the following cohorts:**
  - **Cohorts A1, A2, and B: O**xaliplatin/capecitabine chemotherapy in metastatic/locally advanced oesophageal cancer (OC).
  - **Cohort C: ~~and with n~~N**eoadjuvant **oxaliplatin/capecitabine** chemotherapy before surgery in operable OC.
  - Cohort D: Neoadjuvant paclitaxel/carboplatin chemotherapy + radiotherapy before surgery in operable OC.

  For Cohorts A1, A2, B and C, the immunotherapy will be given for a 4-week period before starting the ~~**standard**~~ chemo~~**(radio)**~~therapy, continuing durvalumab treatment once the chemotherapy starts. **For Cohort D, the immunotherapy will be given for a 4-week period before starting chemoradiotherapy, but the durvalumab dosing will not continue during the chemoradiotherapy. A dose of durvalumab will be given following radiotherapy on Day 64.**
- Section 3.1.6 (Sample Size): a reference to Section 3.1.11 was added for clarification of evaluable subjects.
- Section 3.1.7 Treatment Arms and Treatment Schema). This section was re-written and/or re-organized to reflect the changes to Cohort D. Figure 1 was also updated.
- Section 3.1.8 (Dosing Adjustments, Delays and Discontinuations): The following was added to the end of the paragraph: " ….guidelines for paclitaxel and carboplatin are provided in Section 8.7. If a toxicity occurs that requires toxicity management and the toxicity causing drug can

be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed."

- Section 3.1.10 (Subject Withdrawal): Withdrawal from treatment criterion #7 (initiation of alternative anticancer therapy) was moved to withdrawal from study and re written as "Initiation of alternative anticancer therapy (marketed or investigational)."
- Section 3.1.10.1 (Treatment beyond Progression) was added.
- Section 3.1.11 (Subject Replacement) was updated according to current language (changes in bold):

  In the *dose escalation phase*, subjects are fully evaluable for DLT **if they fulfill the criteria for the Per-Protocol Population for DLT Assessment (as defined in Section 4.1.2)**.

  - ~~**They experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9), or**~~

    ~~**In the absence of a DLT,they fulfill the criteria for the Per-Protocol Population (as defined in Section 4.1.2.**~~

  In Cohorts A1 and A2, subjects who are not evaluable for DLT will be replaced.

  Subjects who are not considered fully evaluable~~**per protocol**~~ for the primary objective of **overall** safety and tolerability per Section 4.1.2 may be replaced.

  ~~**In Cohorts A1 and A2, subjects who are not evaluable for DLT will be replaced**~~
- Section 3.1.13 (Interim Analysis) changes in bold: No formal interim analyses will be performed, except for the cohort safety assessments for DLTs in Cohort**s** A**1, and A2** (see Section 3.1.9).
- Section 3.1.16 (On Study and Post Study Follow-up) changes in bold: "If the determination is made to remove a subject from treatment at a visit that coincides with the first ~~**visit of the**~~ On Study Follow-up **visit**~~**Period**~~ (which is 14 days after the last dose of study treatment), any assessments required in the ~~**14 day post last treatment**~~ **first On Study Follow-up** visit that are not covered as part of the **last** on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the ~~**protocol**~~ **last on-treatment** visit and **the first On Study Follow-up** ~~**4 day post last treatment**~~ visit should not be repeated.

  Following the On Study Follow-up, there will be a Post Study Follow-up, where, clinical outcomes data (dates of progression/relapse and survival) will be collected at least every 6 months for up to 3 years from the initiation of the treatment.

  The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 110 days since the last administration of study drug.
- Section 3.1.16.1 (End of Study Visit) was added
- Section 3.2, Flowchart:
  - Cumulative Study Week Line was added
  - ± 3 was deleted from Day 1
  - ECOG Perf Status was added to Physical Exam, with same frequency as Physical Exam
  - Cohort D was updated to reflect changes in chemoradiotherapy regimen:
    - Durvalumab dosing during Chemoradiotherapy (Weeks 5 to 9) was deleted; one dose of durvalumab was added to Day 64.
    - Oxaliplatin and capecitabine doses over 4 cycles were deleted and replaced with paclitaxel and carboplatin doses once weekly, Weeks 5 to 8.

        - Footnote g regarding reduced dose of oxaliplatin was deleted
        - Surgery was changed from Week 23 to Weeks 16 to 18. This change was due to the change in timing of CRT for Cohort D
        - Radiotherapy for Cohort D was changed **FROM** 45 Gy over 25 fractions (Weeks 11 to 15) **TO** 41.4 Gy over 23 fractions; dosing was changed to a merged field over weeks 5 to 9
        - PET/CT was moved from Week 17 to Week 11 since this is the post CRT visit after the change for Cohort D. This is also the post treatment visit for Cohort C, thus the PET/CT scan remains at this time point for Cohort C.
    - Cohorts C and D post surgery durvalumab visits:
        - PET/CT scan was added to the first visit of the post-surgery durvalumab therapy (footnote c-1 was added to explain).
        - Urine pregnancy was changed from Q2W to Q4W.
    - ECG was added to First On Study Follow-up visit.
    - Vital sign assessments were added to Days 36, 50, 64, 92, 127.
    - Notations were added to blood collections that pertain to Cohorts A1, A2, and B only; Footnote g was re-written as Cohorts A1, A2, and B only
    - Footnote h for correlative and biopsy testing was re-written as "Post treatment for Cohorts A and B (a window of -7 to +14 days is allowed). If subject discontinues from treatment early, include at last study visit"
    - Footnote for correlative and biopsy testing for Cohorts C and D was changed to Footnote "i" and re-written as "On day of surgery for Cohorts C and D (blood draw must be pre-surgery). If subject discontinues from treatment early, include at last study visit."
    - Post Study Follow-up description was changed **FROM** "3 years post initiation of treatment: every 6 months. Telephone contact or medical record review: Vital status, tumor status; directed AE assessment for new onset or worsening of pre-existing autoimmune disease." **TO**: "Every 6 months for up to 3 years post initiation of treatment. Telephone contact or medical record review to include clinical outcomes data (dates of progression/relapse and survival)." This was updated for agreement with language in Section 3.1.16 and per current protocol language.
- Section 4.0 (Study Objectives and Endpoints)
    - Primary Objective #2 was re-written as (changes in bold): "Assess the Safety/Tolerability of durvalumab in combination with neoadjuvant chemo(radio)therapy **(oxaliplatin/capecitabine and paclitaxel/carboplatin/radiotherapy**) before surgery in operable OC."
    - Secondary Objective #2 was re-written as follows (changes in bold): "Assess the Clinical Efficacy of durvalumab in combination with neoadjuvant chemo(radio)therapy **(oxaliplatin/capecitabine and paclitaxel/carboplatin/radiotherapy)** in operable OC. (Endpoints: PFS after surgery, 1-year survival rate, OS, pathological and metabolic response rate)."
- Section 4.1.2 (Subject Evaluation and Statistics) was changed **FROM:** "The *Per-Protocol (PP) Population* for safety and tolerability is defined as all subjects who received at least 75% of the scheduled doses of durvalumab or tremelimumab and durvalumab over the first 3 months of the study, as well as, respective safety assessments without major protocol violations over the entire DLT Evaluation Period (as defined in Section 3.1.9). The *Intent-To-Treat (ITT) Population* for safety and tolerability is defined as all subjects who receive at least

one dose of durvalumab or tremelimumab. In Phase 1, for the primary endpoint of determining DLTs and the RCD, the analysis of safety and tolerability will be based on the PP Population. In both phases, the overall analysis of safety and tolerability will be based on the ITT Population."

TO: "The ***Per-Protocol (PP) Population for DLT Assessment*** is defined as:

- All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9) and
- All subjects with no DLT who received at least 75% of the scheduled doses of durvalumab and chemotherapy or tremelimumab, durvalumab and chemotherapy as well as, respective safety assessments without major protocol violations over the entire DLT Evaluation Period (as defined in Section 3.1.9).

Refer to Section 3.1.11 for subject replacement. The **Safety Population** is defined as all subjects who receive at least one dose of durvalumab or tremelimumab. In Phase 1, for the primary endpoint of determining DLTs and the RCD, the analysis of safety and tolerability will be based on the **PP Population for DLT Assessment.** In both phases, the overall analysis of safety and tolerability will be based on the **Safety Population.**

- Section 5.1 (Inclusion Criteria):
  - the following standard protocol language statement was added "Note: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart."
- Section 5.2 (Exclusion Criteria):
  - Criterion #2 was changed **FROM**: "Participation in another clinical study with an investigational product during the last 6 weeks." **TO**: "Prior treatment in another clinical study with an investigational product within 4 weeks prior to Day 1 of the study; resolution of respective adverse event to Grade 1 or lower should have occurred." Rationale for the change is to provide clarification using updated standard language. The following note was also added: "Note: all prior AEs, regardless of subject's inclusion in a clinical trial, must have resolved to Grade 1 or lower."
  - Prior Criterion # 3 ("Prior or concurrent systemic anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent") was deleted because a modified version of this statement is in Section 5.3.1 (Non-Permitted Concomitant Therapies) Criterion #2.
  - Prior Criterion #5 ("Current or prior use of immunosuppressive medication within 28 days before the first dose of study drugs, 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") was deleted because a modified version of this statement is in Section 5.3.1 (Non-Permitted Concomitant Therapies) Criterion #1.
  - Prior Criterion #11 ("Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab") was deleted because a modified version of this statement is in Section 5.3.1 (Non-Permitted Concomitant Therapies) Criterion #3.
  - Contraception language was updated according to current recommendations from Medimmune/AstraZeneca.

- Prior Criterion # 23 was updated (changes in bold): "Subjects should not donate blood while participating in this study or for at least 90 days following the last infusion of durvalumab, **6 months following the last infusion of tremelimumab**, or until the time specified in the prescribing information of oxaliplatin, capecitabine, **paclitaxel, or carboplatin**, whichever is longest."
- Prior Criterion #24 was updated (changes in bold): "For oxaliplatin, capecitabine, **paclitaxel, and carboplatin**: refer to prescribing information for additional information."

- Section 5.3.1 (Non-permitted Concomitant Therapies):
  - Criterion #2 was changed **FROM**: "Any investigational anticancer therapy other than the protocol specified therapies (wash-out period: 4 weeks prior to Day 1; 6 weeks for nitrosoureas)." **TO**: "Other cancer therapy (e.g., drug, radiation or immunotherapy). Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Day 1; 6 weeks for nitrosoureas)." This was changed for clarification and to update to standard protocol language.
- Sections 5.3.1(Non-permitted Concomitant Therapies) and 5.3.2 (Permitted Concomitant Therapies): Paclitaxel and carboplatin were added to the statement: "For **oxaliplatin, capecitabine, paclitaxel, and carboplatin,** refer to the prescribing information… "
- Section 5.3.2 (Permitted Concomitant Therapies): a correction was made to the following sentence (changes in bold): "All non-drug therapies must be recorded in the respective sections of the case report form**~~ or as AEs~~**.
- Section 6 (Study Drug Preparation and Administration): The following paragraph was changed **FROM**: "On days with concurrent tremelimumab and durvalumab dosing, durvalumab administration will start 60 (± 10) minutes after the end of the tremelimumab infusion. On days with concurrent durvalumab and oxaliplatin dosing, oxaliplatin administration will start 60 (± 10) minutes after the end of the durvalumab infusion. The morning dose of capecitabine is taken after the oxaliplatin infusion.
  TO: "On days with concurrent tremelimumab and durvalumab dosing, durvalumab administration will start at least 60 minutes after the end of the tremelimumab infusion. On days with concurrent durvalumab and oxaliplatin dosing, oxaliplatin administration will start at least 60 minutes after the end of the durvalumab infusion. The morning dose of capecitabine is taken after the oxaliplatin infusion. On days with concurrent paclitaxel and carboplatin dosing, paclitaxel will be infused over 1 hour followed by carboplatin infusion over 1 hour according to local standards."
- Section 6.3 (Paclitaxel) and Section 6.4 (Carboplatin) were added.
- Section 6.5 (Tremelimumab) and Section 6.6 (Durvalumab):
  - The entire sections were updated and reorganized according to current language from AstraZeneca.
  - Dextrose was added as an option to be used as a diluent.
  - The following statement was added "See Section 8.5.1 for guidelines for infusion-related reactions."
  - The following statement was clarified: "After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed."

- The following statement was clarified: “The total time from needle puncture of the tremelimumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion (total infusion time not to exceed 4 hours), the total allowed time for preparation and administration should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.”
- The following statement was added for tremelimumab: “No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed. However, administration sets containing cellulose-based filters should not be used with tremelimumab.

- Section 6.7 (Estimated Study Drug Requirements): Paclitaxel and carboplatin were added.
- Section 6.8 (Monitoring): The following was added: “
  Note: When durvalumab and tremelimumab are to be administered on the same day, durvalumab infusion will start at least 60 minutes after the end of tremelimumab infusion even though vital signs assessment is not required during the entire 60-minute period post tremelimumab.
  If a subject tolerates treatment well for the first 4 doses of durvalumab (i.e., no infusion reactions), subsequent infusions for that subject can be monitored according to the table below. A longer duration of observation after the end of infusion can be used if the Investigator deems it clinically necessary.

Vital Signs Assessment on Study Drug Administration Days (after first 4 doses)				
Drug	**Pre Dose**	**During Infusion**	**End of Infusion (± 5 minutes)**	**15 (± 5) Minutes Post Infusion**
Durvalumab	X	Every 30 (± 5) minutes	X	X

- Section 6.9 (Drug Overdose Management): Paclitaxel and Carboplatin were added.
- Section 7.1.2 (Additional Expedited Reporting Requirements): The following paragraph was changed **FROM**: “For the purpose of this study, the following events are considered medically important conditions and must be reported in an expedited manner (See Section 7.1.6 for Sponsor contact information):”
  TO: “For the purpose of this study, the following events must be reported by phone or email to the Sponsor within 24 hours of knowledge of the event (See Section 7.1.6 for Sponsor contact information) **and may result in submission of an SAE based on certain criteria outlined below:”** This was updated to provide clarification and consistency with other protocols.
- Section 7.1.2.1.1 (Maternal Exposure): The following paragraph was added: “Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer)”
- Section 7.1.2.1.2 (Paternal Exposure): The following paragraph was changed **FROM: “**Male subjects should refrain from fathering a child or donating sperm during the study and for 6 months after the final dose of investigational product.” **TO**: “Male subjects should refrain

from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer).

- Section 7.1.5 (General Reporting Requirements): The section was updated to be consistent with current reporting language. **FROM**: "Documentation of serious and non-serious adverse events includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as the causal relationship between the event and the study drug in accordance with Section 7.1.4. All serious and non-serious adverse events occurring between the date of signing the informed consent and the off-study date must be documented in the source records and on the respective section of the CRF, regardless of the assumption of a causal relationship. During the On Study Follow-up period, all AEs will continue to be documented for 110 days after the last dose of study drug for all subjects. NOTE: For subjects in Cohorts C and D, there may be 2 On Study Follow-up periods. (1) All AEs will be collected for 110 days after the last dose of durvalumab in Cycle 2, with the exception of those AEs that are related to the protocol-defined surgical procedure(s). (2) If any subjects in Cohorts C and D continue durvalumab treatment after the planned surgical procedure, there will be another On Study Follow-up period, and all AEs will be collected for 110 days after the last dose of durvalumab." **TO:** All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4 This documentation is required for all AEs that occur: (a).from the date of signing the informed consent, and (b)until the off-study date or 110 days after the last administration of study drug, whichever is longer, or until a new treatment is initiated (see Section 3.1.10 for subjects who begin other anti-cancer treatment). Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 110 days after the last dose of the last study treatment (regardless of initiation of another therapy). NOTE: For subjects in Cohorts C and D, there may be 2 On Study Follow-up periods: (1) All AEs will be collected for 110 days after the last dose of pre-surgery durvalumab, with the exception of those AEs that are related to the protocol-defined surgical procedure(s). (2) If any subjects in Cohorts C and D continue durvalumab treatment after the planned surgical procedure, there will be another On Study Follow-up period, and all AEs will be collected for 110 days after the last dose of durvalumab.
- Section 7.1.6: The following statement was added; "Serious adverse event reporting to AstraZeneca/Medimmune is described in a separate agreement."
- Section 7.1.8 (AESIs). Additional information was added to the description of the AESIs per the updated guidelines provided by AstraZeneca/Medimmune.
- Section 7.2.3 (CRF Data Collection): The following statement was added: "All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF."
- Sections 8.5, 8.6, 8.7 (Dose Modifications and Management Guidelines): The following paragraph was added: "If a toxicity occurs that requires toxicity management in accordance with Sections 8.5, 8.6, and 8.7,and the toxicity causing agent can be clearly identified, then the respective guideline should be followed. If the toxicity causing agent cannot be identified, then the more conservative guideline should be followed."
- Section 8.5.1 (Durvalumab and Tremelimumab Dose Modification Due to Toxicity):

- The paragraph, which referenced Yervoy, Opdivo, and Keytruda was deleted.
- The statement that referenced tremelimumab guidelines was deleted, as these are included in the combined guidelines from Medimmune.
- Modifications were made to the table based on updated recommendations from Medimmune dated 19Aug2016.

- Section 8.5.2 (Durvalumab and Tremelimumab Dose Modifications not due to Toxicity): The following updated language was added and the previous criteria were deleted (this was done to provide clarification and consistency with other protocols):
  1. The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 10 days. All resulting protocol deviations should be documented.
  2. If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued.
  3. If the dosing interruption is ≤ half the planned dosing interval, the originally planned dose should be given and the next dose(s) should be adjusted in accordance with #1, if necessary.
  4. If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary
- Section 8.7 was added: Dose Modification and Management Guidelines for Paclitaxel/Carboplatin.
- Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable. Sections were numbered as appropriate when additional sections were added. Abbreviations were updated. Modified signature box on Synopsis page to allow space for Local Sponsor Signature.

Amendment 2.1 (Administrative Change)
Issue date: 28-FEB-2017
Summary of Changes:

- Synopsis page: Removed additional space for local sponsor signature, as the additional signature is not required.

Amendment 3
Issue date: 14-JUL-2017
NOTE: Amendment 2 was previously approved by the study team and AstraZeneca; however, it was not submitted to MHRA and Ethics Committee. The changes for Amendment 3 are documented below. For the purposes of MHRA/Ethics submissions, all changes from Amendments 2 and 3 will be combined into one tracked changes document.
Summary of Changes:

- Section 3.1 (Study Design): the next to last paragraph was modified to provide clarity for the durvalumab dose post CRT for Cohort D (changes in bold): "For Cohorts A1, A2, B and C, the immunotherapy will be given for a 4-week period before starting the chemotherapy, continuing durvalumab treatment once the chemotherapy starts. For Cohort D, the immunotherapy will be given for a 4-week period before starting chemoradiotherapy, but the durvalumab dosing will not continue during the chemoradiotherapy. A dose of

durvalumab will be given following **chemo**radiotherapy on Day 64 **(±3 days). If the subject has not completely recovered (per Investigator assessment) by Day 64 (±3 days), the durvalumab dose may be delayed until Day 71 (±3 days)**."

- Section 3.1.4 (Subject Population): the last sentence was changed as follows (changes in bold): "The radiotherapy offered in Cohort D will be ~~**standard of care**~~ **provided per Section 6.13** for these subjects, as already determined by MDT.
- Section 3.1.5 (No. of Sites/Subjects): The following sentence was updated to present the possibility of additional sites (changes in bold): "~~**Two (2)**~~ **Up to 4** sites; and 75 evaluable subjects are estimated for this study."
- Section 3.1.7 (Treatment Arms and Treatment Schema):
  - The following paragraph for Cohort D was updated to reflect changes that were requested by the study team (i.e., 4 weekly doses of Chemotherapy was changed to 5 weekly doses; and the timing of the post-CRT dose of durvalumab was clarified). The 5 week dose regimen for the chemotherapy in Cohort D aligns with the standard for paclitaxel/carboplatin. Changes are shown in bold: "For Cohort D, chemoradiotherapy will start after the 4-week durvalumab immunotherapy period, i.e., on Cycle 1, Day 1 (Study Week 5, Study Day 29). Subjects will receive ~~**(4)**~~ **5** weekly doses of paclitaxel (50 mg/m^2) and carboplatin (AUC 2) concurrent with radiotherapy (41.4 Gy in 23 fractions), but without durvalumab. Radiotherapy will be given over 23 fractions over a period 5 weeks. A dose of durvalumab will be given following **chemo**radiotherapy on Day 64 **(±3 days). If the subject has not completely recovered (per Investigator assessment) by Day 64 (±3 days), the durvalumab dose may be delayed until Day 71 (±3 days)."**
  - In the Phase 2 section, similar changes were made for the Cohort D description. In the table, paclitaxel and carboplatin schedules were changed from Weeks 5-8 to Study Weeks 5-9.
  - Phases 1 and 2 sections: clarifications and formatting consistency were added for the Cohort tables.
- Section 3.1.16 (On Study and Post Study Follow-up): Paragraph 2 was clarified (changes in bold): "For all subjects who complete study treatment or who discontinue treatment prematurely according to Section 3.1.10, there will be an On Study Follow-up period for 110 days after the last ~~**durvalumab or durvalumab + tremelimumab**~~ **study drug** treatment, which will include collection of AE data. NOTE: For subjects in Cohorts C and D, there may be 2 On Study Follow-up periods, **as described in Section 7.1.5.**
- Section 3.2 (Flowchart):
  - Paclitaxel and carboplatin doses were added to Week 9 for Cohort D to align with the changes implemented in Section 3.1.7.
  - For Cohort D, Lab assessments and pregnancy test were added for Day 64. Footnote L was added to the durvalumab dose and the added assessments on Day 64: "For Cohort D, a dose of durvalumab will be given following chemoradiotherapy on Day 64 (±3 days). If the subject has not completely recovered (per Investigator assessment) by Day 64 (±3 days), the durvalumab dose may be delayed until Day 71 (±3 days). Lab assessments and pregnancy test should be done on the day (64 or 71) the durvalumab dose is given.
  - Hematology assessments were added to Days 36, 50, 92, and 134 to align with chemotherapy dosing days.
  - Chemistry assessments were added to Days 36 and 50 for Coh D only (weekly assessments are standard practice during CRT).

- Footnote a. The following clarification was added: “For each on-treatment cohort, hematology, chem, urine and pregnancy safety assessments should coincide with drug administration study visits. With the exception of On Study Follow-up, Lab assessments are not applicable if there is no drug administration visit for a particular cohort. End of study pregnancy test for women of child-bearing potential must be done on serum.”
- Physical exam assessments were added to Days 36, 50, 64, 92, 134, and Post surgery durvalumab dosing days.
- Footnote b. The following clarification was added: ”For each on-treatment cohort, physical exams should coincide with drug administration study visits. With the exception of On Study Follow-up, physical exams are not applicable if there is no drug administration visit for a particular cohort.”
- Footnote e was re-written to provide clarification: “For each on-treatment cohort, vital signs assessments should coincide with drug administration study visits. With the exception of On Study Follow-up, vital sign assessments are not applicable if there is no drug administration visit for a particular cohort. For durva and treme, vital signs are measured before, during and after infusions according to Section 6.8.
- Previous Footnote g was deleted; lab assessments, physical exams, and vital sign assessments were clarified in Footnotes a, b, and, e respectively.
- New Footnote g was added: “Concomitant med and AE information may be collected by telephone if there is no study drug administration/lab test/scan/procedure visit scheduled.”
- Footnote m was added for ECG assessment: “12 Lead ECG - baseline and abnormal ECG at any time will be done in triplicate (2-5 minutes apart); others may be single measurements.

- Section 4.2.1 (Endpoints and Assessment Methods): Last paragraph was clarified (changes in bold): “Evaluation according to irRECIST using CT scanning will be performed every 6 weeks for Cohorts A and B. Subjects in Cohorts C and D, will undergo PET/CT scanning before and after treatment per ~~**standard of care**~~ **the Study Flowchart in Section 3.2.** Metabolic response will be assessed according to PERCIST.[38]
- Section 6: Heading was changed to (changes in bold): Study Drug Preparation and Administration **and Radiotherapy Delivery.**
- Section 6.5.4 (Tremelimumab administration): the following bullet was updated to provide clarity based on current Medimmune/Astrazeneca recommendations. Changed **FROM:** “The total time from needle puncture of the tremelimumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion (total infusion time not to exceed 4 hours), the total allowed time for preparation and administration should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.” **TO:** “The total time from needle puncture of the tremelimumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.”

- Section 6.6.4 (Durvalumab administration): similar change as the one described for tremelimumab in the previous bullet
- Section 6.10 (Radiotherapy Delivery) was added.
- Section 7.1.5 (General Reporting Requirements): the following statement was added: “See Section 8.7.3 for Reference Safety Information (RSI) on radiotherapy; see Sections 8.6.3 and 8.7.4 for RSI on surgery.”
- Section 7.1.8 (AESIs): Based on updated information from Astrazeneca, the following changes were made: 1) diabetes insipidus was added to endocrine disorders; 2) bullet was added: “Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.”
- Section 8.5.1 (Durvalumab and Tremelimumab Dose Modification due to Toxicity): for Infusion-related Reactions Grades 1 and 2, the phrase “total infusion time not to exceed 4 hours” was deleted in order to align with the updates in Sections 6.5.4 and 6.6.4.
- Section 8.6: Heading was changed to (changes in bold): ” Dose Modification and Management Guidelines for Oxaliplatin/Capecitabine **and Surgery**.”
- Section 8.6.3 (Surgery) was added to provide additional study information that was previously not included in the protocol.
- Section 8.7: Heading was changed to (changes in bold): ” Dose Modification and Management Guidelines for Paclitaxel/Carboplatin**, Radiotherapy and Surgery**.”
- Section 8.7.1 (Haematologic Related Toxicity):
  - “Delay chemotherapy” was changed to “omit chemotherapy” to account for the weekly dosing schedule.
  - Table was added for monitoring neutrophils and platelets
- Section 8.7.2 (Non-Haematologic Toxicity):
  - Table was updated based on input from team and NEOSCOPE protocol.
  - Other Non-haematologic Toxicities table was added.
- Section 8.7.3 (Heading was updated from Radiation Toxicity to Radiotherapy Toxicity): The following paragraphs were added to provide additional study information that was previously not included in the protocol: “The following list provides the expected events in relation to radiotherapy (and its possible effect following surgery). This should be used as the Reference Safety Information (RSI) when assessing the expectedness of SAEs causally related to radiotherapy: Mucositis, oesophagitis, dysphagia, lethargy, pain, anaemia, nausea and vomiting, weight loss, poor oral intake, tinnitus, infection, pneumonitis, pericarditis, wound infection, anastomotic leak, chest infection, pleural effusion, thrombo-embolism. In the event of a chemotherapy toxicity or dose modification, the decision to continue radiotherapy rests with the treating clinician. “
- Section 8.7.4 (Surgery) was added to provide additional study information that was previously not included in the protocol.
- Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable. Sections were numbered as appropriate when additional sections were added. Abbreviations were updated.

Amendment 4
Issue date: 08-SEP-2017
NOTE: MHRA review of Amendment 3 resulted in a request for the clarifications/additions, which are included in Amendment 4 and documented below.

- Section 5.2 (Exclusion Criteria), #18. The following Note was added to provide additional requirements for contraception/breastfeeding/fertility with respect to carboplatin and paclitaxel: "**NOTE: additional requirements for carboplatin and paclitaxel treatment.** Women of childbearing potential should avoid becoming pregnant while taking carboplatin and paclitaxel; they should notify the treating physician immediately if pregnancy occurs. Female and male subjects of fertile age and/or their partners should use contraceptives during and for at least 6 months after treatment with these drugs. Male subjects should also avoid sperm donation during and for at least 6 months after treatment with these drugs. Breastfeeding should be discontinued for the duration of treatment with these drugs. Male subjects should be advised regarding cryoconservation of sperm prior to treatment because of the possibility of irreversible infertility due to the treatment."
- Section 5.3.1 (Non-permitted Concomitant Therapies): the following paragraphs were added to provide additional information regarding non-permitted concomitant medications for carboplatin and paclitaxel:
  "**Nephrotoxic/ototoxic drugs:** Auditory defects have been reported during carboplatin therapy. Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics is not recommended as they may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance."

  "**CYP2C8 or CYP3A4 inhibitors/inducers:** Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures."

Amendment 5
Issue date: 10-MAR-2018
Summary of Changes:

- Section 3.1.7 (Treatment Arms and Treatment Schema). Clarification was added to indicate that surgery timing would be according to institutional policies; changes in bold:
  Subjects in Cohorts C and D will undergo **surgery** 6 to 8 weeks after completing chemo(radio)therapy **or according to institutional policies for surgery; ~~and~~** they will be eligible to resume durvalumab dosing (to a maximum of 12 infusions) once recovered from surgery, provided that this is within 3 months of surgery
- Section 3.1.9 (DLT and MTD/RCD for the Combination Therapy): The following exception bullet was added to Point #3: "Grade 3 or 4 asymptomatic increases in amylase or lipase levels for which appropriate evaluation shows no clinical evidence of pancreatitis." This was done to align with the amylase/lipase information in Section 8.5.1 dose modifications.

- Section 3.1.10 (Subject Withdrawal). The following paragraph was moved within the section to allow for better clarity: "Discontinuation from receiving study treatment does not mean that the subject is withdrawn from the study. Subjects who are withdrawn from the study treatment should enter the On Study Follow-up (see Section 3.1.16), if feasible. Subjects who begin other anti-cancer therapy should immediately be considered off-study and proceed to the Post Study Follow-up (Section 3.1.16)."
- Section 3.1.16 (On Study and Post Study Follow-up). The following paragraph was added to provide clarification and to align with the directions in the flowchart: "Refer to Flowchart in Section 3.2 for post treatment biopsies. If the subject discontinues from treatment early, the biopsy specimen should be collected at the last study visit or the first On Study Follow-up visit."
- Section 3.1.16 (On Study and Post Study Follow-up). The Note was clarified to indicate that "For subjects in Cohorts C and D, additional details regarding the On Study Follow-up period are provided in Section 7.1.5." (The note originally indicated there may be 2 On Study Follow-up periods for these 2 cohorts).
- Section 3.2 (Flowchart).
  - The following clarification was added to the surgery lines (changes in bold): "Surgery - 6 to 8 weeks after completion of therapy **or according to institutional policies for surgery"**
  - Footnote c-1 was changed to n and updated as follows:
    PET/CT scan for Cohorts C and D: Scan scheduled after completion of therapy/before surgery may be combined as part of the surgery workup or per local institutional standards. Post surgery scan may be done at first post surgery durvalumab dosing visit. PET scan at the post-surgery and On-Study Follow-Up timepoints may be replaced with a CT scan.
  - Footnote o was added for CT and PET/CT lines
  - Footnotes h and i were updated to reflect change in Section 3.1.16: the phrase "or the first On Study Follow-up visit" was added.
  - Footnote p was added to provide clarification for the collection of AEs for Cohorts C and D during the period after the last dose of pre-surgery durvalumab.
- Section 4.2.1 (Clinical Efficacy, Endpoints and Assessment Methods). The last paragraph was modified to provide clarification (changes in bold): "Evaluation according to irRECIST using CT scanning will be performed every 6 weeks for Cohorts A and B. Subjects in Cohorts C and D, will undergo PET/CT scanning before and after treatment per the Study Flowchart in Section 3.2. **The scans should be carried out according to local institutional standards and reported according to irRECIST and RECIST1.1 (see the guidelines in Section 8.8). The information to be captured at each scan is outlined in the eCRF. Scanning protocols and modalities should remain consistent throughout the study.** Metabolic response will be assessed according to PERCIST.[38]"
- Section 5.1 (Inclusion Criteria). Criterion #1 was updated to include the following: "Have not received full dose systemic chemotherapy." Rationale: this intention was previously included with other criteria, but was inadvertently deleted during previous updates.
- Section 5.2 (Exclusion Criteria). Criterion #13 was updated for clarification (changes in bold): "Peripheral sensitive neuropathy with functional impairment ~~**prior to first course**~~."
- Section 5.3.2 (Permitted Concomitant Therapies). Item #7 was added: "Subjects may receive localized palliative radiotherapy on study if clinically indicated after discussion

with the LICR medical monitor." Rationale: This was added to provide clarification, as it was previously inadvertently omitted based on other changes.

- Section 7.1.5 (General Reporting Requirements). The Note for Cohorts C and D was edited to provide clarification. The changes implemented are shown in bold:
  "NOTE: For subjects in Cohorts C and D, the**~~re may be 2~~** On Study Follow-up period**~~s~~ is defined as follows**: 1. All AEs will be collected for 110 days after the last dose of pre-surgery durvalumab, with the exception of those AEs that are related to the protocol-defined surgical procedure(s). **If the decision is made that a subject will not receive continued durvalumab, the subject must start On Study Follow-up and have at least one On Study Follow-up visit at 110 days (+30 days) after last dose of durvalumab or at the point of the decision (+30 days), whichever is later. See Flowchart in Section 3.2 for details.**
  2. If any subjects in Cohorts C and D continue durvalumab treatment after the planned surgical procedure, the**~~re~~y** will **follow the** On Study Follow-up period **according to the Flowchart in Section 3.2,** and all AEs will be collected for 110 days after the last dose of durvalumab.
- Section 7.1.8 (AESIs):
  The section was updated and reorganized based on updated recommendations from Medimmune in the updated IB. Specifically:
  - Endocrine disorders-deleted diabetes insipidus.
  - Myocarditis and myositis/polymyositis were added
  - Other inflammatory responses was updated (changes in bold):
    "Other inflammatory responses that are rare **/ less frequent** with a potential immune-mediated aetiology include, **but are not limited to, ~~myocarditis~~,** pericarditis**, sarcoidosis,** uveitis**, and other events involving the eye, skin, hematological and rheumatological events.**
- Section 8.3 (Participating Laboratories): The table that listed participating laboratories was deleted and replaced with "Information regarding participating laboratories is provided in the Clinical Study File." Rationale: additional sites have been added and the table no longer provides current information.
- Section 8.5 (Dose Adjustment and Delays for Durvalumab). The following note was added: "Note: the Medimmune guideline refers to dose modifications for durvalumab (MEDI4736) and tremelimumab. For this protocol, however, only 1 dose of tremelimumab is given to certain cohorts, and no dose modification is possible. Therefore, this section has been modified to refer to dose modifications for durvalumab only." References to tremelimumab dose modifications throughout the section were deleted, as appropriate.
- Section 8.5.1 (Durvalumab and Tremelimumab dose modification due to toxicity): Immune-related AEs were updated based on updated Toxicity Mgt Guidelines from Medimmune (Dated 01Nov2017). Specifically, myocarditis, myositis/polymyositis were added; Diarrhea/colitis and endocrinopathies were updated.
- Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

Amendment 6
Issue date: 18-MAY-2018
Summary of Changes:

- Per rationale in Section 2.2, Cohort C-FLOT was added.
- Updates related to Cohort C-FLOT were added to the following sections, as appropriate:
  - Synopsis
  - Section 2.2 (Rationale for Amendment 6) was added.
  - Section 3.1 (Study Design)
  - Section 3.1.2 (Enrollment/Randomization)
  - Section 3.1.4 (Subject Population)
  - Section 3.1.5 (No. of Sites/Subjects)
  - Section 3.1.6 (Sample Size and Statistical Considerations)
  - Section 3.1.7 (Treatment Arms and Treatment Schema)
  - Figure 1 – Treatment Schema
  - Section 3.1.7.2 (Phase 2 – Expansion Phase
  - Section 3.1.8 (Dosing Adjustments, Delays, and Discontinuations)
  - Section 3.1.9 (DLT)
  - Section 3.1.12 (Optional Study Treatment Extension)
  - Section 3.1.14 (Safety Monitoring and Study Stopping Rules)
  - Section 3.1.15 (Duration of Study)
  - Section 3.1.16 (On Study and Post Study Follow-up)
  - Section 3.2 (Study Flowcharts). A clarification was added to footnotes “a and f” to record times as well as dates.
  - Section 3.2.1 (Study Flowchart for all Cohorts except Cohort C-FLOT) – new section was added
  - Section 3.2.2 (Study Flowchart for Cohort C-FLOT) – new flowchart and new section were added.
  - Section 4 (Study Objectives and Endpoints)
  - Section 4.1.1 (Safety Endpoints and Assessment Methods)
  - Section 4.2 (Clinical Efficacy) and sub sections
  - Section 4.3 (Immune Monitoring)
  - Section 5.1 (Inclusion Criteria): C-FLOT was added to #1
  - Section 5.2 (Exclusion Criteria)
    - FLOT was added to the NOTE in #18 (contraception)
    - FLOT was added to Criteria #20 and 21
  - Section 5.3.1 (Non-permitted Concomitant Therapies) was updated. See details below.
  - Section 5.3.2 (Permitted Concomitant Therapies). Last row was updated as follows (changes in bold): “For oxaliplatin, capecitabine, paclitaxel, carboplatin, **and FLOT (5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel)**, refer to prescribing information for additional information.”
  - Section 6 (Study Drug Preparation). The following paragraph was added: “On days with concurrent durvalumab and FLOT dosing, the cytotoxic chemotherapy drugs should be administered at least 60 minutes after the end of the durvalumab infusion. Local standard procedures for the administration of 5-fluorouracil, leucovorin, oxaliplatin and docetaxel will apply. Note that leucovorin should not be mixed in the same infusion as 5-fluorouracil because a precipitate may form.”

- Sections 6.5 (Fluorouracil), 6.6 (Leucovorin), and 6.7 (Docetaxel) were added. Subsequent Sections were re-numbered, as appropriate.
- Newly numbered Section 6.10 (Estimated Study Drug Requirements) was updated to include FLOT drugs
- Newly numbered Section 6.12 (Drug Overdose Management) was updated to include FLOT drugs
- Section 7.1.5 (General Reporting Requirements): Note in last paragraph was updated for addition of Cohort C-FLOT.
- Section 8.6 (Dose Modification and Management Guidelines for Oxaliplatin/Capecitabine and Surgery) was updated to include FLOT and/or specific elements of FLOT, as appropriate.
- Section 8.7.4 (Surgery)
- Section 8.10 (List of Abbreviations)
- Section 9 (References) – Al-Batran et al. 2017 was added
- Section 5.3.1 (Non-permitted Concomitant Therapies) was updated as follows (changes in bold):

"For oxaliplatin, capecitabine, paclitaxel, carboplatin, **and FLOT (5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel)** refer to the prescribing information and the additional information below:

Warfarin: INR (International normalised ratio) control may be affected by capecitabine. If a subject requiring coumarin-derived anticoagulants such as warfarin is taking capecitabine, more frequent INR monitoring is required. The use of low molecular weight heparin instead of warfarin is at the discretion of the Investigator.

Phenytoin: Blood phenytoin levels may increase with capecitabine or **5-fluorouracil.** If a subject is taking phenytoin concomitantly with ~~**capecitabine**~~ **these drugs**, they should be monitored regularly for increased phenytoin plasma concentrations and associated clinical symptoms.

Other anti-epileptic substances: Leucovorin may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures (a decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed).

Allopurinol: Interactions with allopurinol have been observed for 5-fluorouracil; with possible decreased efficacy of 5-fluorouracil. Concomitant use of allopurinol with capecitabine **or 5-fluorouracil** should be avoided.

Antivirals: Brivudine and sorivudine must not be prescribed with capecitabine as they may produce a life-threatening interaction.

Brivudin, sorivudin and analogues: 5-fluorouracil must not be given in combination with brivudin, sorivudin and analogues. Brivudin, sorivudin and analogues are potent inhibitors of the 5-fluorouracil metabolising enzyme dihydropyrimidine dehydrogenase (DPD).

5-Fluorouracil must not be given to subjects known to be homozygotic for dihydropyrimidine dehydrogenase (DPD).

Vaccination with a live vaccine should be avoided in subjects receiving 5-fluorouracil due to the potential for serious or fatal infections. Contact should be avoided with people who have recently been treated with polio virus vaccine.

Photosensitivity: It is not advisable to have prolonged exposure to sunlight because of the risk of photosensitivity with 5-fluorouracil.

Nephrotoxic/ototoxic drugs: Auditory defects have been reported during carboplatin therapy. Concurrent therapy with nephrotoxic drugs or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics is not recommended as they may increase or exacerbate toxicity, particularly in renal failure patients, due to carboplatin induced changes in renal clearance.
CYP2C8 or CYP3A4 inhibitors/inducers: Caution should be exercised when administering paclitaxel concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.
The concomitant use of docetaxel with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided.
Cytochrome P450-3A: The metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A such as ciclosporine, ketoconazole and erythromycin."

- Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

Amendment 6.1
Issue date: 10-JUL-2018
Summary of Changes:
Per Investigator request, the following changes/clarifications were made to the flowchart:

- Footnote "i" in both flowcharts was updated to indicate that blood draw for correlatives may be up to 3 days before surgery.
  - This clarification was also added to Section 4.3, Immune Monitoring.
- Footnote "q" in Flowchart 3.2.1 (all cohorts except C-FLOT) and footnote "m" in Flowchart 3.2.2 (C-FLOT) were added to indicate that "Saliva samples may be collected at each biopsy collection time point; photographs at endoscopy may be taken."
- For Flowchart 3.2.2 (Cohort C-FLOT), the following corrections were incorporated: the collection of the full chemistry panel and urinalysis samples were added to Cycle 2 Day 1 and the urine pregnancy test was moved from Cycle 2 Day 15 to Cycle 2 Day 1.

Amendment 6.2 (Administrative Change)
Issue date: 20-JUL-2018
Summary of Changes:

- For Flowchart 3.2.2 (Cohort C-FLOT), the following assessments, which were inadvertently included in the surgery column, were deleted: physical exam, vital signs, and hematology, chemistry, urinalysis, and pregnancy labs. According to the footnotes, these assessments are only done on drug administration days.

Amendment 7
Issue date: 03-MAR-2019
Summary of Changes:

- Cohort D2, a subset of Cohort D, was added. Rationale for Cohort D2 is provided in Section 2.3 (which was added for Amendment 7).
- Changes related to the addition of Cohort D2 were made in the following sections:
  - Synopsis
  - Section 2.3, Rationale for Amendment 7
  - Section 3.1, Study Design
  - Section 3.1.2, Enrollment/Randomization
  - Section 3.1.4, Subject Population
  - Section 3.1.5, No. of Sites/Subjects
  - Section 3.1.6, Sample Size and Statistical Considerations
  - Section 3.1.7, Treatment Arms and Treatment Schema
  - Figure 1, Treatment Schema
  - Section 3.1.7.2, Phase 2 -Expansion Phase
  - Section 3.1.12, Optional Treatment Study Extension
  - Section 3.1.14, Safety Monitoring and Study Stopping Rules
  - Section 3.1.15, Duration of Study
  - Section 3.2.1 Flowchart was re-named as Flowchart for all Cohorts except C-FLOT and D2
  - Section 3.2.3 Study Flowchart for Cohort D2 was added.
  - Section 4.1.1, Safety Endpoints and Assessment Methods
  - Section 4.2, Clinical Efficacy
  - Section 4.2.1, Efficacy Endpoints and Assessment Methods
  - Section 4.2.1.2, Progression-free Survival Rate
  - Section 5.1, Inclusion Criteria
  - Section 7.1.5, General Reporting Requirements
- The following was added: “The option to approach subjects with long-term survival (PFS > 1 year, still in remission) from the metastatic cohorts (A and B) of the trial to request blood (up to 300 mL, acquired in aliquots of 100 mL at a time) for additional testing.”
  - The rationale for this addition was provided in Section 2.3, Rationale for Amendment 7.
  - The change was added to Section 4.3, Immune Monitoring
  - The change was also added to Section 3.2.1 (Flowchart for all Cohorts except C-FLOT and D2), Footnote r
- Section 3.1.2 (Enrollment/Randomization). In addition to the changes listed above, the following notes were added:
  “See note in Section 3.1 regarding enrollment to Cohort D2.
  See notes in Section 3.1.7 (Cohort D), for information regarding safety assessment of subjects in Cohort D and prior to enrollment into Cohort D2.”
- Section 3.1.7 (Treatment Arms and Treatment Schema). In addition to the changes listed above, the following note was added:
  “Note: The Cohort D subset, Cohort D2, will start enrollment after several Cohort D subjects have been treated with the non-concurrent immunotherapy/ chemoradiotherapy schedules; ongoing safety review of those Cohort D subjects will inform enrollment into Cohort D2.”
- Section 3.1.16 (On Study and Post Study Follow-up).

The Note was changed **FROM**: "NOTE: For subjects in Cohorts C/C-FLOT and D, additional details regarding the On Study Follow-up period are provided in Section 7.1.5." **TO:** "NOTE: For each of the cohorts, additional details regarding the On Study Follow-up period are provided in Section 7.1.5."

- Section 3.2.1 (Flowchart for all Cohorts except C-FLOT and D2). In addition to the changes listed above, the following change was made:
  - For footnote a, the following clarification was added: "Day 1 lab assessments may be performed within 3 days prior to Day 1."
  - Footnote L was clarified, and the footnote was added to Day 64 safety assessments (physical exam, vitals, AEs, Con meds).
  - Footnote p – "See Section 7.1.5 for details on Cohorts A and B" was added.
- Section 6 (Study Drug Preparation and Administration). The following statement was added: "For chemotherapy, banded doses may be used according to institutional guidelines."
- Section 6.10 (Estimated Drug Requirements). Durvalumab estimate was updated:

Durvalumab¤	~~2335~~ 2400 x 500 mg vials¤

- Section 7.1.1 (General AE/SAE Definitions per ICH Guidelines). The following statement was added: "NOTE: If a subject is hospitalized for a planned standard of care procedure that is not related to an AE, the hospitalization does not require an SAE report. However, if there is an additional AE or complication during the hospitalization, or if the hospitalization is prolonged, the SAE procedures described in Section 7.1 must be followed."
- Section 7.1.5 (General Reporting Requirements for AEs). The following note was added for clarification:
  NOTE: For subjects in Cohorts A and B: 1) If durvalumab is discontinued early, subjects will follow the On Study Follow-up period according to the Flowchart in Section 3.2, and all AEs will be collected for 110 days after the last dose of durvalumab. 2) If any subjects continue chemotherapy treatment alone (no durvalumab), they will complete the first On Study Follow-up at Day 28 (+14 days) post last dose of chemotherapy. All AEs will be collected for at least 28 (+14) days after the last dose of chemotherapy; however, per point #1, subjects must still be followed for On Study Follow-up post last dose of durvalumab for 110 days.
- Section 8.6 (Dose Modification and Management Guidelines for Oxaliplatin/Capecitabine, FLOT, and Surgery). The last sentence was clarified as follows (changes in bold): "The following outlines provide guidance for the management of toxicities for subjects treated with oxaliplatin/capecitabine **or the FLOT regimen**."
- Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

Amendment 7.1 (Administrative Change)
Issue date: 26-APR-2019
Summary of Changes:
In Sections 2.3 (Rationale for Amendment 7) and Section 4.3 (immune Monitoring), the following change was made (changes in bold):
The Investigator(s) will have the option to approach subjects with long-term survival (PFS > 1 year, still in remission) from the metastatic cohorts (A and B) of the trial to request blood (up to 300 mL~~**, acquired in aliquots of 100 mL at a time**~~) for additional testing.

This change was also applied to Section 3.2.1 (Study Flowchart for all cohorts except C-FLOT and D2) in footnote "r".

Amendment 8
Issue date: 11-JAN-2022
Summary of Changes:
1. All subjects have completed treatment and On Study Follow-up. This amendment provides that the Post Study Follow-up for the collection of survival data will be discontinued as of 30 June 2022, and the study will be completed. As of 30 June 2022, all but up to 8 subjects will have completed the 3-year Post Study Follow-up, which would have occurred by December 2022 for the remaining subjects. (The preceding paragraph was added to the synopsis).
    a. The following note was added to Sections 3.1.15 (Duration of Study), 3.1.16 (On Study and Post Study Follow-up), and 4.2.1.4 (Overall Survival): "NOTE: Per Amendment 8, all post study follow-up for the collection of survival data will be discontinued as of 30 June 2022 (see rationale in Section 8.1, Amendment 8 on Page 96)"
    b. Section 3.2 (Study Flowchart). The following footnote was added to each of the 3 flowcharts: "Per Amendment 8, all post study follow-up for the collection of survival data will be discontinued as of 30Jun2022 (see Section 8.1, Amendment 8).
2. Section 7.1.6 (Expedited SAE Reporting Requirements): updated address for Drug Safety Contact and Primary Sponsor Contact due to office move.
Ludwig·Institute·for·Cancer·Research←
~~666~~·600·3rd·Ave·~~28th~~·32nd·Floor¶
New·York,·New·York·~~10017~~10016↵
3. Administrative edit: In Section 7.1.6, the title of Primary Sponsor Contact was changed from Director to Senior Director.

8.2 Participating Study Sites, Investigators and Staff

Site and Investigator information is provided in the Clinical Study File.

8.3 Participating Laboratories

Information regarding participating laboratories is provided in the Clinical Study File.

8.4 Sponsor Information

Sponsor Information is provided in the Clinical Study File.

8.5 Dose Adjustments and Delays for Durvalumab

If a toxicity occurs that requires toxicity management in accordance with Sections 8.5, 8.6, and 8.7, and the toxicity causing agent can be clearly identified, then the respective guideline should be followed. If the toxicity causing agent cannot be identified, then the more conservative guideline should be followed.

8.5.1 Durvalumab Dose Modification Due to Toxicity

Durvalumab (MEDI4736) administration may be modified or discontinued as a result of toxicities as described the table below.

Additional information and guidance regarding dose modification due to toxicity are provided from Medimmune in the following guidelines:

"***Medimmune's 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: the Medimmune guideline refers to dose modifications for durvalumab (MEDI4736) and tremelimumab. For this protocol, however, only 1 dose of tremelimumab is given to certain cohorts, and no dose modification is possible. Therefore, this section has been modified to refer to dose modifications for durvalumab only.

Dose modifications will not be required for AEs that are clearly not attributed to durvalumab or tremelimumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

MEDI4736 (M) Dose Modification Due to Toxicity
Note: If M dosing is held temporarily until resolution of the event as per instructions below, treatment should resume at the next <u>scheduled</u> treatment date.
<u>Immune-related Adverse Events (irAEs)</u> Immune-related adverse events are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. Maximum supportive care, including immunosuppressive medications, such as high dose steroids, is allowed to induce resolution of the event. **However, infliximab should not be used for management of immune-related hepatitis**. In addition to the criteria for permanent discontinuation of M depicted below, **<u>permanently discontinue M</u>** also for: • Any Grade rash with bullous skin formations. • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/regimen. • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing. • **Any Grade biopsy-proven immune-mediated myocarditis.**

Grade 1

- In general, no dose modification required.
- For *pneumonitis/interstitial lung disease and myocarditis*, consider holding M dosing as clinically appropriate and during diagnostic work-up for other etiologies.

Grade 2

- In general, hold M until resolution to ≤ Grade 1 and after the end of any steroid taper, and discontinue M permanently if such resolution does not occur within 60 days (30 days for neurotoxicities). Criteria for temporary hold or permanent discontinuation of M may differ by event as detailed below.
- For *myositis/polymyositis*, hold M until resolution to ≤ Grade 1; permanently discontinue M if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency.
- For *pneumonitis/interstitial lung disease and myocarditis*, the decision to reinitiate M upon resolution shall be based upon treating physician's clinical judgment (as long as the event does not meet DLT criteria).
- For *peripheral neuromotor syndromes*, such as *Guillain-Barre* and *Myasthenia Gravis*, follow general instructions above, but always discontinue M permanently if there are signs of respiratory insufficiency or autonomic instability.
- For *endocrinopathies, other than isolated hypothyroidism and isolated Type 1 diabetes mellitus*, follow general instructions above, but patients may be retreated if the endocrinopathy is controlled and the patient is clinically stable while requiring steroid doses of ≤ 10 mg/day prednisone equivalent.
- For *isolated hypothyroidism* managed with hormone replacement therapy, *isolated Type 1 diabetes mellitus* treated with appropriate diabetic therapy, and for *sensory neuropathy/neuropathic pain*, holding M is at the discretion of the investigator.
- For *elevated creatinine* or *rash*, M should be held until resolution to ≤ Grade 1 or baseline and after completion of steroid taper.
- For *vitiligo*, no dose modification required.

Grade 3

- In general, hold M until resolution to ≤ Grade 1, and after the end of any steroid taper, and discontinue M permanently if such resolution does not occur within 60 days (30 days for neurotoxicities and rash). Criteria for permanent discontinuation of M may differ by event as detailed below.
- For *myositis/polymyositis*, follow Grade 2 instructions above.
- For *peripheral neuromotor syndromes (*such as *Guillain-Barre* and *Myasthenia Gravis),* apply respective Grade 2 rules.
- For *endocrinopathies*, follow Grade 2 instructions above.
- For *diarrhea/colitis*, permanently discontinue M if toxicity does not improve to ≤ Grade 1 within 14 days.
- For *pneumonitis/interstitial lung disease, myocarditis, and elevated serum creatinine (e.g., nephritis or renal dysfunction)*, always discontinue M permanently.
- For *asymptomatic increases of amylase or lipase* levels, hold M, and if complete work up shows no evidence of pancreatitis, M may be continued.
- For *hepatitis*, discontinue M permanently for (1) transaminases or bilirubin not resolving to ≤ Grade 1 or baseline within 14 days, (2) transaminases > 8 × the upper limit of normal (ULN) or bilirubin > 5

MEDI4736 (M) Dose Modification Due to Toxicity
× ULN, or (3) any case meeting Hy's law criteria (as defined in FDA Guidance Document "Drug-Induced Liver Injury"). • For *rash*, M should be held until resolution to ≤ Grade 1 or baseline. **Grade 4** • In general, discontinue M permanently. • For *endocrinopathies,* follow Grade 2 instructions above. • For *asymptomatic increases of amylase or lipase* levels, hold M , and if complete work up shows no evidence of pancreatitis, M may be continued.
Infusion-related Reactions **Grade 1** • The infusion rate of M and T may be decreased 50% or temporarily interrupted until resolution of the event. • Acetaminophen and/or antihistamines may be administered per institutional standards at the discretion of the Investigator. • Premedication for subsequent doses should be considered. • Steroids should not be used for routine premedication of ≤ Grade 2 infusion reactions. **Grade 2:** • **Same as Grade 1**, but consider giving subsequent infusions at 50% of the initial infusion rate. **Grade 3 and 4:** • **The infusion must be stopped i**mmediately and treatment permanently discontinued. • Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).
All other Adverse Events **Grade 1** • No dose modification required. **Grade 2** • Hold M until resolution to ≤ Grade 1 or baseline, and discontinue M permanently if such resolution does not occur within 60 days. **Grade 3** • Hold M. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume M administration at next scheduled dose. Otherwise, discontinue M permanently. **Grade 4** • In general, discontinue M permanently. • For isolated lab results, decision to discontinue should be based on accompanying clinical signs/symptoms and per Investigator's clinical judgment and in consultation with the Sponsor

8.5.2 Durvalumab Dose Modification Not Due to Toxicities

Durvalumab administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply:

1. The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 10 days. All resulting protocol deviations should be documented.
2. If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued.
3. If the dosing interruption is ≤ half the planned dosing interval, the originally planned dose should be given and the next dose(s) should be adjusted in accordance with #1, if necessary.
4. If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary

8.6 Dose Modification and Management Guidelines for Oxaliplatin/Capecitabine, FLOT, and Surgery

If a toxicity occurs that requires toxicity management in accordance with Sections 8.5, 8.6, and 8.7, and the toxicity causing agent can be clearly identified, then the respective guideline should be followed. If the toxicity causing agent cannot be identified, then the more conservative guideline should be followed.

Every effort should be made to administer trial treatment on the planned schedule. The toxicity of each cycle of chemotherapy must be recorded before the administration of the next one and graded according to the current version of the Common Terminology Criteria for Adverse Events (CTCAE Version 4.03). If individual subjects experience treatment related toxicity, subsequent trial treatment may be delayed, omitted and/or dose modified according to the worst toxicity observed during the previous cycle as described below. Dose reductions are permanent (no dose re-escalation permitted). The following outlines provide guidance for the management of toxicities for subjects treated with oxaliplatin/capecitabine or the FLOT regimen.

8.6.1 Non Haematological Toxicity

If a DLT occurs during Cycle 1, then oxaliplatin/capecitabine or FLOT can be reduced to 75% and then to 50% of the starting dose, at the discretion of Investigator, if this is felt to be the basis for toxicity. No dose modifications for tremelimumab or durvalumab (MEDI4736) will be made if, in the Investigator's opinion, the toxicity is specifically exclusively related to oxaliplatin, capecitabine or FLOT (e.g., neuropathy or hand foot syndrome).

For Grade 3, Grade 4 or intolerable Grade 2 toxicity, the treatment will be interrupted until recovery to < Grade 2 or baseline (in the judgement of the Investigator). If the subject fails to recover to this extent within 3 weeks of treatment will be discontinued. If a subject cannot tolerate treatment after two successive dose reductions trial treatment will be discontinued.

8.6.1.1 Rash

In the event of a rash, unless the Investigator is of the opinion that oxaliplatin/capecitabine or FLOT is causative, chemotherapy should be continued as planned. (Note: Hand/foot syndrome is considered below.) For Grades 1 and 2 rash, treatment should be continued. Consider using alcohol free emollient cream/moisturiser and/or topical 1-2.5% hydrocortisone cream to the affected areas. If the rash persists or worsens, oral antibiotics (doxicycline 100 mg b.d. or minocycline 100 mg b.d.) or topical clindamycin 1% should be added.

8.6.1.2 Diarrhoea

Supportive care should be provided according to local clinical practices (e.g., loperamide). In the event of Grade 2 or higher symptoms, capecitabine or FLOT dosing should be interrupted. Once symptoms have resolved to Grade 1 or better, capecitabine/all elements of FLOT may be resumed at a reduced dose (75% of starting dose). If diarrhoea was Grade 3 or 4, then the capecitabine/all elements of FLOT dose(s) should be reduced by 50%.

8.6.1.3 Mucositis/Stomatitis

Supportive care should be provided according to local clinical practices (e.g., mouth wash, topical anesthetics or systemic analgesics). In the event of Grade 2 or higher symptoms, capecitabine or FLOT dosing should be interrupted. Once symptoms have resolved to Grade 1 or better, capecitabine/all elements of FLOT may be resumed at a reduced dose (75% of starting dose if Grade 2 toxicity, 50% of starting dose if Grade 3 or 4). If there is no improvement to Grade 1 or better within 3 weeks of stopping, capecitabine or FLOT should be discontinued permanently.

8.6.1.4 Neuropathy

Oxaliplatin commonly causes peripheral sensory symptoms. Many subjects experience transient paraesthesia of hands and feet, and some experience dysaesthesia in the throat. These symptoms are precipitated by cold and last from a few hours to a few days after each oxaliplatin administration. They do not require treatment or dose reduction. In the case of Laryngeal Spasm Syndrome, increase the oxaliplatin infusion time from 2 to 6 hours.

Asymptomatic (Grade 1) neuropathy requires no dose adjustment. Where there are moderate symptoms limiting day to day activity persisting for more than 7 days, subsequent oxaliplatin doses should be reduced by 25%. If symptoms persist despite this, a further reduction to 50% of the starting dose can be performed. In the event of Grade 3 and 4 toxicity, or Grade 2 toxicity despite 2 dose reductions, discontinue oxaliplatin. Where subjects are on the FLOT regimen, the docetaxel dose should be reduced by the same percentage as for oxaliplatin.

8.6.1.5 Hand/Foot Syndrome

Supportive care should be provided according to local clinical practices (e.g., topical therapy and oral pyridoxine). In the event of Grade 2 or higher symptoms, capecitabine/5-fluorouracil and leucovorin dosing should be interrupted. Once symptoms have resolved to Grade 1 or better, capecitabine/5-fluorouracil and leucovorin may be resumed at a reduced dose (75% of starting dose if grade 2 toxicity, 50% of starting dose if Grade 3). If there is no improvement to Grade 1 or better within 3 weeks of stopping, capecitabine/5-fluorouracil and leucovorin should be discontinued permanently.

8.6.1.6 Allergic Reactions to Oxaliplatin

The occasional subject (approximately 0.5% of subjects) develops acute hypersensitivity to oxaliplatin, usually after more than 6 cycles have been administered. During drug administration, the subject may develop rash, fever, swollen mouth or tongue, hypo- or hypertension and other signs/symptoms of hypersensitivity. This rarely develops to full-blown anaphylaxis, even with repeated treatment.

1. If acute hypersensitivity occurs, discontinue the infusion and treat with IV corticosteroid and antihistamine.
2. After full recovery, the subject may continue with capecitabine.
3. At the Investigator's discretion, the subject may be rechallenged with oxaliplatin at the next cycle. In this case, premedication is recommended with hydrocortisone 100 mg IV or Dexamethasone 8mg IV 30 minutes pre dose + Chlorphenamine 10mg (or equivalent) + ranitidine 50 mg (or equivalent) IV.

8.6.1.7 Dose Modification for Other Non-haematological Toxicity

8.6.1.7.1 Renal Toxicity

If serum creatinine ≥ 2 x ULN has been demonstrated, this parameter must be repeated at least twice a week until resolution to ≤ CTCAE Grade 1, and then at least weekly until either resolution to allow for initiation of re-treatment or until stabilization.

Oxaliplatin is not nephrotoxic but is renally cleared. Check serum creatinine at each cycle. If this rises to >25%, re-check serum creatinine clearance or EDTA clearance or 24-hour urinary creatinine, and adjust oxaliplatin and capecitabine doses according to the Table 8.6-1 below. If the glomerular filtration rate (GFR) drops to between 30ml/min to 50ml/min, reduce capecitabine dose by 25% until recovery. If GFR drops to below 30ml/min, omit oxaliplatin and capecitabine until recovery.

8.6.1.7.2 Hepatic Toxicity

If bilirubin ≥ 2 x ULN or ≥ CTCAE Grade 3 AST/ALT has been demonstrated, these parameters must be repeated at least twice a week until resolution to ≤ CTCAE Grade 1 (or ≤ Grade 2 if liver metastasis were present at baseline), and then at least weekly until either resolution to allow for initiation of re-treatment or until stabilization.

Table 8.6-1 Adverse Event Management for other Non-haematological Toxicity

Serum Creatinine	
Grade 1 (< 2 x ULN) (GFR > 50ml/min)	Maintain full dose oxaliplatin/capecitabine or FLOT
Grade 2 (2 - 3 x ULN) (GFR 30 - 50ml/min)	Oxaliplatin: full dose; Capecitabine or 5-fluorouracil: reduce by 25%
Grade 3 (> 3.0 - 6.0 x ULN) (GFR < 30ml/min) or Grade 4 (> 6.0 x ULN)	Oxaliplatin: do not give; Capecitabine or 5-fluorouracil: do not give
Bilirubin	
Grade 1 or 2 (<2 - 3 x ULN)	Oxaliplatin and Capecitabine: full dose Docetaxel: do not give
Grade 3 (> 3.0 - 10.0 x ULN)	Oxaliplatin: withhold until to ≤ Grade 1, reduced by 50%; Capecitabine: withhold until to ≤ Grade 1, then ↓ 50%
Grade 4 (> 10.0 x ULN)	discontinue treatment
AST or ALT	
Grade 1 (>ULN - 3.0 x ULN)	Maintain full dose oxaliplatin/capecitabine
Grade 2 (Asymptomatic with ALT >3.0 - 5.0 x ULN)	Oxaliplatin: full dose Capecitabine and 5-fluorouracil: reduce by 25% Docetaxel: do not give
Grade 3 (>5.0 - 20.0 x ULN)	Oxaliplatin: withhold until to ≤ Grade 1, ↓ by 25%; Capecitabine and 5-fluorouracil: withhold until to ≤ Grade 1, then ↓ by 25%

Grade 4 (> 20.0 x ULN)	Oxaliplatin: withhold until to ≤ Grade 1, then ↓ by 50% Capecitabine and 5-fluorouracil: withhold until to ≤ Grade 1, then ↓ by 50%

ULN = upper limit of normal; GFR = glomerular filtration rate

8.6.2 Haematological Toxicity

The complete blood count is analyzed on (or up to 3 days before) Day 1 of each cycle. The following guidelines are applied (also see Table 8.6-2, below):

1. Treatment should only be given when neutrophils ≥ 1.5 x 10^9/L and platelets ≥ 75 x 10^9/L.
2. If these criteria are not met, delay oxaliplatin/capecitabine for 1 week and restart with the full dose on recovery.
3. If a delay of 2 weeks occurs, reduce the doses of capecitabine and oxaliplatin 25% upon recovery and continue at the lower dose for subsequent cycles unless further toxicity occurs.
4. If more than 2 weeks delay or further delay(s) for myelotoxicity occur despite a 25% reduction, a further dose reduction may be made, at the discretion of the treating Investigator.

Table 8.6-2 Dose Modification Guidance for Haematological Toxicity

Neutropaenia or Thrombocytopaenia	
Grade 1 (ANC < LLN - 1.5 x 10^9/L or PLT < LLN - 75 x 10^9/L) and Grade 2 (ANC < 1.5 - 1.0 x 10^9/L, or PLT < 75 - 50 x 10^9/L)	Maintain dose of oxaliplatin/capecitabine or FLOT
Grade 3 (ANC < 1.0 - 0.5 x10^9/L or PLT < 50-25 x 10^9/L, febrile neutropenia)	Oxaliplatin: withhold until to ≤ Grade 1, then ↓ 25%* Capecitabine: withhold until to ≤ Grade 1, then full dose FLOT: withhold until to ≤ Grade 1, then ↓ 25%*
Grade 4 (ANC < 0.5 x 10^9/L or PLT < 25 x 10^9/L)	Oxaliplatin: withhold until to ≤ Grade 1, then ↓ 25%* Capecitabine: withhold until to ≤ Grade 1, then ↓ 25%*

ANC = absolute neutrophil count; LLN = lower limit of normal; PLT = platelets

* at second occurrence reduce to 50% dose

8.6.3 Surgery

See Section 8.7.4 for details regarding events related to surgery for applicable cohort.

8.7 Dose Modification and Management Guidelines for Paclitaxel/Carboplatin, Radiotherapy, and Surgery

If a toxicity occurs that requires toxicity management in accordance with Sections 8.5, 8.6, and 8.7, and the toxicity causing agent can be clearly identified, then the respective guideline should be followed. If the toxicity causing agent cannot be identified, then the more conservative guideline should be followed.

8.7.1 Haematologic Related Toxicity

On each dosing day for paclitaxel and carboplatin, if the white blood cell count (WBC) is < 1.0 x 10^9/L and/or platelet count is < 50 x 10^9/L, omit chemotherapy for that week.

In case of febrile neutropenia (granulocytes < 0.5 x 10^9/L and fever > 38.5 °C) or in case of severe bleeding or requiring ≥ 2 platelet transfusions, further chemotherapy will be withheld.

Additional management guidelines are provided in the following table:

Neutrophil count once weekly during CRT		Platelet count once weekly during CRT	Action
≥1.0 x 10^9/L	AND	≥75 x 10^9/L	Full dose paclitaxel and carboplatin
<1.0 x 10^9/L	OR	<75 x 10^9/L	Omit both drugs that week and omit chemotherapy weekly until recovery (N≥1.0 x 10^9/L and platelets ≥75 x 10^9/L). Dose reduce by 25% for subsequent doses
ANY	AND	<25 x 10^9/L	Omit both drugs that week and omit chemotherapy weekly until recovery (N≥1.0 x 10^9/L and platelets ≥75 x 10^9/L). Dose reduce by 50% for subsequent doses

8.7.2 Non-Haematologic Toxicity

These effects will be graded according to CTCAE recommendations for grading of acute and sub-acute toxicity.

Hypersensitivity Reactions

Hypersensitivity reactions will be classified as mild, moderate or severe. Definitions and management guidelines are outlined below:

Classification of Reactions	Management of reactions
Mild symptoms (e.g. mild flushing, rash, pruritis)	Complete infusion. Supervise at bedside. No treatment required.
Moderate symptoms (e.g. moderate rash, flushing mild dyspnea, chest discomfort, mild hypotension)	Stop infusion; give IV antihistamine (Clemastine 2 mg IV and Dexamethasone 10 mg IV) → After recovery of symptoms, resume infusion at a rate of 20 mL/h for 15 minutes then 50 mL/h for 15 minutes then, if no further symptoms, at full dose rate until infusion is complete.
Severe symptoms (e.g. one or more of the following): respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy)	Stop infusion; give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated; report as an adverse event; the subject will go off protocol therapy.

Other toxic reactions and the prescribed management of these reactions are outlined in the following table:

Reaction	Management of Reaction
Renal	
GFR < 20 mL/min	Carboplatin is contraindicated Paclitaxel- no dose modification
Hepatic	Carboplatin – no dose modification required
Bilirubin <1.25 x ULN and ALT <10 x ULN,	Paclitaxel - continue full intended dose. If these parameters are exceeded, further treatment should be discussed with the study team.
Cardiac	
Asymptomatic bradycardia or isolated and asymptomatic ventricular extrasystoles.	Continue therapy under continuous cardiac monitoring.
First degree AV block.	Continue therapy under continuous cardiac monitoring.

Symptomatic arrhythmia or AV block (except1st degree) or other heart blocks.	Stop chemotherapy, manage arrhythmia according to standard practice; subject goes off therapy.

Other Non-haematologic toxicities:

INCIDENCE	CTCAE Grade 2	CTCAE Grade 3	CTCAE Grade 4
1st occurrence	Interrupt until resolved to Grade 0-1, then resume at original dose	Interrupt until resolved to Grade 0-1, then resume at 75% dose	Discontinue treatment unless investigator continues this is in best interest for patient, in which case interrupt until resolved to Grade 0-1, then resume at 50% dose
2nd occurrence of same toxicity	Interrupt until resolved to Grade 0-1, then resume at 75% dose	Interrupt until resolved to Grade 0-1, then resume at 50% dose	N/A
3rd occurrence of same toxicity	Interrupt until resolved to Grade 0-1, then resume at 50% dose	Discontinue treatment	N/A
4th occurrence of same toxicity	Discontinue treatment	N/A	N/A

8.7.3 Radiotherapy Toxicity

Radiotherapy, especially concurrent with chemotherapy can lead to acute esophagitis. In some cases, medical support and/or a feeding tube will be necessary. In the event of Grade 4 radiation induced esophagitis, both chemotherapy and radiotherapy will be withheld until the esophagitis recovered to Grade 3.

Other acute complications of the radiation therapy are erythema, cough, nausea, fatigue and weight loss. In the first weeks to six months after the irradiation radiation pneumonitis or fistula formation can occur.

The following list provides the expected events in relation to radiotherapy (and its possible effect following surgery); this should be used as the Reference Safety Information (RSI) when assessing the expectedness of SAEs causally related to radiotherapy:

- Mucositis
- Oesophagitis
- Dysphagia
- Lethargy
- Pain
- Anaemia
- Nausea and vomiting
- Weight loss
- Poor oral intake
- Tinnitus
- Infection
- Pneumonitis
- Pericarditis
- Wound infection
- Anastomotic leak
- Chest infection
- Pleural effusion
- Thrombo-embolism

In the event of a chemotherapy toxicity or dose modification, the decision to continue radiotherapy rests with the treating clinician.

8.7.4 Surgery

Hospitalizations for surgical procedures, which are planned for Cohorts C/C-FLOT and D per this protocol, should not be considered SAEs.

The table below provides the expected events in relation to surgery. This should be used as the RSI when assessing the expectedness of SAEs causally related to surgery.

Bleeding	**Genitourinary**	**Neurological**
Anaemia requiring transfusion Post-operative bleed other than gastrointestinal Wound haematoma	Renal failure Urinary retention	Delirium / agitation Loss of consciousness Vertigo
Cardiac	**Infectious**	**Pulmonary**
Angina Arrythmia Congestive heart failure Hypertension Hypotension Myocardial Infarction	Abscess Fever of unknown origin (FUO) Systemic sepsis Urinary tract infection	Atelectasis Pleural effusion Pneumonia Pneumothorax Respiratory distress
Gastrointestinal	**Wound Infection**	**Surgical**
Clostridium difficile colitis Constipation (inability to have a bowel movement postoperative Day 5 with no signs of ileus or SBO) Diarrhoea Emesis	Deep or superficial wound dehiscence Wound infection Wound seroma	Bowel injury Incisional hernia Retained foreign body Vascular injury Thoracic duct injury Cranial nerve and/or sympathetic chain injury Brachial plexus injury
Miscellaneous	**Thromboembolic**	
Acidosis Decubitis ulcer Dehydration Lymphocele Peripheral arterial ischemia Psychological illness Thrombocytopenia	Deep vein thrombosis (DVT) Superficial phlebitis Pulmonary embolism	
Note: Many of the side effects to surgery can be exacerbated by chemoradiotherapy		

8.8 RECIST 1.1 and irRECIST Guidelines

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were revised in 2009 as RECIST 1.1.[41] These guidelines have been the widely accepted criteria to assess response and progression in solid tumors; however, limitations have been noted in the use of RECIST 1.1 for immunotherapy trials. With immunotherapeutic agents, clinical trials have shown that complete response, partial response, or stable disease status can still be achieved after an initial increase in overall tumor burden, and regression of initial lesions may occur despite development of new lesions. The Immune-related Response Criteria (irRC) were developed to address the need for response criteria in an immunotherapy setting.[42] The main difference with irRC was that it considered the subject's total tumor burden at each subsequent assessment and required confirmation of suspected disease progression with subsequent imaging, approximately four weeks later. In addition, a greater number of lesions (10 vs. 5) were measured in a bidimensional manner instead of unidimensionally as in RECIST 1.1. In 2013, Nishino et al. demonstrated that immune-related response criteria using unidimensional measurements were highly concordant with the bidimensional results of irRC, but with less measurement variability.[43] Based on these findings and in order to utilize both the established criteria of irRC and RECIST 1.1, the two systems have been adapted, modified, and combined into the Immune-related Response Evaluation Criteria in Solid Tumors (irRECIST).[44] The adapted irRECIST criteria are modifications to the irRC, incorporating the findings of Nishino et al. and the advantages of RECIST 1.1 while overcoming the shortcomings of each of the other guidelines.

The guidelines for RECIST 1.1 are summarized below, followed by a summary for irRECIST.

RECIST 1.1

The following section outlines the RECIST 1.1 guidelines as published[41] and as summarized by National Cancer Institute for CTEP-involved clinical trials**.**

I. Disease Parameters for RECIST 1.1

Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST 1.1 criteria.

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

NOTE for irRECIST: During target lesion selection the radiologist will consider information on the anatomical sites of previous intervention (e.g. previous irradiation, RF-ablation, TACE, surgery, etc.). Lesions undergoing prior intervention will not be selected as target lesions unless there has been a demonstration of progress in the lesion.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

NOTE for irRECIST:
Lesions that are partially cystic or necrotic can be selected as target lesions. The longest diameter of such a lesion will be added to the Total Measured Tumor Burden (TMTB) of all target lesions at baseline. If other lesions with a non-liquid/non-necrotic component are present, those should be preferred.
Brain lesions detected on brain scans can be considered as both target or non-target lesions depending on the protocol definition.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any non-measureable as well as measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

II. Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to

the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.[45-47] In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.[48]

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

III. Response Criteria for RECIST 1.1

A. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

B. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

C. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

1. For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

2. For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an end-point for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

D. Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

irRECIST

Immune-related RECIST (irRECIST) guidelines according to Bohnsack et al.[44] are presented below.

I. Baseline Assessments in irRECIST

In irRECIST, baseline assessment and measurement of measurable/non-measurable and target/non-target lesions and lymph nodes are in line with RECIST 1.1. One new definition is added: If a subject has no measurable and no non-measurable disease at baseline the radiologist will assign 'No Disease' (irND) as the overall tumor assessment for any available follow-up time points unless new measurable lesions are identified and contribute to the total measured tumor burden (TMTB). irND is a valid assessment in studies with adjuvant setting where the protocol and study design allow the inclusion of subjects with no visible disease

II Follow-up Assessments in irRECIST

A. Follow-up recording of target and new measurable lesions

A key difference in irRECIST is that the appearance new lesions does not automatically indicate progression. Instead, all measured lesions (baseline-selected target lesions and new measurable lesions) are combined into the total measured tumor burden (TMTB) at follow up. Baseline-selected target lesions and new measurable lesions are NOT assessed separately. Measurements of those lesions are combined into the TMTB, and one combined assessment provided.

In order to be selected as new measurable lesions (≤ 2 lesions per organ, ≤ 5 lesions total, per time point), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in long diameter and minimum 15 mm in short axis for new measurable lymph nodes. New measurable lesions should be prioritized according to size, and the largest lesions elected as new measured lesions.

B. Follow-up non-target assessment

RECIST 1.1 definitions for assessment of non-target lesions apply. The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNN). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progress in the TMTB is indicative of irPD. In alignment with RECIST 1.1, baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent time points and become measurable. Only true new lesions can be measured and contribute to the TMTB**.**

C. Follow-up for New Non-Measurable Lesions

All new lesions not selected as new measurable lesions are considered new non-measurable lesions and are followed qualitatively. Only a massive and unequivocal progression of new non-measurable lesions leads to an overall assessment of irPD for the time point. Persisting new non-measurable lesions prevent irCR.

III Overall Assessments for irRECIST

The irRECIST overall tumor assessment is based on TMTB of measured target and new lesions, non-target lesion assessment and new non-measurable lesions.

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment, the SumD of the target lesions and of new, measurable lesions (up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB).

Overall Assessments by irRECIST	
Complete Response (irCR)	Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease of ≥ 30% in TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions • If new measurable lesions appear in subjects with **no target lesions at baseline**, irPD will be assessed. That irPD time point will be considered a new baseline, and all subsequent time points will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreases by ≥ 30% compared to the first irPD documentation • irRECIST can be used in the **adjuvant setting**, in subjects with no visible disease on CT/MRI scans. The appearance of new measurable lesion(s) automatically leads to an increase in TMTB by 100% and leads to irPD. These subjects can achieve a response if the TMTB decreases at follow-up, as a sign of delayed response. • Based on the above, sponsors may consider enrolling subjects with no measurable disease and/or no visible disease in studies with response related endpoints.
Stable Disease (irSD)	Failure to meet criteria for irCR or irPR in the absence of irPD
Progressive Disease (irPD)	Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment. An irPD confirmation scan may be recommended for subjects with a minimal TMTB %-increase over 20% and especially during the flare time-window of the first 12 weeks of treatment, depending on the compound efficacy expectations, to account for expected delayed response. • In irRECIST a substantial and unequivocal increase of **non-target lesions** is indicative of progression. • IrPD may be assigned for a subject with multiple **new non-measurable lesions** if they are considered to be a sign of unequivocal massive worsening
Other	**irNE:** used in exceptional cases where insufficient data exist. **irND:** in adjuvant setting when no disease is detected **irNN:** no target disease was identified at baseline, and at follow-up the subject fails to meet criteria for irCR or irPD

8.9 Laboratory Procedures

Peripheral blood and biopsy samples will be collected at the time points designated in Section 3.2, and the assays described in Section 4.3 and Section 4.4 will be performed. Please refer to the Laboratory Manual for this study to obtain additional instructions and information on lab specimen handling and logistics.

8.9.1 Additional Translational and Exploratory Studies

Optional research studies may only be performed for subjects who voluntarily gave their consent for additional correlative research on the informed consent document. Subjects who declined consent to participate in additional translational studies will have their samples destroyed at the end of the study. Refusal to participate in this optional research will involve no penalty or loss of benefits to which the subject would otherwise be entitled. Based on the data generated during the study and/or in other studies, not all samples from subjects consenting to this optional research may be utilized.

8.10 List of Abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
b.d.	Twice a day
CBC	Complete Blood Count
CRT	Chemoradiotherapy
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
DACH	1,2-diaminocyclohexane
DLT	Dose-limiting Toxicity
eCRF	Electronic Case Report Form
FFPE	Formalin-fixed paraffin-embedded
FLOT	5-fluorouracil (5-FU), leucovorin, oxaliplatin, and docetaxel
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICT	induction chemotherapy
IgG2	immunoglobulin G2
IHC	Immunohistochemistry
irAE	Immune-related Adverse Events
irCR	Immune-related Complete Response
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
irSD	Immune-related Stable Disease
IV	intravenous
LICR	Ludwig Institute for Cancer Research
LLN	Lower limit of normal
mAb	Monoclonal antibody
MDSC	Myeloid derived suppressor cells
MDT	multidisciplinary team
OAC	Oesophageal adenocarcinoma
OC	Oesophageal cancer
OSCC	Oesophageal squamous cell carcinoma
OS	Overall survival
PD-1	programmed cell death-1
PFS	Progression-free survival

Q2W	Every 2 weeks
RCD	Recommended combination dose
REC	Research Ethics Committee
RSI	Reference Safety Information
RT	Radiotherapy
SAE	Serious Adverse Event
SCCHN	Squamous cell carcinoma of the head and neck
SD	Standard Deviation
ULN	Upper limit of normal

9 References

1. Oesophageal. Cancer. Available at : www.cancerresearchuk.org. Accessed May 30, 2015.
2. Schweigert M, Dubecz A, Stein HJ. Oesophageal cancer--an overview. *Nat Rev Gastroenterol Hepatol.* 2013;10(4):230-244.
3. Pohl H, Welch H. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. *J Natl Cancer Inst.* 2005;97(2):142-146.
4. Royal College of Surgeons: National Oesophago-Gastric Audit. 2013.
5. OSullivan K, Phelan J, O'Hanlon C, Lysaght J, O'Sullivan J, Reynolds J. The role of inflammation in cancer of the esophagus. *Expert Rev Gastroenterol Hepatol.* 2014;8(7):749-760.
6. Kohata Y, Fujiwara Y, Machida H, et al. Role of Th-2 cytokines in the development of Barrett's esophagus in rats. *J Gastroenterol.* 2011;46(7):883-893.
7. Levine DM, Ek WE, Zhang R, et al. A genome-wide association study identifies new susceptibility loci for esophageal adenocarcinoma and Barrett's esophagus. *Nat Genet.* 2013;45(12):1487-1493.
8. Burnette BC, Liang H, Lee Y, et al. The efficacy of radiotherapy relies upon induction of type I interferon-dependent innate and adaptive immunity. *Cancer Res.* 2011;71(7):2488-2496.
9. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med.* 2010;363(8):711-723.
10. Kyi C, Postow MA. Checkpoint blocking antibodies in cancer immunotherapy. *FEBS Lett.* 2014;588(2):368-376.
11. Azijli K, Stelloo E, Peters GJ, Van Den Eertwegh A. New developments in the treatment of metastatic melanoma: immune checkpoint inhibitors and targeted therapies. *Anticancer Res.* 2014;34(4):1493-1505.
12. Ohigashi Y, Sho M, Yamada Y, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. *Clin Cancer Res.* 2005;11(8):2947-2953.
13. Segal N, Hamid O, Hwu W, Massard C, et al. A Phase 1 Multi-arm Dose-expansion Study of the Anti-programmed Cell Death-ligand-1 (PD-L1) Antibody MEDI4736: Preliminary Data. *Ann Oncol.* 2014;25(Suppl 4):iv365 ESMO Poster 1058PD.
14. Pedoeem A, Azoulay-Alfaguter I, Strazza M, Silverman GJ, Mor A. Programmed death-1 pathway in cancer and autoimmunity. *Clin Immunol.* 2014;153(1):145-152.
15. De Santo C, Arscott R, Booth S, et al. Invariant NKT cells modulate the suppressive activity of IL-10-secreting neutrophils differentiated with serum amyloid A *Nat Immunol.* 2010;11(11):1039-1046.
16. Lu M, Breyssens H, Salter V, et al. Restoring p53 function in human melanoma cells by inhibiting MDM2 and cyclin B1/CDK1-phosphorylated nuclear iASPP. *Cancer Cell.* 2013;23(5):618-633.
17. Yang L, Lu X, Nossa CW, Francois F, Peek RM, Pei Z. Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. *Gastroenterology.* 2009;137(2):588-597.
18. Dovedi S, Adlard A, Lipowska-Bhalla G, McKenna C, Jones S, et al. Acquired Resistance to Fractionated Radiotherapy Can Be Overcome by Concurrent PD-L1 Blockade *Cancer Res.* 2014;74(19):5458–5468.

19. Stewart R, Morrow M, Hammond S, et al. Identification and Characterization of MEDI4736, an Antagonistic Anti-PD-L1 Monoclonal Antibody. *Cancer Immunol Res.* 2015;3(9):1052-1062.
20. Walsh TN, Grennell M, Mansoor S, Kelly A. Neoadjuvant treatment of advanced stage esophageal adenocarcinoma increases survival. *Dis Esophagus.* 2002;15(2):121-124.
21. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. *Am J Surg.* 2003;185:538-543.
22. Conroy T, Galais MP, Raoul JL, et al. Definitive chemoradiotherapy with FOLFOX versus fluorouracil and cisplatin in patients with oesophageal cancer (PRODIGE5/ACCORD17): final results of a randomised, phase 2/3 trial. *Lancet Oncol.* 2014;15(3):305-314.
23. Javle MM, Yang G, Nwogu CE, et al. Capecitabine, oxaliplatin and radiotherapy: a phase IB neoadjuvant study for esophageal cancer with gene expression analysis. *Cancer Invest.* 2009;27(2):193-200.
24. Thukral A, Metz J, Hwang WT, et al. Toxicity data for preoperative concurrent chemoradiotherapy with oxaliplatin and continuous infusion 5-fluorouracil for locally advanced esophageal cancer. *Dis Esophagus.* 2011;24(5):330-336.
25. Wahba HA, El-Hadaad HA, Abd-Ellatif EA. Neoadjuvant concurrent chemoradiotherapy with capecitabine and oxaliplatin in patients with locally advanced esophegeal cancer. *Med Oncol.* 2012;29(3):1693-1698.
26. Mukherjee S, Hurt C, Gwynne S, et al. NEOSCOPE: a randomised Phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine or paclitaxel/carboplatin based chemoradiation as pre-operative regimen for resectable oesophageal adenocarcinoma. *BMC Cancer* 2015;15(48):doi:10.1186/s12885-12015-11062-y.
27. van Hagen P, Hulshof MC, van Lanschot JJ, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med.* 2012;366(22):2074-2084.
28. Mukherjee S, Hurt C, Gwynne S, et al. NEOSCOPE: A randomised Phase II study of induction chemotherapy followed by either oxaliplatin/capecitabine (OXCAP) or carboplatin/paclitaxel (CarPac) based chemoradiation (CRT) as pre-operative regimen for resectable oesophageal adenocarcinoma. *J Clin Oncol.* 2016;34(suppl 4S):abstr 3.
29. Blom RL, Sosef MN, Nap M, et al. Comparison of two neoadjuvant chemoradiotherapy regimens in patients with potentially curable esophageal carcinoma. *Dis Esophagus.* 2014;27(4):380-387.
30. Yoon DH, Jang G, Kim JH, et al. Randomized phase 2 trial of S1 and oxaliplatin-based chemoradiotherapy with or without induction chemotherapy for esophageal cancer. *Int J Radiat Oncol Biol Phys.* 2015;91:489-486.
31. Ajani JA, Xiao L, Roth JA, et al. A phase II randomized trial of induction chemotherapy versus no induction chemotherapy followed by preoperative chemoradiation in patients with esophageal cancer. *Ann Oncol.* 2013;24:2844-2849.
32. Nabavizadeh N, Shukla R, Elliott DA, et al. Preoperative carboplatin and paclitaxel-based chemoradiotherapy for esophageal carcinoma: results of a modified CROSS regimen utilizing radiation doses greater than 41.4 Gy. *Dis Esophagus* 2015;doi: 10.1111/dote.12377. [Epub ahead of print].
33. Al-Batran SE, Pauligk C, Homann N, et al. Docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) for resectable esophagogastric cancer: updated results

from multicenter, randomized phase 3 FLOT4-AIO trial (German Gastric Group at AIO). *European Society for Medical Oncology (ESMO)* 2017:Abstract LBA27.
34. Maity A, Mick R, Huang AC, et al. A phase I trial of pembrolizumab with hypofractionated radiotherapy in patients with metastatic solid tumours. *Br J Cancer.* 2018;119(10):1200-1207.
35. Luke JJ, Lemons JM, Karrison TG, et al. Safety and clinical activity of pembrolizumab and multisite stereotactic body radiotherapy in patients with advanced solid tumors. *J Clin Oncol.* 2018;36(16):1611-1618.
36. Lesueur P, Escande A, Thariat J, et al. Safety of combined PD‐1 pathway inhibition and radiation therapy for non‐small‐cell lung cancer: A multicentric retrospective study from the GFPC. *Cancer Med.* 2018;7(11):5505-5513.
37. Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. *N Engl J Med.* 2018;DOI: 10.1056/NEJMoa1809697.
38. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: Evolving Considerations for PET response criteria in solid tumors. *J Nucl Med.* 2009;50 Suppl 1:122S-150S.
39. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med.* 2012;366(26):2455-2465.
40. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med.* 2012;366(26):2443-2454.
41. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247.
42. Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. *Clin Cancer Res.* 2009;15(23):7412-7420.
43. Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya N, Hodi F. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements *Clin Cancer Res.* 2013;19(14):3936-3943.
44. Bohnsack O, Ludajic K, Hoos A. Adaptation of the immune-related response criteria: irRECIST. ESMO 2014 Poster *Annals of Oncology* 2014;25(S4):iv361-iv372.
45. Rustin GJ, Quinn M, Thigpen T, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). *J Natl Cancer Inst.* 2004;96(6):487-488.
46. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol.* 1999;17(11):3461-3467.
47. Scher HI, Halabi S, Tannock I, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. *J Clin Oncol.* 2008;26(7):1148-1159.
48. Vergote I, Rustin GJ, Eisenhauer EA, et al. Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup. *J Natl Cancer Inst.* 2000;92(18):1534-1535.