LUDWIG CANCER RESEARCH	Study Protocol	LUD2015-008	US-IND# 17217
	Amendment 6.1	Final	10-MAR-2022

Protocol Title
A Phase 1/2 dose escalation study with expansion cohorts to investigate the safety, biologic and anti-tumor activity of ONCOS-102 in combination with durvalumab in subjects with advanced peritoneal malignancies

Objectives and Synopsis
This is a two-part Phase 1/2 dose escalation and dose expansion study of the GMCSF-encoding adenovirus, ONCOS-102, in combination with anti-programmed death ligand-1 (PD-L1) antibody, durvalumab, in adult subjects with peritoneal disease who have histologically confirmed epithelial ovarian cancer or metastatic colorectal cancer (CRC) and have failed prior standard therapies. Note: the CRC cohort may include subjects with cancer originating from the appendix. ONCOS-102 will be administered intraperitoneally (IP) at weekly intervals for 6 weeks. A bolus dose of 300 mg cyclophosphamide (CPO) will be administered intravenously (IV) 1 to 3 days before the first infusion of ONCOS-102. Durvalumab will be administered by IV infusion once every four weeks (Q4W) for a total of 12 four-week cycles. Phase 1 of the study is a dose escalation phase, which will use a 3+3 design to evaluate the safety of ONCOS-102 monotherapy before initiation of durvalumab and to identify the recommended combination dose (RCD) of a fixed dose of durvalumab (1500 mg) + ONCOS-102 at 2 dose levels (1 x 10^{11} viral particles (VPs) and 3 x 10^{11} VPs). Phase 2 of the study is the dose expansion phase, which will further explore the safety and anti-tumor activity for the RCD in 2 expansion cohorts with peritoneal disease: 1) Platinum-resistant epithelial ovarian cancer 2) Metastatic colorectal cancer Simon's 2-Stage MINIMAX Design will be used in Phase 2 for Expansion Cohorts 1 and 2 (see Section 3.1.6 for sample size considerations). In the first stage, 18 subjects will be enrolled in Cohort 1 and 13 subjects in Cohort 2 (including the 6 subjects at the RCD from the dose escalation phase). If 5 or more subjects in Cohort 1, or one or more subjects in Cohort 2, demonstrate clinical benefit (defined as percentage of subjects who are not in progression **at end of Week 24)**, 15 additional subjects will be enrolled in Stage 2 of Cohort 1, and 14 additional subjects will be enrolled in Stage 2 of Cohort 2. **Per Amendment 5**, optional durvalumab treatment extension beyond the initial 12-cycle treatment period (Core Study) will be available for subjects who complete the Core Study with Stable Disease or better. The optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator, and it may continue until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Section 8.8 for details.

Per Amendment 6.1:

By the date of implementation of this amendment, all subjects will have completed treatment and applicable On Study Follow-up, with the exception of one subject in optional treatment extension who will complete treatment and On Study Follow-up by 30 June 2022. 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.

Primary Objectives [Endpoints]	**Dose Escalation Phase:** *Safety and Tolerability* [DLTs, RCD according to CTCAE 4.03] **Expansion Phase:** *Clinical efficacy by RECIST 1.1* [Clinical Benefit (CB), defined as percentage of subjects who are not in progression **at end of Week 24**].
Secondary Objectives [Endpoints]	**Dose Escalation and Expansion Phases (all subjects):** *Safety and Tolerability* [CTCAE 4.03] *Clinical Efficacy by RECIST 1.1/irRECIST* [Durable Clinical Benefit (DCB, defined as the percentage of subjects meeting criteria of Stable Disease (SD), partial response (PR), or complete response (CR) **over a period of at least 24 weeks**); ORR after 8 and 24 weeks; PFS; and OS]
Exploratory Objectives [Endpoints]	**Dose Escalation and Expansion Phases (all subjects):** *Biologic Activity* [Effects on immune biomarkers, Immune Response, mechanisms of therapeutic resistance]. This will include CD8+ T cells in biopsies. PBMCs will be analysed for the presence of tumour and virus antigen specific CD8+ T cells as well as different immune cell subpopulations, such as T regulatory cells and effector cells.

DLT=Dose-limiting Toxicity; RCD=Recommended Combination Dose; ORR=Objective Response Rate; DCB=Durable Clinical Benefit; PFS=Progression-free Survival; OS=Overall Survival; CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST= Response Evaluation Criteria in Solid Tumors; irRECIST=immune-related RECIST

Sponsor: Ludwig Institute for Cancer Research Ltd. New York, NY	**Study Chair:** [redacted], Memorial Sloan Kettering Cancer Center, New York, NY
Sponsor Representative Signature and Date	**Study Chair Signature and Date**

Confidentiality Statement

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1 Background

1.1 Intraperitoneal Cancer

Intraperitoneal carcinomatosis is a serious complication of various cancers and is essentially considered incurable once established. Some cancers respond better than others to therapy consisting typically of surgery and chemotherapy. For ovarian carcinoma, which typically presents with peritoneal metastasis at an advanced stage, the administration of intraperitoneal chemotherapy versus systemic intravenous chemotherapy has conclusively demonstrated a survival benefit and has become standard of care for this disease since 2005.(1)

The benefit of intraperitoneal chemotherapy for other malignancies with a propensity of originating or spreading to the peritoneal cavity has not been conclusively proven for mesothelioma, colorectal, or gastric cancers; nor has a survival benefit been demonstrated for hyperthermic perfusion of the abdominal cavity administered with or without chemotherapy in a randomized trial. Nevertheless, key opinion leaders believe that certain patients would benefit from such therapy. The problem is the heterogeneity of patients and their diseases and the inability of properly stratifying patients according to their disease characteristics. Clinicians and researchers are trying to develop tools which could better identify patients who benefit from hyperthermic intraperitoneal chemotherapy such as the peritoneal surface disease severity score (PSDSS).(2) However, there is currently no universally accepted criteria for selecting patients for such treatment, and most decision making is up to the discretion of the treating physician.

1.2 Checkpoint Blockade in the Treatment of Gastrointestinal and Gynecologic Malignancies

Recent breakthroughs in tumor immunology and immunotherapy have led to development of novel therapeutic agents aiming to enhance activation of anti-tumor immune responses or to reverse immunosuppressive mechanisms governing tumor resistance to the immune system.(3) Exciting results have been reported in the clinical setting against multiple human cancers by the use of antibodies that target the inhibitory receptor PD-1 expressed on activated T-cells.(4) Durvalumab is a highly selective, human monoclonal IgG1–kappa isotype antibody targeting programmed cell death 1 ligand 1 (PD-L1; B7-H1; CD274) that is designed to block the negative immune regulatory signaling of the PD-1/PD-L1 pathway.

Despite the significant promise of the immune checkpoint-targeting agents, the observed clinical efficacy, however, has not been universal and has been particularly poor in patients with gastrointestinal and gynecologic malignancies. These findings highlight the marked immunosuppressive nature of these tumors and call for development of appropriate predictive biomarkers and combinatorial strategies. This presents an opportunity for numerous combinatorial approaches, which most commonly involve combinations of immune checkpoint blocking antibodies with strategies thought to promote presentation of tumor antigens, either through exogenous vaccination or by induction of “in situ” vaccination through therapies thought to induce immunogenic cell death (ICD) and antigen release such as radiation therapy and chemotherapy.(5-7)

Analysis of different tumor types consistently demonstrates that tumor infiltration with T cells is a good prognostic marker in a variety of tumor types, with most extensive data existing in

ovarian and colorectal cancers.(8-20) Presumably, the T cell-infiltrated tumors are a marker of an ongoing spontaneous anti-tumor immune response, which results in better tumor control and leads to more favorable clinical outcomes. Interestingly, the prognostic value of this phenotype has been shown to be more powerful than traditional staging in colorectal cancer,(21) and studies are currently underway to validate this marker prospectively.(22) Consistent with these findings, data from clinical trials indicate that patients with evidence of pre-existing anti-tumor immune response, namely, patients with increased tumor immune infiltration are more likely to benefit from such therapies.(12, 13, 23) These findings suggest that therapies that could potentially increase immune infiltration into tumors could sensitize patients to the effect of the immunomodulatory antibody therapy.

Oncolytic viruses (OV) represent another class of emerging cancer therapeutics, which for the past 60 years have been evaluated in a variety of cancer types.(24) While promising activity of OVs has been demonstrated in a variety of animal models (primarily with intratumoral injection), the clinical results have not been as impressive. The major limitation of OVs is their poor delivery to metastatic cancer sites with systemic administration and the rapid development of neutralizing antibodies by the host, which limits the utility of further systemic administration.(25) However, in the few patients that did achieve response to oncolytic virotherapy, the observed clinical benefit was often durable even after completion of therapy, an effect reminiscent of the responses seen with immunotherapeutic approaches.(26-28) Indeed, it has become increasingly recognized that modification of tumor cells by OVs may promote their recognition by the immune system, with activation of adaptive immune responses specific not only for viral, but also for tumor antigens.(29) Evidence has emerged from both preclinical and clinical studies demonstrating the immune therapeutic potential of OVs, marking a new era in the development of these agents and suggesting a tantalizing possibility that the immunostimulatory properties of OVs can be steered to improve the efficacy of immunomodulatory agents.(30) Recently, studies combining talimogene laherparepvec (T-VEC; an oncolytic virus) and pembrolizumab (31) or ipilimumab (32) in melanoma patients showed promising results.

Given the preclinical rationale, as well as the evidence of superior prognosis in ovarian and colorectal cancer patients whose tumors exhibit immune infiltration, the current study will evaluate whether the immune response and tumor immune infiltration induced by OV could potentiate the therapeutic efficacy of PD-L1 blockade in these cancer types.

1.3 Study Drugs

This study will evaluate oncolytic virus (ONCOS-102) with the PD-L1 checkpoint inhibitor, durvalumab.

1.3.1 Durvalumab (MEDI4736)

Durvalumab is briefly described in this section below. Refer to the current Investigator's Brochure 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 durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity.

As of the data cutoff dates in the IB (15Apr2015 to 18Sep2015), a total of 1,910 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,910 subjects, 1,279 received durvalumab monotherapy, 454 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 163 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 adverse events (AEs). 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, 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 (see Section 8.3).

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.

1.3.2 ONCOS-102

ONCOS-102 is briefly described in the section below. Refer to the current Investigator's Brochure (IB) for complete and current information.

ONCOS-102 (formerly CGTG-102; Ad5/3-D24-GMCSF) is a replication competent adenovirus that has been classified by the Gene Technology Board of Finland as a genetically modified micro-organism (GMM). The virus properties are close to the wild type serotype 5 adenovirus but ONCOS-102 contains an adenovirus 3 serotype knob replacing the wild type serotype 5 knob. Other modifications include a 24 base pair (bp) deletion in the E1A region for tumor selectivity, and an added transgene coding for granulocyte-macrophage colony stimulating factor (GMCSF). GMCSF is an immunostimulatory cytokine that is targeted to prime the anti-tumor immune response in the tumor environment.

Clinical data on the efficacy and safety of ONCOS C1 are provided from a completed Phase 1 clinical trial (ONCOS C1) and an Advanced Therapy Access Program (ATAP).

Clinical Study ONCOS C1

ONCOS C1 was a single center, exploratory, open label study of ONCOS-102 given in combination with low dose cyclophosphamide (CPO) in subjects with refractory injectable solid tumors. Twelve subjects (5 male, 7 female; aged 38 to 68 years [median age 63 years]) were treated with ONCOS-102 (intratumorally): 3 subjects were treated with 3×10^{10} viral particles (VP)/injection, 3 subjects with 1×10^{11} VP/injection, and 6 subjects with 3×10^{11} VP/injection. Dosing was scheduled on Days 1, 4, 8, 15, 29, 57, 85, 113, and 141. Five subjects received the maximum of 9 doses of ONCOS-102, and 3 subjects completed the study as planned. The most common reason for discontinuation from the study was disease progression (6 subjects). Subjects also took oral cyclophosphamide 50 mg daily throughout the treatment period of the trial. The underlying cancer types differed widely across the study population with 9 different cancer types reported in 12 subjects.

Treatment with ONCOS-102 in combination with low dose CPO was well tolerated, with no dose-limiting toxicity. Therefore, a maximum tolerated dose was not established and is believed not to be relevant after treatment with rapidly replicating virus. The recommended dose for further development of ONCOS-102 is 3 x 10^{11} VP/injection, although all 3 doses of ONCOS-102 examined in this study could potentially be used.

ONCOS-102 induced a systemic anti-tumor CD8+ T-cell response that was correlated with a clinical response. Computed tomography (CT)/PET imaging suggested signals of efficacy as 40.0% of these severely ill subjects with progressive disease had stable disease at 3 months.

All subjects reported pyrexia, which was managed successfully with antipyretic medication. This was also the most common treatment-related AE. Peak body temperatures were mostly recorded 6 to 10 hours after injection and were managed successfully with paracetamol or ibuprofen. Therefore, acetaminophen (1 g) can, if needed, be given 4 to 6 hours after each dose of ONCOS-102 to reduce the incidence of chills or fever, which are expected after viral therapy. Prophylactic medication should be avoided to allow the initial induction of cytokines and fever. Other common AEs reported in at least 50% of subjects were fatigue, nausea, injection site pain, chills and decreased appetite. Most of the AEs were Grade 1 or 2. Grade 3 AEs were reported in 6 subjects and there were no Grade 4 AEs. Seven serious adverse events (SAEs) were reported by 5 subjects: 5 of these SAEs were deemed unrelated to study medication while 2 (peripheral oedema and hypoalbuminaemia in the same subject) were deemed possibly related to study medication. This last subject died due to underlying malignant disease 1 month after her last ONCOS-102 treatment. There were no significant laboratory or haematological changes suggesting an association or toxic effect of the study medication. The safety profile seen in ONCOS C1 was similar to that seen in ATAP.

Advanced Therapy Access Program
An ATAP for the treatment of patients with chemo-refractory tumors with oncolytic viruses was operational between 2007 and 2012. The ATAP was not a trial but an individualized treatment program regulated by the Finnish Medicines Agency as determined by EC/1394/2007. One hundred and fifteen patients with chemo-refractory tumors were treated with ONCOS-102 in the ATAP, either alone or in combination with other ATAP viruses with excellent safety data and signals of clinical response in individual patients.

Efficacy: As ATAP was not a study with a predetermined protocol, assessment of efficacy with certainty was not possible. However, clinical responses were seen in individual patients.(33) Median survival of 115 patients who received ONCOS-102 either alone or in combination with other ATAP viruses was 164 days or 5.5 months (95% CI: 122 to 206 days) in this heavily pre-treated refractory population. A total of 30% of patients survived for more than 300 days and 15% for up to 600 days.

Safety: The 115 patients treated in the ATAP were evaluated for safety. Only adverse reactions possibly related to treatment were reported in the ATAP. All patients reported at least one adverse reaction, regardless of the route of administration. The most frequently reported adverse reactions overall were pyrexia (94 patients, 81.7%), fatigue (91 patients, 79.1%), nausea (63 patients, 54.8%), hemoglobin decreased (54 patients, 47.0%), and chills (53 patients, 46.1%). Abdominal pain and thrombocytopenia were reported more frequently after IP administration (abdominal pain 12 patients [44.4%]; thrombocytopenia 6 patients, [22.2%]) compared with the overall population (31.1% and 14.8%, respectively). After intrapleural administration, the most

common adverse events were pain, leukopenia, and dyspnea (8 patients, 44.4% for each event), and influenza-like illness and cough (5 patients, 27.8% for each event).

A total of 60 grade 3 adverse reactions were reported in 34 patients (29.6%) overall. The most common grade 3 adverse reactions overall were decreased hemoglobin (7 patients, 6.1%), and increased AST (6 patients, 5.2%). A total of 8 grade 4 adverse reactions were reported in 6 patients (5.2%) overall: hemoglobin decrease (2 episodes in 1 patient), pulmonary embolism, thrombocytopenia, dyspnea, pleural effusion, ketoacidosis, and AST increase. In addition, 1 patient experienced pulmonary embolism with fatal outcome (grade 5) after a single administration of 3×10^{11} VP ONCOS- 102 by a combination of intratumoral, intravenous (IV), and intraperitoneal (IP) routes. This event was considered not related to ONCOS-102. Eleven patients (9.6%) overall experienced a total of 15 grade 3 to 5 adverse reactions that were rated as serious.

ONCOS-102 is classified as a GMM and should be handled according to biosafety level 2 (BSL-2). It is selectively replicative in cancer cells, and the ability to replicate in normal cells is negligible.

There is a theoretical risk of spread of ONCOS-102 into the environment from patients who are undergoing treatment. In the Phase I study, no virus was detected in urine or buccal swabs at discharge after dosing in any patient. Virus was detected before dosing on one occasion (Day 4): in the urine of 1 patient, and in the buccal swabs in 3 patients, but not on subsequent dosing days. ONCOS-102 is an adenovirus that is genetically modified to replicate selectively in cancer cells; therefore, it is attenuated, compared to the wild type adenoviruses (e.g. serotypes 5 and 3) that commonly infect the human population. In the unlikely event of person to person spread, it is unlikely that ONCOS-102 would pose any clinically significant risk to patient contacts.

ONCOS-102 can be inactivated using a suitable adenovirus neutralizing agent such as 10% bleach or 1.5% Barrydin liquid (PAN Biotech, Germany). These are to be used for the inactivation of spills and devices used for administration.

2 Study Rationale

Recent pre-clinical studies demonstrated that combination of intratumorally administered oncolytic virus in combination with systemic immune checkpoint blockade act in synergistic manner.(34, 35) Recently, clinical validation of these findings have been presented.

In a Phase 1 study, T-VEC was combined with ipilimumab in advanced melanoma patients where the combination appeared to have greater efficacy than either T-VEC or ipilimumab monotherapy.(32, 36) In this study, objective response rate (ORR) was 50%; 44% of patients had a durable response lasting ≥ 6 months; 18-month progression-free survival was 50%; and 18-month overall survival was 67%.

In another Phase 1 study, T-VEC was combined with pembrolizumab in advanced melanoma patients, where the combination was associated with clinical benefit as assessed by ORR and Complete Response rate. (31) A randomized, double-blind phase 3 trial of T-VEC and pembrolizumab vs T-VEC placebo and pembrolizumab is under way.

Given the preclinical and preliminary clinical rationale, the current study will evaluate a combination of locoregionally-administered ONCOS-102, an oncolytic adenovirus genotype 5/3 encoding GM-CSF transgene, with systemic PD-L1 blockade using durvalumab. The choice for ONCOS-102 stems from existing clinical data with the virus, demonstrating safety and evidence of induction of anti-tumor immune responses with the virus administered as a single agent.(37-39) Based on these findings, ONCOS-102 was granted an orphan drug designation in relapsed ovarian cancer, mesothelioma and soft tissue sarcoma by the FDA and the EMA in 2014 and 2015. Other intraperitoneally administered oncolytic adenoviruses have been evaluated in several trials in subjects with advanced ovarian cancer, with evidence of safety and some evidence of clinical activity (40-44), supporting the use of oncolytic adenovirus in this setting.

The current study is a two-part dose escalation/dose expansion Phase 1/2 study of intraperitoneally administered ONCOS-102 with systemically administered durvalumab in subjects with advanced gynecologic and colorectal cancers with peritoneal carcinomatosis. The main objectives of the study will be to test the feasibility and safety of this approach, evaluate a range of translational endpoints, and provide initial indicators of clinical efficacy. If successful, this study would provide further rationale for evaluation of other locoregionally-administered oncolytic viruses with antibodies targeting immune checkpoints, a strategy that could be extended to other malignancies.

In the dose escalation phase, a 3+3 design will be used to evaluate the safety of ONCOS-102 monotherapy before initiation of durvalumab (Cohort A) and to identify the recommended combination dose (RCD) of a fixed dose of durvalumab (1500 mg) + ONCOS-102 at 2 dose levels (Cohorts B and C). The data from Cohort A will be used to evaluate the safety of the ONCOS-102 regimen in this type of administration (which has not been used before) prior to the combination with durvalumab.

2.1 Durvalumab Dose

A durvalumab dose of 20 mg/kg every 4 weeks (Q4W; equivalent to a fixed dose of 1500 mg Q4W, which will be used in this study) is supported by in-vitro data, non-clinical activity, clinical PK/pharmacodynamics, biomarkers, and activity data from Study 1108 in patients with advanced

solid tumors and from a Phase I trial performed in Japanese patients with advanced solid tumor (D4190C00002). See durvalumab IB for details.

2.1.1 Pharmacokinetics (PK)/Pharmacodynamics (PD) Data

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

Data from Study D4190C00006 (Phase I trial in NSCLC patients using the combination of durvalumab and tremelimumab) also show an approximately dose-proportional increase in PK exposure for durvalumab over the dose range of 3 to 20 mg/kg durvalumab Q4W or Q2W. For further information on PK observations in Study 006, please see the current IB.

The observed durvalumab PK data from the combination study were well in line with the predicted monotherapy PK data (5th median and 95th percentiles) for a Q4W regimen.

A population PK model was developed using the data from Study 1108 (doses=0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W.(45) Multiple simulations indicate that a similar overall exposure is expected following both 10 mg/kg Q2W and 20 mg/kg Q4W regimens, as represented by the area under the concentration-time curve (AUC) at 4 weeks. Median maximum concentration (Cmax) is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median Ctrough is expected to be higher with 10 mg/kg Q2W (~1.25 fold). Clinical activity with the 20 mg/kg Q4W dosing regimen is anticipated to be consistent with 10 mg/kg Q2W with the proposed similar dose of 20 mg/kg Q4W expected to (a) achieve complete target saturation in majority of patients; (b) account for anticipated variability in PK, pharmacodynamics, and clinical activity in diverse cancer populations; (c) maintain sufficient PK exposure in case of ADA impact; and (d) achieve PK exposure that yielded maximal antitumor activity in animal models.

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

2.1.2 Clinical Data

Refer to the current durvalumab IB for a complete summary of clinical information including safety, efficacy and PK for the 20mg/kg Q4W (1500 mg Q4W) regimen.

2.1.3 Fixed Dosing for Durvalumab

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (study 1108; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors).

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

Similar findings have been reported by others.(46-49) Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in PK/PD parameters.(48)

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, it was considered feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 750 mg Q2W durvalumab (equivalent to 10 mg/kg Q2W) or 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is recommended.

This dosing of durvalumab is recommended only for subjects with > 30 kg body weight, due to endotoxin exposure. Subjects with a body weight ≤ 30 kg are not eligible for enrollment in the current study. If a subject's body weight drops to ≤ 30 kg while on the study, the durvalumab dose will be weight based as long as the body weight remains ≤ 30 kg. See Section 6.1.3 for details.

3 Experimental Plan

3.1 Study Design

This is a two-part Phase 1/2 dose escalation and dose expansion study of the GMCSF-encoding adenovirus, ONCOS-102, in combination with anti-PD-L1 antibody, durvalumab, in adult subjects with peritoneal disease who have histologically confirmed epithelial ovarian cancer or metastatic colorectal cancer and have failed prior standard therapies.

ONCOS-102 will be administered intraperitoneally (IP) via a peritoneal Hickmann catheter (or institutionally preferred alternative) at weekly intervals for 6 weeks. A bolus dose of 300 mg cyclophosphamide (CPO) will be administered intravenously (IV) 1 to 3 days before the first infusion of ONCOS-102. Durvalumab will be administered by IV infusion once every four weeks (Q4W) for a total of 12 four-week cycles.

Phase 1 of the study is a dose escalation phase with 3 cohorts (see Section 3.1.4 for subject population), which will use a 3+3 design to evaluate the safety of ONCOS-102 monotherapy before initiation of durvalumab (Cohort A) and to identify the recommended combination dose (RCD) of a fixed dose of durvalumab (1500 mg) + ONCOS-102 at 2 dose levels (Cohorts B and C). The data from Cohort A will be used to evaluate the safety of the ONCOS-102 regimen in this type of administration prior to the combination with durvalumab. The 3 cohorts are defined as follows:

- Cohort A: ONCOS-102, 1 x 10^{11} viral particles (VPs) monotherapy for 6 weeks, followed by durvalumab 1500 mg starting on Day 71
  (**NOTE:** Upon agreement between Investigator and Sponsor, if a subject in Cohort A has tolerated the ONCOS treatment well but is starting to get symptomatic, the first dose of durvalumab may be given on Day 43 (Cycle 2/Day15); durvalumab dosing will then continue per flowchart in Section 3.2).
- Cohort B: ONCOS-102, 1 x 10^{11} VPs + durvalumab 1500 mg.
- Cohort C: ONCOS-102, 3 x 10^{11} VPs + durvalumab 1500 mg.

NOTE: if a subject's body weight drops to ≤ 30 kg while on the study, the durvalumab dose will be weight based as long as the body weight remains ≤ 30 kg. See Section 6.1.3 for details.

Phase 2, the dose expansion phase, will have 2 cohorts and will explore the safety and anti-tumor activity for RCD defined in Phase 1. In Phase 2, there are 2 expansion cohorts with peritoneal disease:

- Cohort 1: Platinum-resistant epithelial ovarian cancer
- Cohort 2: Metastatic colorectal cancer

3.1.1 Study Phase

Phase 1/2

3.1.2 Enrollment

Subjects will be screened for eligibility for up to 28 days after signing the informed consent form. Enrollment will be under ongoing review by an internal data safety-monitoring panel (see Section 3.1.14). Eligible subjects will be registered centrally with the Sponsor before enrollment.

In the dose escalation phase, subjects will be enrolled sequentially into 3 cohorts (see Figure 1). In Cohorts A and B of the dose escalation phase, as a safety precaution, there will be a waiting period between the first study drug administration for the first and second subjects of the cohort.

For Cohort A, (where ONCOS-102 is administered as a monotherapy until durvalumab is started on Day 71), the waiting period will be 2 weeks. After completion of the ONCOS-102 monotherapy, there will be a safety review prior to the initiation of durvalumab. (See Cohort A Note in Section 3.1.)

For Cohort B, where the combination of ONCOS-102 and durvalumab will be evaluated, the waiting period will be 4 weeks; i.e., the second subject will not receive the first study drug administration until the first subject has completed Cycle 1 (Day 29 of the study).

Per Amendment 4, a waiting period between the first study drug administration for the first and second subjects in the cohort is not required for Cohort C. This was based on the completion of the safety reviews for Cohort B (ONCOS-102 $1x10^{11}$ VP +1500 mg durvalumab) and Cohort A (ONCOS-102 $1x10^{11}$ VP +delayed 1500 mg durvalumab, which started after completion of the 6 weekly doses of ONCOS-102).

In the dose expansion phase, subjects will be enrolled in parallel in a non-randomized, sequential manner, with competitive enrollment between study sites. The subjects will be assigned to a disease-specific cohort, and Simon's 2-Stage MINIMAX Design (50) will be used to determine enrollment (see Figure 1). Enrollment of 18 and 13 subjects to Cohorts 1 and 2 (including the 6 subjects at the RCD from the dose escalation phase), respectively, will occur in the first stage, followed by:

- For Cohort 1: if 5 or more subjects demonstrate clinical benefit (defined as percentage of subjects who are not in progression at end of Week 24), an additional 15 subjects will be enrolled to that cohort in Stage 2 for a total of 33 subjects.
- For Cohort 2: if 1 or more subjects demonstrate clinical benefit at end of Week 24, an additional 14 subjects will be enrolled to that cohort in Stage 2 for a total of 27 subjects.

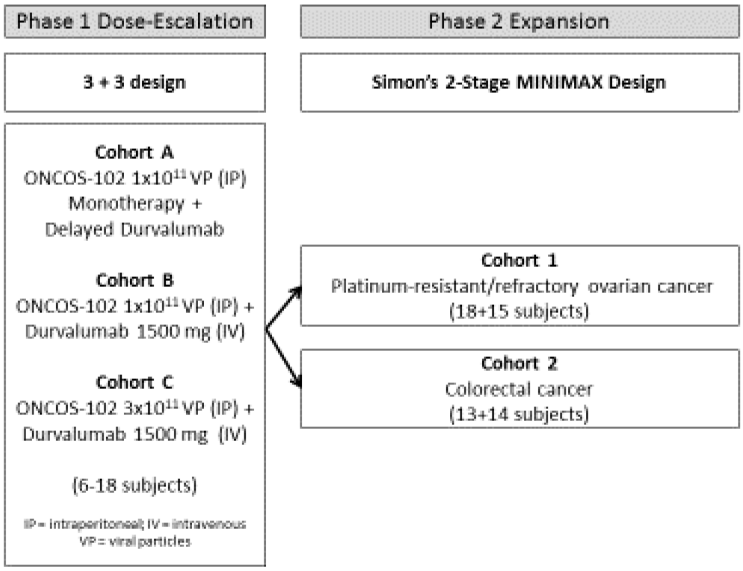

Figure 1. Enrollment Schema

3.1.3 Blinding/Unblinding

This is an open-label study.

3.1.4 Subject Population

Subjects with peritoneal disease who have histologic confirmation of epithelial ovarian cancer or metastatic colorectal cancer (CRC) will be enrolled. Note: the CRC cohort may include subjects with cancer originating from the appendix.

Subjects should have failed prior treatment for advanced cancer and deemed by the Investigator to no longer be eligible for or have reasonable standard of care alternatives, which are felt to have a clinically meaningful impact on their survival.

Subjects with ovarian cancer must have either received one line of platinum based therapy and have progressed within 6 months (defined as platinum resistant) or have received 2 or more lines of standard therapy.

Subjects with CRC must have at least failed two lines of therapy (e.g., fluropyrimidine based therapies, oxaliplatin or irinotecan based therapies with or without anti-VEGF component, or for RAS wild-type, with or without anti-EGFR therapy).

Co-existing distant metastases and parenchymal organ metastases will be allowed. Subjects may have received prior intraperitoneal therapy.

Details on subject eligibility are found in Section 5.

3.1.5 Number of Sites/Subjects

Up to 78 subjects will be enrolled in the study. The study will be conducted in 5 US sites.

3.1.6 Sample Size Considerations

The dose escalation phase will utilize a standard 3 + 3 design for 3 cohorts, which will result in the enrollment 12 to 18 subjects.

In the expansion phase, up to 33 subjects will be enrolled in Cohort 1, and up to 27 subjects will be enrolled in Cohort 2, for a total of up to 60 subjects.

The sample size rationale for Cohorts 1 and 2 of the expansion phase is based on Simon's 2-Stage MINIMAX Design with a Type I error rate of 0.05 and 80% power.

Cohort 1
Based on recent studies of anti-PD-1/PD-L1 therapies in ovarian cancer,(51-53) the null hypothesis for the clinical benefit rate (number of subjects who are not in progression) at end of Week 24 for the ovarian cancer cohort (Cohort 1) will be 20%, which will be tested against a one-sided alternative of 40%. In the first stage, 18 subjects will be accrued to Cohort 1. If clinical benefit at end of Week 24 is seen in <5 of these subjects, the study of Cohort 1 will be stopped. If 5 or more subjects demonstrate clinical benefit at end of Week 24, an additional 15 subjects will be accrued to a total of 33. The null hypothesis will be rejected if 11 or more subjects experience clinical benefit at end of Week 24.

Cohort 2
For the metastatic colorectal cancer cohort (Cohort 2), the null hypothesis for the clinical benefit rate at end of Week 24 will be 5%, which will be tested against a one-sided alternative of 20%. In the first stage, 13 subjects will be accrued to Cohort 2. If clinical benefit at end of Week 24 is seen in <1 of these subjects, the study of Cohort 2 will be stopped. If 1 or more subjects demonstrate clinical benefit at end of Week 24, an additional 14 subjects will be accrued to a total of 27. The null hypothesis will be rejected if 4 or more subjects experience clinical benefit at end of Week 24.

3.1.7 Treatment Arms and Treatment Schema

ONCOS-102 will be administered for a total of 6 weeks while durvalumab will be given for a total of 12 four-week cycles (or 10 four-week cycles for Cohort A; see Section 3.1.7.1).

Per Amendment 5, optional durvalumab treatment extension beyond the initial 12-cycle treatment period (Core Study) will be available for subjects who complete the Core Study with Stable Disease or better. The optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator, and it may continue until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Section 8.8 for details.

Treatment with ONCOS-102:
Subjects' ascites must be manageable, as determined by the Investigator; volume and frequency of necessary paracentesis should not interfere with the conduct of the study. Indwelling paracentesis catheters are permitted per discretion of the Investigator.

A bolus dose of 300 mg cyclophosphamide (CPO) IV will be given 1 to 3 days before the first administration of ONCOS-102.

After accessing the IP port and aspirating any ascites, if present, the ONCOS-102 will be infused in a total volume of 500 mL saline (0.9 mg/mL NaCl in water for injection) by gravity feed or per institutional procedures for IP infusions. The infusion should be given as soon as possible after preparation of the infusion solution. It is recommended that the total infusion time not exceed 2 hours. To ensure uniform distribution of ONCOS-102 in the peritoneal cavity during infusion, it is recommended that the subjects are rotated every 30 minutes, or institutional procedures may be followed. See Section 6.2.3 regarding administration of ONCOS-102.

ONCOS-102 will be administered weekly for a total of 6 weeks, starting on Day 1. Any ascites that re-accumulate before the next scheduled treatment dose can be drained as clinically indicated for comfort. If palliative paracentesis is necessary, it is recommended that at least 72 hours have passed from ONCOS-102 instillation to the procedure.

Treatment with Durvalumab:
Durvalumab will be administered at a fixed dose of 1500 mg using a 250 mL IV bag containing 0.9% (w/v) saline or dextrose and delivered through an IV administration set. Durvalumab will be administered Q4W for 12 cycles, starting on Day 15 (with the exception of dose escalation Cohort A; see Section 3.1.7.1). NOTE: if a subject's body weight drops to ≤ 30 kg while on the study, the durvalumab dose will be weight based as long as the body weight remains ≤ 30 kg. See Section 6.1.3 for details.

3.1.7.1 Dose Escalation Phase

Dose escalation studies of ONCOS-102 have previously been done with intratumorally administered virus and several subjects have received the virus IP in the advanced therapy access program. A safe dose of 3×10^{11} VPs has been established in these studies.

During Phase 1 of the study, subjects will be evaluated for DLTs, as defined in Section 3.1.9 before proceeding to a subsequent cohort. Dose escalation for the determination of RCD will be performed based on the available dose levels (see Table 1) and the respective rules for a standard 3 + 3 dose escalation study design (see Figure 2).

Table 1. Phase 1 Dose Level Cohorts:

Cohort	Dose Level	Durvalumab Q4W (IV)	ONCOS-102 (IP)
A	**0 (Starting Level)**	1500 mg starting on Day 71 (Figure 3)	1×10^{11} VP
B	+1	1500 mg (Figure 4)	1×10^{11} VP
C	+2	1500 mg (Figure 4)	3×10^{11} VP

NOTE: if a subject's body weight drops to ≤ 30 kg while on the study, the durvalumab dose will be weight based as long as the body weight remains ≤ 30 kg. See Section 6.1.3 for details.
See Cohort A Note in Section 3.1.

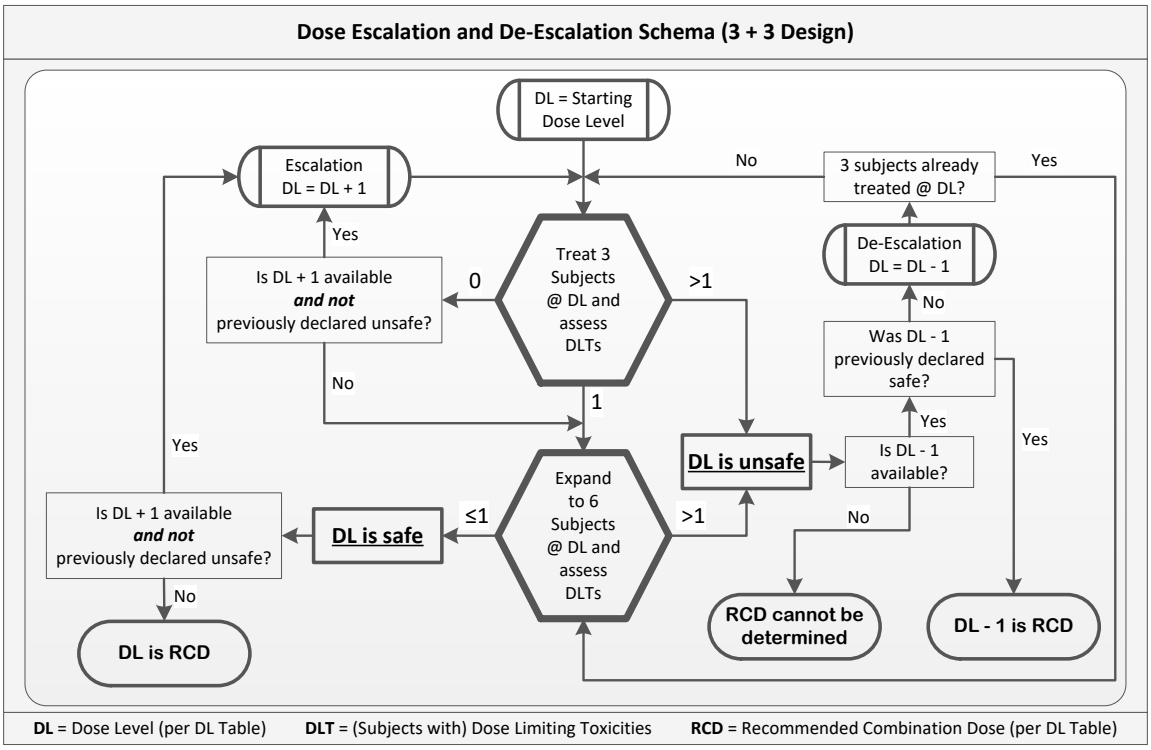

Figure 2. Dose Escalation and De-Escalation Schema

In this study, the dose for Cohort A is the starting dose level (DL); the dose for Cohort B is DL +1; and the dose for Cohort C is DL +2. The dose escalation for this study may proceed as follows:

1. **Cohort A**: Three subjects will be enrolled into Cohort A and treated at the DL.
   a) If 0 of the 3 subjects in Cohort A has a DLT, Cohort B (DL+1) will open to enrollment (see #2, Cohort B)
   b) If 1 of the 3 subjects in Cohort A has a DLT, an additional 3 subjects will be enrolled at the DL:
      - If no further subjects (i.e., ≤1 of 6 subjects) have a DLT, Cohort B (DL+1) will open to enrollment (see #2, Cohort B).
      - If any additional subjects (i.e., >1 of 6 subjects) have a DLT, the study will be stopped.
   c) If >1 of the 3 subjects in Cohort A has a DLT, the study will be stopped.
2. **Cohort B**: If Cohort A clears, Cohort B (DL +1) will open to enrollment; 3 subjects will be treated at DL +1:
   a) If 0 of 3 subjects in Cohort B has a DLT, Cohort C (DL+2) will open to enrollment (see #3, Cohort C).
   b) If 1 of the 3 subjects in Cohort B has a DLT, an additional 3 subjects will be enrolled at DL +1:
      - If no further subjects (i.e., ≤1 of 6 subjects) have a DLT, Cohort C (DL+2) will open to enrollment (see #3, Cohort C).
      - If any additional subjects (i.e., >1 of 6 subjects) have a DLT, the dose will be de-escalated to DL (Cohort A):

- If 6 subjects were evaluated at DL with ≤1 DLT, DL will be considered the RCD.
- If 3 subjects were evaluated at DL, the DL will be expanded to 6 subjects:
  - If ≤1 of the 6 subjects has a DLT, DL will be considered the RCD
  - If > 1 of the 6 subjects have a DLT, the study will be stopped.

c) If >1 of the 3 subjects in Cohort B has a DLT, the dose will be de-escalated to DL (Cohort A) and evaluated as above.

3. **Cohort C**: If Cohort B clears, Cohort C (DL +2) will open to enrollment; 3 subjects will be treated at DL +2:
   a) If ≤ 1 of the 3 subjects in Cohort C has a DLT, the dose will be expanded to 6 subjects:
      - If ≤1 of 6 subjects in Cohort C has a DLT, DL +2 will be considered the RCD.
      - If > 1 of 6 subjects in Cohort C have a DLT, the dose will de-escalate to DL +1 (Cohort B):
        - If 6 subjects were evaluated at DL +1 (Cohort B) with ≤1 DLT, DL +1 will be considered the RCD.
        - If 3 subjects were evaluated at DL +1 (Cohort B), the DL will be expanded to 6 subjects:
          - If ≤1 of the 6 subjects in Cohort B has a DLT, DL +1 will be considered the RCD
          - If > 1 of the 6 subjects in Cohort B have a DLT, the dose will be de-escalated to DL (Cohort A):
            - If 6 subjects were evaluated at DL (Cohort A) with ≤1 DLT, DL will be considered the RCD>
            - If 3 subjects were evaluated at DL, the DL will be expanded to 6 subjects:
              - If ≤1 of the 6 subjects has a DLT, DL will be considered the RCD
              - If > 1 of the 6 subjects have a DLT, the study will be stopped.

   b) If >1 of the 3 subjects in Cohort C has a DLT, the dose will be de-escalated to DL+1 (Cohort B) and evaluated as above

The RCD for each cohort 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 levels fulfill that criterion.

For Cohort A, ONCOS-102 (1×10^{11} VP) will be given as monotherapy the first six weeks, and then durvalumab (1500 mg) will be started on Day 71 (See Figure 3). See Cohort A Note in Section 3.1.

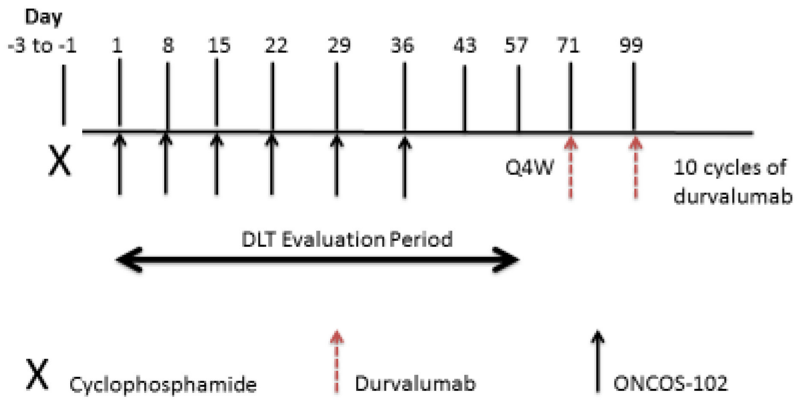

Figure 3. Treatment Schema for Cohort A Only

For Cohorts B and C, ONCOS-102 will be administered for a total of 6 weeks while durvalumab will be given for a total of 12 four-week cycles, starting on Day 15 (See Figure 4).

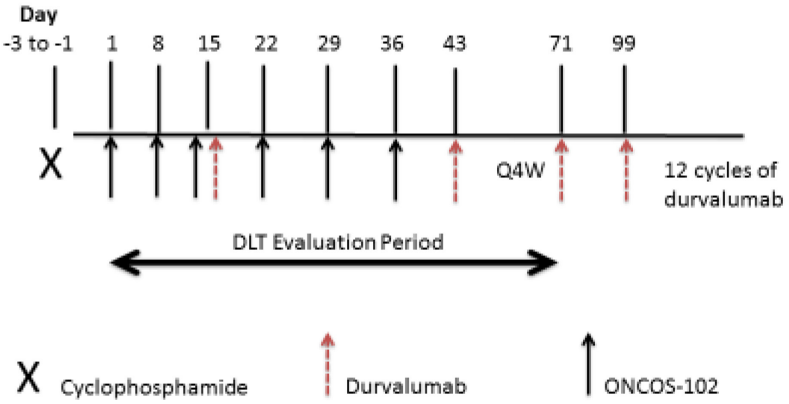

Figure 4. Treatment Schema for All Subjects except Cohort A

See Section 3.1.2 for details regarding the waiting period between the first study drug administration for the first and second subjects of Cohorts A and B of the dose escalation phase.

All subjects in the dose escalation phase will remain in the facility for observation for 8 to 12 hours after each ONCOS-102 infusion. See Section 6.4.2 for additional details.

Based on the safety data from the dose escalation phase, the internal data safety monitoring panel (as defined in Section 3.1.14) will decide if an observation period will be required for the expansion phase. The safety review for the dose escalation phase was conducted, and it was

agreed that the observation period would be shortened for the expansion phase. See note below for expansion phase requirements, per Amendment 5.

Note: Per Amendment 5, all subjects in the expansion phase will remain in the facility for observation for a minimum of 6 hours after the first dose of ONCOS-102 infusion; for subsequent doses, the observation period will be a minimum of 4 hours, but it may be longer based on Investigator's discretion. See Section 6.4.2 for additional details.

3.1.7.2 Dose Expansion Phase

The subjects will be assigned to a disease-specific cohort and will receive treatment at the RCD determined from the dose escalation phase. In Phase 2, there are 2 expansion cohorts with peritoneal disease:

- **Cohort 1**: Platinum-resistant epithelial ovarian cancer
- **Cohort 2**: Metastatic colorectal cancer

See Section 3.1.2 for details of enrollment into the expansion phase according to the Simon's 2-Stage MINMAX Design.

As above, ONCOS-102 will be administered for a total of 6 weeks, while durvalumab will be administered for a total of 12 cycles, starting on Day 15. See Section 6.4 for monitoring details before/during/after drug administration.

3.1.8 Dosing Adjustments, Delays, and Discontinuations

Dose adjustment and management guidelines for toxicity related to durvalumab and ONCOS-102 are outlined in Section 8.3 and Section 8.4, respectively. If a toxicity occurs that requires toxicity management in accordance with Sections 8.3. or 8.4, 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.

3.1.9 DLT and MTD/RCD

MTDs will not be determined. Instead, RCDs will be determined in the context of the predefined dose levels used during the dose escalation phase per Section 3.1.7.1.

For Cohort A, DLTs will be assessed for the period from Day 1 of the study up to and including the Week 9 (Cycle 3 Day 1) study assessments, defined as the DLT Evaluation Period.

For Cohorts B and C, the DLT Evaluation Period will be the period from Day 1 of the study up to and including the Week 11, (Cycle 3, Day 15) pre-dose study assessments. The decisions for dose escalations, de-escalations 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 ONCOS-102 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 *following exception*:

- Grade 2 pneumonitis, neurological event or uveitis that downgrades 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 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 reactions attributed to a local antitumor 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 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, and (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
   - Grade 3 and 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.
4. Any Grade 3 intra-abdominal infection
5. Any intra-abdominal hemorrhage
6. Any intestinal perforation or fistula formation

Immune-related AEs (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, other AEs that do not fulfill the DLT criteria above may nevertheless be classified as DLTs after consultation between Sponsor and Investigators, based on the emerging safety profiles of durvalumab and ONCOS-102, respectively and in combination. 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 discontinued from study treatment and will enter the On Study Follow-up and Post Study Follow-up phases of the study (see Section 3.1.16). However, if it is in the best interest of the subject, the Investigator and Sponsor may agree to continue treatment, possibly at a lower dose level (if applicable) or discontinue one or more of the study drugs.

3.1.10 Subject Withdrawal from Treatment or from Study

A subject will be **withdrawn from study treatment** for any of the following reasons:

1. Withdrawal of consent for further treatment.
2. Pregnancy or intent to become pregnant.
3. Dose-limiting toxicity at any time (see Section 3.1.9).
4. Progressive disease by RECIST 1.1 and irRECIST confirmed on subsequent imaging (see Treatment beyond Progression, Section 3.1.10.1).
5. Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal.
6. Development of intercurrent, non-cancer related illnesses or complications that prevent either continuation of therapy or regular follow-up.
7. 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. If applicable, subjects who are withdrawn from study treatment should undergo the planned On Study and Post Study Follow-up procedures according to Section 3.1.16 and the flowchart in Section 3.2.

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 anti-cancer therapy (marketed or investigational)
3. Withdrawal of consent for all follow-up.
4. Lost to follow-up.
5. Death

Subjects who begin other anti-cancer therapy should immediately be considered off study and proceed to the Post Study Follow-up.

See also Sections 8.3 and 8.4 for subject withdrawal due to necessary dosing interruptions or discontinuations.

Section 7.2.6 provides additional details regarding documentation for early subject withdrawal from study treatment and early withdrawal from study.

3.1.10.1 Treatment beyond Progression

Accumulating evidence suggests that some subjects treated with immunotherapeutics may develop apparent progression of disease (by conventional response criteria) before demonstrating objective responses and/or stable disease. Some subjects may experience rapid responses that are consistent with the classical definition of response observed after

chemotherapy as defined by RECIST 1.1 or WHO criteria; however, other subjects may experience non-classical responses. Some of these non-classical responses include the appearance of new lesions (or potentially growth of existing lesions), in some cases a few new lesions will grow while other lesions actually shrink, or prolonged stable disease.(54-56) This phenomenon was observed in approximately 10% of subjects in the Phase 1 study of nivolumab, a humanized monoclonal antibody against PD-1, and has also been reported for ipilimumab monotherapy.(54)

Subjects meeting criteria for progression by irRECIST (Section 8.5) will be allowed to continue on therapy until confirmation of progression by irRECIST if the subject agrees and signs an appropriate informed consent form regarding continuation of treatment and 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 8.5 for additional information regarding RECIST 1.1 and irRECIST.

3.1.11 Subject Evaluability and 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).

Subjects who are not fully evaluable for DLT per Section 4.1.2 will be replaced.

In the expansion phase, subjects are fully evaluable for the primary endpoint of Clinical Benefit (percentage of subjects who are not in progression at end of Week 24) if they fulfill the criteria for the Per-Protocol Population for Clinical Efficacy (as defined in Section 4.2.2).

Subjects who are not fully evaluable for Clinical Benefit at end of Week 24 may be replaced.

3.1.12 Optional Study Treatment Extension

Per Amendment 5, optional durvalumab treatment extension beyond the initial 12-cycle treatment period (Core Study) will be available for subjects who complete the Core Study with Stable Disease or better. The optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator, and it may continue until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Section 8.8 for details.

3.1.13 Interim Analysis

Interim analyses will be performed at the at the end of Simon Stage 1 for Cohorts 1 and 2 as described in Section 3.1.2. Safety analyses will be performed to assess DLTs in the dose escalation cohorts (see Section 3.1.7.1).

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's Medical Monitor/Clinical Advisor, and drug safety personnel from Medimmune (AstraZeneca)/ TARGOVAX, providers of the study drugs. Additional investigators and staff, or additional Sponsor personnel and consultants, shall participate in reviews, if indicated. The internal data safety-monitoring panel will communicate by phone and/or email on a regular basis, and in particular, to review the safety of individual cohorts for the purpose of dose escalation per Section 3.1.7.1.

An Independent Data Monitoring Board will not be utilized for this open-label study.

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 study drug.
2. Severe anaphylactic reaction (i.e., with respiratory and cardiovascular failure) to any of the study drugs.
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 1 or more study drugs 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.

Study stopping rules may be applied to individual study cohorts, if the internal data safety monitoring panel concludes that the identified risk to one study cohort does not carry over to another.

3.1.15 Duration of Study

Duration of Treatment and On Study Follow-up:	Up to 15 months See Section 3.1.12 for optional durvalumab treatment extension
Enrollment Period:	27 months
Length of Study:	42 months
Post Study Follow-up	3 years from initiation of treatment NOTE: Per Amendment 6.1, 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 6.1).

3.1.16 On Study and Post Study Follow-up

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

Subjects who complete study treatment or discontinue treatment prematurely will enter an On Study Follow up period for 90 days after the last study drug administration (see Section 3.2). Refer to Section 7.1.5 for details on recording of 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 visit of the On Study Follow-up (which is 28 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 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.

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 (± 1 month) for 3 years from initiation of treatment.

The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 90 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.

See Section 3.1.12 for optional durvalumab treatment extension.

NOTE: Per Amendment 6.1, 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 6.1).

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 Flowchart

LUD2015-008 - Study Flowchart (part 1 of 2)	Screening / Baseline		Treatment												
			Cycle 1				Cycle 2			Cycle 3		Cycle 4	Cycle 5		Cycle 6
Cycle week (4-week cycles)			1	2	3	4	1	2	3	1	3	3	1	3	3
Study Week			1	2	3	4	5	6	7	9	11	15	17	19	23
Visit Day per Cycle	-28 to -1	-3 to -1	1	8±2	15±2	22±2	1±2	8±2	15±3	1±4	15±3	15±7	1±4	15±7	15±7
Target Cumulative Visit Day			1	8	15	22	29	36	43	57	71	99	113	127	155
Study Drug Administration															
Cyclophosphamide 300 mg IV		x													
ONCOS-102 intraperitoneally			x	x	x	x	x	x							
Durvalumab 1500 mg IV (Dose Escalation Cohort A only)											x	x		x	x
Durvalumab 1500 mg IV (Dose Escalation Cohorts B and C; and Expansion Cohorts)					x				x		x	x		x	x
Tumor and Disease Assessments															
Disease Assessment by RECIST 1.1/irRECIST (see Sections 4.2 and 8.5 for details on scans and confirmation)	x									x			x		
Blood for CA-125 for ovarian or CEA for CRC (must be at same time points as disease assessments; test will be performed by local lab)[h]	**x**									x			x		
Study Procedures and Examinations															
Eligibility Assessment and Informed Consent (IC)[d,K]	x														
Demographics (incl. DoB; sex; height; race; ethnicity)	x														
Medical history	x	x													
Physical Exam (incl. weight and ECOG Perf Status)	x	x	x[i]	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead ECG[a]	x											x	x		
Vital Signs (T, HR, BP, RR) - See Section 6.4 for monitoring before/during/after drug admin	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant Medication / Procedure (name, indication, dose, route, start & end dates)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events (starting or worsening after IC)[e]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Specimens for Routine Laboratory Procedures															
Blood Hematology (CBC, differential, platelets)[a]	Day -7 to -1		x[J]	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry (glucose, BUN, creat., Na, K, Cl, CO_2, Ca, Mg, protein, alb, TBili, AST, ALT, ALP, LDH)[a]	Day -7 to -1		x[J]	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry Cont. (Free T_3, Free T_4, TSH)[a]	X		x[J]		x				x		x	x		x	x
Chemistry Cont. (amylase, lipase)[a]	Day -7 to -1		x[J]		x				x		x	x		x	x
Urinalysis[a]	Day -7 to -1		x[J]	x	x	x	x	x	x	x	x	x	x	x	x
Coagulation parameters (PT, aPTT, INR)[a]	Day -7 to -1		x[J]	x	x	x	x	x	x						
Serum pregnancy test (urine only on Day 1)[a]	Day -7 to -1		x[J]								x			x	
Specimens for Biological Markers and Correlative Studies															
Blood for PBMC Collection and Banking[f]		x	x (*[f])		x		x		x		x				
Blood for viral particles (Collected only during dose escalation phase)			x[b]	x[b]	x[b]	x[b]	x[b]	x[b]							
Blood for Th1/Th2/Th17 cytokines in serum			x[b]	x[b]	x[b]	x[b]	x[b]	x[b]	x[a]		x[a]				
Other Procedures															
Archival tumor[K]	x														
Tumor Biopsy (FFPE and frozen) for tumor microenvironment[c,K]	x						x[a]								
Post Study Follow-up[L]															
Overall Survival															
Progression Free Survival[g]															

LUD2015-008 - Study Flowchart (part 2 of 2)	Treatment							On Study Follow-up			Post Study Follow-up[L]
	Cycle 7		Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Last Study Drug Dose +28 (±3) days	Last Study Drug Dose +56 (±7) days	Last Study Drug Dose +91 (±7) days End of Study	Every 6 months (± 1 month) for 3 years from initiation of
Cycle week (4-week cycles)	1	3	3	3	3	3	3				
Study Week	25	27	31	35	39	43	47				
Visit Day per Cycle	1±4	15±7	15±7	15±7	15±7	15±7	15±7				
Target Cumulative Visit Day	169	183	211	239	267	295	323				
Study Drug Administration											
Cyclophosphamide 300 mg IV											
ONCOS-102 intraperitoneally											
Durvalumab 1500 mg IV (Dose Escalation Cohort A only)		x	x	x	x	x	x				
Durvalumab 1500 mg IV (Dose Escalation Cohorts B and C; and Expansion Cohorts)		x	x	x	x	x	x				
Tumor and Disease Assessments											
Disease Assessment by RECIST 1.1/irRECIST (see Sections 4.2 and 8.5 for details on scans and confirmation)	x			x		x		Every 8 weeks (± 1 week) starting 8 weeks (± 1 week) after last disease assessment			
Blood for CA-125 for ovarian or CEA for CRC (must be at same time points as disease assessments; test will be performed by local lab)[h]	x			x		x		Every 8 weeks (± 1 week) starting 8 weeks (± 1 week) after last disease assessment			
Study Procedures and Examinations											
Eligibility Assessment and Informed Consent (IC)[d,K]											
Demographics (incl. DoB; sex; height; race; ethnicity)											
Medical history											
Physical Exam (incl. weight and ECOG Perf Status)	x	x	x	x	x	x	x	x	x	x	
12-Lead ECG[a]								x			
Vital Signs (T, HR, BP, RR) - See Section 6.4 for monitoring before/during/after drug admin	x	x	x	x	x	x	x	x	x	x	
Concomitant Medication / Procedure (name, indication, dose, route, start & end dates)	x	x	x	x	x	x	x	x	x	x	
Adverse Events (starting or worsening after IC)[e]	x	x	x	x	x	x	x	x	x	x	
Specimens for Routine Laboratory Procedures											
Blood Hematology (CBC, differential, platelets)[a]	x	x	x	x	x	x	x	x	x	x	
Chemistry (glucose, BUN, creat., Na, K, Cl, CO_2, Ca, Mg, protein, alb, TBili, AST, ALT, ALP, LDH)[a]	x	x	x	x	x	x	x	x	x	x	
Chemistry Cont. (Free T_3, Free T_4, TSH)[a]		x	x	x	x	x	x	x	x	x	
Chemistry Cont. (amylase, lipase)[a]		x	x	x	x	x	x	x	x	x	
Urinalysis[a]		x	x	x	x	x	x	x	x	x	
Coagulation parameters (PT, aPTT, INR)[a]								x			
Serum pregnancy test (urine only on Day 1)[a]		x		x		x		x		x	
Specimens for Biological Markers and Correlative Studies											
Blood for PBMC Collection and Banking[f]							x	x			
Blood for viral particles (Collected only during dose escalation phase)											
Blood for Th1/Th2/Th17 cytokines in serum							x[a]	x			
Other Procedures											
Archival tumor[K]											
Tumor Biopsy (FFPE and frozen) for tumor microenvironment[c,K]											
Post Study Follow-up[L]											
Overall Survival											x[L]
Progression Free Survival[g]											x[L]

Flowchart Footnotes

a - pre-dose (if applicable). Note: It is strongly recommended that test results are reviewed before dosing for hematology, chemistry (including amylase, lipase, and thyroid pre durvalumab) and pregnancy (when applicable).
b - pre-ONCOS-102 dose, 4-6 hours after ONCOS-102 dose, and prior to discharge (Note: the cytokine collection prior to discharge is for dose escalation phase only).
c - core needle biopsy (one 14G core divided in 3 pieces or three 18G cores); 1 for FFPE, 2 snap-frozen and stored at -70 ±10°C. Biopsies will be taken from the same lesion pre- and on-treatment. Optional: FFPE pre- and on-treatment biopsy of extraperitoneal site
d - Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart
e - See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration
f - Six CPT tubes per time point (pre-dose) -> PBMC isolation; used for banking PBMCs and plasma (* Only one CPT tube is required on Day 1 -> PBMC isolation for assessment of T regs)
g - For subjects who did not experience progression while on study
h - Collected together with routine lab assessment blood draw (pre-dose, if applicable)
i - The physical exam on Cycle1/Day1 does not need to be repeated if it was performed on Day -1, prior to the cyclophosphamide injection.
J - The Cycle1/Day 1 lab assessments may be done on Day -1
K- Microsatellite instability (MSI)/MMR status should be available at baseline for all subjects (ovarian cancer and colorectal cancer(CRC)); KRAS and NRAS status should be available for subjects with CRC. If these results are not available, the testing may be done on archival tissue or on tissue that is obtained pre-treatment.
L - Per Amendment 6.1, all post study follow-up for the collection of survival data will be discontinued as of 30 June 2022 (see Section 8.1, Amendment 6.1)

4 Study Objectives and Endpoints

Primary Objective [Endpoints]	**Dose Escalation Phase:** *Safety and Tolerability* [DLTs, RCD according to CTCAE 4.03] **Expansion Phase:** *Clinical Efficacy by RECIST 1.1* [Clinical Benefit (CB), defined as percentage of subjects who are not in progression **at end of Week 24**].
Secondary Objectives [Endpoints]	**Dose Escalation and Expansion Phases (all subjects):** *Safety and Tolerability* [CTCAE 4.03] *Clinical Efficacy by RECIST 1.1/irRECIST* [Durable Clinical Benefit (DCB, defined as the percentage of subjects meeting criteria of SD, PR, or CR **over a period of at least 24 weeks**); ORR after 8 and 24 weeks; PFS; and OS]
Exploratory Objectives [Endpoints]	**Dose Escalation and Expansion Phases (all subjects):** *Biologic Activity* [Effects on immune biomarkers, Immune Response, mechanisms of therapeutic resistance]. This will include CD8+ T cells in biopsies. PBMCs will be analysed for the presence of tumour and virus antigen specific CD8+ T cells as well as different immune cell subpopulations, such as T regulatory cells and effector cells.
DLT=Dose-limiting Toxicity; RCD=Recommended Combination Dose; ORR=Objective Response Rate; DCB=Durable Clinical Benefit; PFS=Progression-free Survival; OS=Overall Survival; CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; RECIST= Response Evaluation Criteria in Solid Tumors; irRECIST=immune-related RECIST	

4.1 Safety and Tolerability

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. The safety and tolerability of each regimen will be evaluated using DLT criteria (Section 3.1.9).

4.1.1 Endpoints and Assessment Methods

Clinical laboratory tests, vital sign and weight measurements, physical exams, performance status evaluation, imaging scans and any other medically indicated assessments, including 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 the informed consent to the end of study visit will be recorded in the Case Report Forms as adverse events and graded according to the CTCAE Version 4.03. See further adverse event documentation and reporting requirements in Section 7.1.

For the dose escalation phase, DLTs and RCDs will be assessed as per Sections 3.1.9 and 3.1.7.1, respectively.

4.1.2 Subject Evaluation and Statistics

The **Per-Protocol (PP) Population for DLT Assessment** includes:

- All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9)
- All subjects with no DLT who receive at least 60% of the scheduled doses of ONCOS-102 and at least 1 dose of durvalumab (Cohorts B and C only) as well as respective safety assessments without major protocol violations during the 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 ONCOS-102.

In the dose escalation phase, 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 (dose escalation and expansion), the overall analysis of safety and tolerability will be based on the Safety Population.

Appropriate summaries of AEs, SAEs, laboratory data and vital sign data will be presented for the Safety Population overall and by cohort. 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 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 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 for the changes from baseline to each post-treatment assessment time point. Descriptive statistics will be presented for the changes in vital signs from baseline to each post-treatment assessment time point.

4.2 Clinical Efficacy

4.2.1 Endpoints and Assessment Methods

Clinical efficacy will be assessed by RESIST 1.1 and irRECIST (see Section 8.5), measuring CB at end of Week 24, DCB over a period of at least 24 weeks, ORR after 8 and 24 weeks (based on disease assessments at the scheduled Weeks 9 and 25 visits), PFS, and OS. Tumor response will be assessed by measurement of tumor markers as applicable to each tumor type and by CT/MRI using RECIST 1.1 and irRECIST criteria approximately every 8 weeks (see flowchart in Section 3.2). 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 first post treatment tumor assessments (during On Study Follow-up) will be at least 4 weeks from the prior assessment.

4.2.1.1 Clinical Benefit (CB)

Clinical Benefit is defined as percentage of subjects who are in the study and not in progression **at end of Week 24.**

4.2.1.2 Objective Response Rate (ORR)

ORR is defined as the percentage of subjects meeting criteria of Complete Response (CR) or Partial Response (PR) over a period of at least 4 weeks.

4.2.1.3 Durable Clinical Benefit (DCB)

DCB is defined as the percentage of subjects meeting criteria of Stable Disease (SD), partial response (PR), or complete response (CR) over a period of at least 24 weeks.

4.2.1.4 Progression-free Survival (PFS)

PFS is defined as the interval between the date of first dose to the date of earliest determination of Progressive Disease (PD), or to the date of death, if PD does not occur. Subjects without documentation of progression at the time of the analysis will be censored at the date of last response assessment. Subjects with no tumor response assessment will be censored at the start date of the treatment.

4.2.1.5 Overall Survival (OS)

OS is defined as the interval between the date of first dose until the date of death or the date of last follow-up. Subjects who are still alive will be censored on the date of last follow-up. Every effort will be made to follow subjects for OS after they discontinue study treatment or complete the On Study Follow-up according to Section 3.1.16.

NOTE: Per Amendment 6.1, 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 6.1).

4.2.2 Subject Evaluation and Statistics

The **Intent-To-Treat (ITT) Population for Clinical Efficacy** is defined as all subjects who receive at least one dose of durvalumab or ONCOS-102.

The **Per-Protocol (PP) Population for Clinical Efficacy** of the combination therapy is defined as all subjects who receive at least 60% of the scheduled doses of ONCOS-102 and at least 1 dose of durvalumab (Cohorts B and C only) over the first 2 cycles, as well as respective disease assessments, without major protocol violations.

The analysis will be based on both ITT and PP populations. Each of the 2 cohorts in the expansion phase will be analyzed separately.

Tumor Response will be summarized and analyzed descriptively for each cohort and analysis population.

A 95% CI based on binomial distribution will be constructed for the estimated CB, ORR, and DCB. The primary endpoint analyses of CB will be conducted as follows (please refer to Section 3.1.6 for sample size rationale):

Cohort 1: The null hypothesis of CB = 20% will be tested against a one-sided alternative of CB = 40% at 0.05 level of significance based on Simon 2-stage Minimax criterion. The null hypothesis will be rejected if 11 or more subjects experience clinical benefit at end of Week 24.
Cohort 2: The null hypothesis of CB = 5% will be tested against a one-sided alternative of CB = 20% at 0.05 level of significance based on Simon 2-stage Minimax criterion. The null hypothesis will be rejected if 4 or more subjects experience clinical benefit at end of Week 24.

The number and percentage of subjects who died or had a confirmed progression, who survived without a confirmed progression, and who were lost to follow up (unknown survival and/or progression status) will be summarized.

PFS and OS will be summarized using the 25th percentile, Median, and 75th percentile as well as the minimum and maximum survival time, calculated by Kaplan-Meier method, and will be displayed graphically.

4.3 Biological Activity

4.3.1 Endpoints and Assessment Methods

Specimens for immune monitoring assays will be collected according to the flowchart in Section 3.2. The Specimen requirements are summarized in Table 2, and full details are provided in the Laboratory Manual.

Table 2. Biomarker specimen requirements

Specimen
FFPE Archival primary or metastatic tumor 1st Choice: block 2nd Choice: 35 unstained slides
FFPE and frozen Pre-treatment biopsy Optional: FFPE Pre-treatment biopsy of extraperitoneal site
FFPE and frozen On-treatment biopsy Optional: FFPE on-treatment biopsy of extraperitoneal site
Pre-treatment and on treatment PBMC six CPT tubes per time point (pre-dose) Note: only one CPT tube is required on Day 1 -> PBMC isolation for assessment of T regs)
Pre-treatment and on treatment plasma (from PBMC collection tubes)
Blood for cytokines in serum
Whole blood for viral particles
Blood for CA-125 for ovarian or CEA for CRC (must be collected at same time points as disease assessments; test will be performed by local lab)

4.3.1.1 Viral assessment

Viral assessments in whole blood will be done during the dose escalation phase of the study. Whole blood for viral particles will be collected according to the flowchart in Section 3.2. The samples will be tested for the presence of viral particles by quantitative PCR.

4.3.1.2 Assessment of dynamic changes in tumor microenvironment

Pre-treatment and on-treatment tumor biopsy tissue will be processed for RNA isolation and evaluated for gene expression using Nanostring nCounter PanCancer Immune Profiling Panel, which consists of 770 genes related to angiogenesis, inflammation, and innate and adaptive immune response. Among these, the expression of the known activating co-stimulatory receptors such as 4-1BB (CD137), OX40, GITR, CD40, and ICOS, as well as known immune inhibitory proteins such as PD-L1, indoleamine dioxygenase (IDO), B7-H3, B7-H4, LAG3, TIM-3, PD-1, CTLA-4, VISTA, and BTLA will be assessed. The platform will in addition assess for the expression of around 30 know cancer-testis antigens, which will provide a potential marker for monitoring of peripheral serologic and cellular immune responses. Transcriptional findings will be validated by immunohistochemistry/ immunofluorescence for expression of PD-L1 as a predictive biomarker and presence of various infiltrating immune cell subsets, including CD8 cells, $CD4^+$ effector cells ($FoxP3^-$), $CD4^+$ regulatory T cells ($FoxP3^+$), and myeloid cells. Depending on tissue availability, tumors will be assessed for expression of immune inhibitory receptors and proteins (such as indoleamine dioxygenase (IDO), B7-H3, B7-H4, LAG3, TIM3, PD-1, CTLA-4, VISTA, and BTLA), and immune-activating receptors (such as 4-1BB (CD137), OX40, GITR, CD40, and ICOS). DNA extracted from tumors will be sent for deep sequencing of T cell receptor V beta chain to determine repertoire composition.

Biomarker	Approach	Parameters*
Immune cell subsets	Nanostring +/- IHC**	CD3, CD4, CD8, CD56, CD68, CD14, CD33, CD19, CD11c, CD103, CD163
Targetable immune activating genes	Nanostring +/- IHC**	4-1BB, OX40, GITR, CD40, and ICOS
Targetable immune inhibitory genes	Nanostring +/- IHC**	PD-L1, IDO, B7-H3, B7-H4, LAG3, TIM-3, PD-1, CTLA-4, VISTA, and BTLA
Cancer-testis antigens	Nanostring +/- IHC**	e.g. NY-ESO-1, MAGE A4, etc.
T cell receptor repertoire	DNA deep sequencing	T cell density, TCR clonality, clonal overlap.

*Additional parameters will be added from the panel, depending on the results from the initial subjects

**Validation by IHC will depend on tissue availability

4.3.1.3 Exploration of peripheral blood biomarkers

Pre-treatment and on-treatment samples will be analyzed by Nanostring platform and by flow cytometry to study the effects of treatment on various peripheral blood immune cell subsets. PBMC isolated from whole blood will be processed for multicolor flow cytometry analyses looking at different cell subsets such as $CD4^+$, $CD8^+$, NK, NKT, and regulatory T cells ($CD25^+FoxP3^+$), markers of T cell activation (CD25, CD62L, HLA-DR, CD150, ki67, granzyme B,

ICOS, CD137, OX40, GITR), inhibition/exhaustion (PD-1, LAG3, TIM3, CD160), and percentages of myeloid-derived suppressor cells (MDSCs) (HLA-DR, CD33, CD14, CD15, CD3, CD19, CD56, CD16). DNA extracted from PBMC would be sent for deep sequencing of T cell receptor V beta chain to determine repertoire composition. Serum cytokines and chemokines will be measured to evaluate for evidence of Th1/Th2/Th17 or other type of immune response.

Biomarker	Approach	Parameters
Transcriptional profile	Nanostring	Markers related to immune activation and inhibition, as discussed in text
T cell activation	Flow cytometry	CD25, CD62L, HLA-DR, CD150, ki67, granzyme B, ICOS, CD137, OX40, GITR
T cell exhaustion	Flow cytometry	PD-1, LAG3, TIM3, CD160
MDSC	Flow cytometry	HLA-DR, CD33, CD14, CD15, CD3, CD19, CD56, CD16
T cell receptor repertoire	DNA deep sequencing	T cell density, TCR clonality, clonal overlap.
Cytokines/chemokines	Serum multiplex ELISA	Inflammatory cytokine/chemokine panel
Adenovirus-specific immune responses	Intracellular cytokine staining	Production of IFNg and TNFa by antigen-stimulated PBMCs
Adenovirus-neutralizing antibodies	Serum multiplex ELISA	Neutralizing antibodies to ONCOS-102

4.3.1.4 Exploration of genetic predictors of response

To determine whether specific tumor genetic determinants influence the response to treatment, DNA isolated from pre-treatment or archived tumor samples will be processed for whole exome analysis to assess for specific driver mutations and for potential neoantigens using appropriate bioinformatics algorithms developed at Memorial Sloan-Kettering Cancer Center.

Biomarker	Approach	Parameters
Genetic drivers	Whole exome sequencing	Presence of mutations/alterations in a panel of known oncogenes/tumor suppressors
Neoantigen signature	Whole exome sequencing	Presence of immunogenic epitopes based on prediction algorithms

4.3.1.5 Assessment of cellular neoantigen responses

Pre-treatment and on-treatment PBMCs will be collected according to the time points in Section 3.2. Overlapping pools of peptides synthesized based on the predicted neoepitopes will be used

to stimulate the PBMCs and antigen-specific responses will be assessed by intracellular cytokine staining.

4.3.1.6 Assessment of responses to CT antigens

Expression of CT antigens will be evaluated by the Nanostring nCounter PanCancer Immune Profiling Panel and validated by IHC for the specific proteins. Serologic responses to the particular CT antigens will be assessed by ELISA before and after therapy. CD4 and CD8 antigen-specific responses will be assessed by intracellular cytokine staining.

Biomarker	Approach	Parameters
Serology	ELISA	Reactivity to known cancer-testis antigens
T cell responses	Intracellular cytokine staining	Production of IFNg and TNFa by antigen-stimulated PBMCs

4.3.2 Subject Evaluation and Statistics

Only subjects who receive at least 1 dose of durvalumab and ONCOS-102 and provide the baseline and at least 1 post-treatment sample (if applicable) will be evaluated. As these analyses represent exploratory evaluations of potential biomarkers of response or resistance to therapy, descriptive statistics will be used to describe findings and potential relationships to outcomes to 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.

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

<table>
<tr><td>1.</td><td>Subjects with peritoneal disease who have histologic confirmation of epithelial ovarian cancer or metastatic colorectal cancer (CRC) will be enrolled. Note: the CRC cohort may include subjects with cancer originating from the appendix.
Subjects should have failed prior treatment for advanced cancer and deemed by the Investigator to no longer be eligible for or have reasonable standard of care alternatives, which are felt to have a clinically meaningful impact on their survival.
Subjects with ovarian cancer must have either received one line of platinum based therapy and have progressed within 6 months (defined as platinum resistant) or have received 2 or more lines of standard therapy.
Subjects with CRC must have failed prior therapy containing fluropyrimidine, oxaliplatin and irinotecan, with or without anti-VEGF component, or for RAS wild-type, with or without anti-EGFR therapy.
Co-existing distant metastases and parenchymal organ metastases will be allowed.
Subjects may have received prior intraperitoneal therapy.</td></tr>
<tr><td>2.</td><td>Measurable disease according to RECIST 1.1, defined as ≥ 1 lesion that can be accurately measured in at least 1 dimension (longest diameter to be recorded for non-lymph node lesions, shortest diameter to be recorded for lymph node lesions). Each lesion must be ≥ 10 mm when measured by CT or MRI. See Section 8.5.</td></tr>
<tr><td>3.</td><td>Availability of microsatellite instability (MSI)/MMR status for all subjects (OC and CRC)
Availability of KRAS and NRAS status for subjects with CRC. NOTE: if these results are not available, the testing may be done on archival tissue or on tissue that is obtained pre-treatment.</td></tr>
<tr><td>4.</td><td>The subject is willing to undergo a core needle biopsy during screening and during Cycle 2, Study Week 5.
Archival tumor samples are requested but are not required for eligibility.</td></tr>
<tr><td>5.</td><td>Laboratory parameters for vital functions should be in the normal range, unless not clinically significant. 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>> 1500/mm^3</td></tr>
<tr><td>Platelet count</td><td>≥ 100 x 10^9 /L (100,000/mm^3)</td></tr>
<tr><td>Serum creatinine or Creatinine Clearance</td><td>≤ 1.5 x Institutional Upper Limit of Normal (ULN), or >40 mL/min (by Cockcroft-Gault formula) or by 24-hour urine collection for determination of creatinine clearance</td></tr>
</table>
</td></tr>
</table>

		Serum bilirubin	≤ 1.5 x ULN (except for subjects with Gilbert's syndrome who will be allowed after consultation with their physician)	
		AST/ALT	≤ 2.5 x ULN	
		Alkaline phosphatase	≤ 2.5 x ULN	
6.	ECOG PS ≤ 1.			
7.	Age ≥ 18 years.			
8.	Able and willing to provide valid written informed consent and to comply with the protocol. Agrees to return to the study site for study visits and examinations.			
9.	Body weight > 30 kg			

5.2 Exclusion Criteria

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

1.	Treatment with an investigational agent within 4 weeks of starting study treatment, and any prior drug-related toxicity (except alopecia) should have recovered to Grade 1 or less.
2.	Prior treatment with checkpoint inhibitor, including durvalumab.
3.	The subject has known active central nervous system metastasis, glioma and nervous system malignancies including carcinomatous meningitis. Subjects with asymptomatic brain metastases or spinal cord compression who have been treated, are considered stable, and who have not received corticosteroids or anticonvulsants for at least 28 days prior to screening may be included.
4.	Active infection including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). Subjects with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Subjects positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA. Subjects with treated hepatitis virus infections (Hepatitis B or Hepatitis C) are eligible if they have been definitively treated for 6 months, have no detectable viral load on quantitative PCR, and LFTs meet eligibility requirements.
5.	Subjects who are immunosuppressed, including those with known immunodeficiency.
6.	Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, current pneumonitis, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial or other current severe lung disease, or psychiatric illness/social situations that would limit compliance with study requirement or compromise the ability of the subject to give written informed consent.
7.	History of small or large bowel obstruction within 3 months of registration, including subjects with palliative gastric drainage catheters. Subjects with palliative diverting ileostomy or colostomy are allowed if they have been symptom-free for more than 3 months.

8.	Ongoing bowel perforation or presence of bowel fistula or abscess within 3 months of registration.
9.	Subjects with rapidly progressing or advanced disease with life expectancy <3 months.
10.	Subjects with clinically significant cardiovascular disease, including: a. New York Heart Association (NYHA) Class II or higher congestive heart failure. b. Myocardial infarction, unstable angina, cerebrovascular accident or transient ischemic attack within 6 months of Day 1. c. Clinically significant supraventricular or ventricular arrhythmia. d. Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction. e. Clinically uncontrolled hypertension.
11.	Any prior Grade ≥ 3 immune-related adverse event (irAE) or hypersensitivity reaction to monoclonal antibodies, other therapeutic proteins, or immunotherapy and the reaction could not be controlled or prevented on subsequent infusion with standard therapies such as antihistamines, 5-HT3 antagonists, or corticosteroids.
12.	Any unresolved irAE > Grade 1 at the time of screening.
13.	The subject has a history of organ transplant or allogeneic bone marrow transplant.
14.	Active known autoimmune disease or history of autoimmune disease that might recur. These include but are not limited to subjects with a history of immune related pneumonitis, neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease, Crohn's, ulcerative colitis, hepatitis; and subjects with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome. Subjects with vitiligo, alopecia (caused by autoimmune disease), Graves disease, or psoriasis not requiring systemic treatment (within the past 3 years) are allowed.
15.	Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of investigational products or still recovering from prior surgery.
16.	Concurrent enrollment in another investigational study, with the exception of follow-up period.
17.	History of severe allergic reactions to any unknown allergens or components of the study drugs (see specific exclusions for ONCOS-102 below).
18.	Other serious illnesses (e.g., serious infections requiring antibiotics, bleeding disorders).
19.	Active or prior malignancy except for history of other prior malignancy treated with curative intent which, in the opinion of the treating investigator and the Sponsor, has minimal risk of interfering with safety or efficacy endpoints of the study.
20.	Current or prior use of immunosuppressive medication within 14 days before the first dose of investigational product with the exceptions of topical or systemic corticosteroids at physiological doses that are not to exceed 10 mg/day of prednisone or equivalent. See Section 5.3.2 for permitted steroids.
21.	Any condition that, in the clinical judgment of the treating physician, is likely to interfere with the interpretability of the data or prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.

22.	Subjects with refractory ascites, for example, ascites needing drainage catheter or therapeutic paracentesis more often than every 4 weeks.
23.	Subjects must not donate blood while on study and for at least 90 days following the last durvalumab treatment.
24.	Women of childbearing potential who are found to be pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) or nursing.
25.	**For ONCOS-102, there is a requirement for the use of barrier contraception (condom) for each treated subject (and/or partner), regardless of their sex or fertility, during treatment and for 2 months after the last dose of ONCOS-102. This can be combined with other contraceptive methods.** **Requirements for durvalumab to prevent pregnancy are as follows; however, during ONCOS-102 treatment and for 2 months after the last dose of ONCOS-102, the ONCOS-102 requirement stated above would also apply**: **Female subjects of childbearing potential** who are sexually active with a non-sterilized 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 final dose of investigational products. Non-sterilized male partners of a female subject must use male condoms 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 also 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. **Non-sterilized 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 receipt of the final dose of investigational products. 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 (e.g., 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	

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 glucocorticosteroids 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, non-palliative radiation, or immunotherapy). Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Day 1 (6 weeks for nitrosoureas, 7 days for crizotinib).
3.	Live/attenuated vaccines 1 month prior to Day 1 and for at least 6 months after the last dose of treatment.
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.	

5.3.2 Permitted Concomitant Therapies

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

1.	Inhaled or oral steroids for treating mild to moderate asthma or allergies, or topical steroids for localized (< 5% of body surface area) dermatitis, not to exceed 10 mg/day prednisone or bioequivalent corticosteroid.
2.	Physiologic replacement of glucocorticoids as maintenance therapy for adrenal insufficiency. Standard doses of hydrocortisone for maintenance therapy are up to 10–20 mg/m2/day divided 2–4 times per day. For a subject with a body surface area (BSA) of 1.73 m^2, this translates to a total dose of up to 34.6 mg of hydrocortisone per day. The equivalent dose of dexamethasone is up to 1.2 mg per day. Some subjects may additionally receive mineralocorticoid-replacement maintenance therapy with fludrocortisone. The maintenance dose of fludrocortisone for this indication is 0.05–0.1 mg/day.
3.	Paracetamol, NSAIDs, acetylsalicylic acid, and specific COX-2 inhibitors. Subjects are likely to develop fever. This is normal and part of the desired innate immunological reaction after viral therapy and can be treated with paracetamol or ibuprofen. Subjects should however not be premedicated with antipyretics before treatment as this may impact immune activation.
4.	Antihistamines and other non-steroidal anti-allergy medication.
5.	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 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. Use of anticoagulants such as warfarin is permitted; however, caution should be exercised and additional international normalized ratio (INR) monitoring is recommended.

6.	Palliative locoregional therapy (e.g. radiation, ablation, resection) to the isolated sites of progressive disease, if the subject continues to derive benefit from the therapy at other sites.
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.	

6 Study Drug Preparation and Administration

TARGOVAX will provide ONCOS-102 directly to the sites. MedImmune will supply the durvalumab, which will be provided to the site by the Sponsor. Commercially available water for injection (WFI) and 0.9% (w/v) saline or dextrose will be supplied by each site.

When durvalumab and ONCOS-102 are administered on the same day, durvalumab is administered first, and there should be at least 1 hour between the end of infusion of the durvalumab and the start of the infusion of ONCOS-102. See Section6.4.1 for observation period following administration of durvalumab. See Section 6.4.2 for observation period following administration of ONCOS-102.

6.1 Durvalumab (MEDI4736)

6.1.1 Durvalumab 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 per vial of durvalumab. This 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:* 10 mL	*Concentration:* 50 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		

6.1.2 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.

6.1.3 Durvalumab Preparation

Preparation of durvalumab and preparation of the intravenous bag are to be performed aseptically by the IP manager or designated personnel. No incompatibilities between durvalumab and polyvinylchloride or polyolefin copolymers have been observed.

Dose Calculation:
Subjects will receive a fixed dose of durvalumab: 1500 mg Q4W for subjects > 30 kg.

NOTE: if a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing equivalent to 20 mg/kg of durvalumab as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500

mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of durvalumab 1500 mg.

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 1500 mg dose (for subjects > 30 kg in weight), 30.0 mL of durvalumab is to be diluted in a 250 mL IV bag. First, 30.0 mL of diluent is removed from the IV bag, and then 30.0 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; any unused portion must be discarded

6.1.4 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 product(s). 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 be administered at room temperature by controlled infusion into a peripheral vein or central line.
- 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.
- 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-um 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.

- See Section 8.3.1 for guidelines for infusion-related reactions.
- 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 6.4.1.
- Durvalumab does not contain preservatives, and any unused portion must be discarded.

6.2 ONCOS-102

6.2.1 ONCOS-102 Study Drug Information

Manufacturer	Targovax Oy, Finland		
Expiration/Retest Date	*Expiration/retest dates are documented on the Certificate of Analysis and/or stability certification.*		
Container Description	*Type:* Single use vial	*Material:* Injection vial, Clear Neutral Glass, Type I	*Size:*
Formulation	Clear or opalescent liquid		
Active Ingredient Content	*Mass/Weight:* 4×10^{11} VP/vial	*Volume:* 0.8 mL per vial	*Concentration:* 5×10^{11} VP/mL
Storage Conditions	-20 ± 5°C		
Stability after addition to the infusion bag	8 hours at +15 to +25 °C Note: this is from the time the ONCOS-102 is added to the infusion bag to the end of infusion.		
Labeling	Product name, lot number, route of administration, and storage conditions		

ONCOS-102 is formulated as a clear or opalescent liquid that is presented in glass vials sealed with a rubber stopper and an aluminum cap for single use. The final filling volume is 0.8 mL, and the VP-titer of each vial is 4×10^{11}. Vials of ONCOS-102 must be stored at -20 ± 5°C and marked with a biohazard symbol.

6.2.2 ONCOS-102 Preparation

ONCOS-102 like other adenoviruses belong to Risk Group 2 (moderate individual risk, low community risk). Biosafety level 2 (BSL-2) containment is required for work with ONCOS-102, including BSL-2 facilities, equipment, practices and procedures. The room or area used for ONCOS-102 preparation must be approved for handling BSL-2 organisms.

ONCOS-102 is an adenovirus that is genetically modified to replicate selectively in cancer cells. The ability to replicate in normal non-dividing cells is attenuated. Therefore, it is unlikely that ONCOS-102 would pose any clinically significant health issues to non-tumor-bearing individuals as it is less harmful for the healthy people than wild type adenoviruses (e.g. serotypes 5 and 3)

that commonly infect the human population. Moreover, GMCSF production makes viruses more immunogenic, enhancing clearance from normal tissues, further increasing their safety. Therefore, there is little potential harm to the environment.

There is a theoretical risk of spread of ONCOS-102 into the environment from subjects who are undergoing treatment. However, in the Phase I study, no virus was detected in urine or buccal swabs at discharge after dosing in any subject. Virus was detected before dosing on one occasion (Day 4): in the urine of 1 subject, and in the buccal swabs in 3 subjects, but not on subsequent dosing days.

ONCOS-102 can be inactivated using a suitable adenovirus neutralising agent or virucidal disinfectant, or similar. These are to be used for the inactivation of spills and devices used for administration. When preparing the infusion solution, only the required number of vials should be thawed; re-freezing is not allowed.

The dose of ONCOS-102 will be diluted with saline in a 500-mL infusion bag prior to administration. The diluted product is stable for treatment at a temperature of +15 to +25°C for a maximum of 8 hours (from the time the ONCOS-102 is added to the infusion bag to the end of infusion). The dilution must be performed within a biosafety cabinet with a Closed System Transfer Device to reduce the risks posed by the possibility of generation and inhalation of aerosols.

Full details of virus handling instructions and preparation will be provided in a separate ONCOS-102 Handling Guideline.

Waste should be handled according to local guidance and procedures. Typically, standard operating procedures for disposal within medical facilities will be consistent with the guidance given in the WHO Laboratory Biosafety Manual, 3rd Ed (2004).

Biohazard waste containers are required both in the pharmacy/laboratory and in the treatment room. A separate biohazard waste bag for disposable waste, including single-use lab coats, sleeve covers, gloves, packaging materials and used paper wipes or textile cloths, should be available.

A puncture-proof sharp item waste container is also required. Needles are not recapped or removed: the complete administration assembly is placed in sharps container and later disposed in a manner consistent with the standard practice of the institution for potentially biohazardous sharps waste. Full details of virus handling instructions will be provided in a separate ONCOS-102 Handling Guideline.

6.2.3 ONCOS-102 Administration

ONCOS-102 will be delivered by intraperitoneal (IP) infusion via a peritoneal Hickmann catheter (or institutionally preferred alternative). The ONCOS-102 will be infused in a total volume of 500 mL saline (0.9 mg/mL NaCl in water for injection) by gravity feed or per institutional procedures for IP infusions. The infusion should be given as soon as possible after preparation of the infusion solution. It is recommended that the total infusion time not exceed 2 hours.

To ensure uniform distribution of ONCOS-102 in the peritoneal cavity during the infusion, it is recommended that the subjects are rotated every 30 minutes, or institutional procedures may

be followed. ONCOS-102 will be administered weekly for a total of 6 weeks (see separate ONCOS-102 Handling Guideline for additional details).

See Section 6.4.2 for monitoring period after administration of ONCOS-102.

6.3 Estimated Study Requirements

Drug	***Required Quantity of Vials****
Durvalumab	3326
ONCOS-102	562
Cyclophosphamide	94

(*includes 20% overage for 78 subjects)

6.4 Monitoring of Study Drug Administration

6.4.1 Monitoring for Durvalumab Administration

Subjects will be monitored before, during and after infusion of 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**
Durvalumab	X	Every 15 (± 5) minutes	X	X	X

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.

Drug	**Pre Dose**	**During Infusion**	**End of Infusion (± 5 minutes)**	**15 (± 5) minutes Post infusion**
Durvalumab	X	Every 30 (± 5) minutes	X	X

6.4.2 Monitoring for ONCOS-102 Administration

All subjects in the dose escalation phase will remain in the facility for observation for 8 to 12 hours after each ONCOS-102 infusion.

NOTE: Per Amendment 5, all subjects in the expansion phase will remain in the facility for observation for a minimum of 6 hours after the first dose of ONCOS-102 infusion; for subsequent doses, the observation period will be a minimum of 4 hours, but it may be longer, based on Investigator's discretion.

During this period, subjects should be monitored according to institutional policy. Further guidance is provided below.

It is suggested that vital signs and temperature are taken every 4 hours. Discharge or admission for further observation are at the discretion of the Investigator. Subjects are expected to develop fever. Fever without associated other symptoms, such as hemodynamic instability, is generally not a reason for admission.

The following suggested guidelines may be used for the management of ONCOS-102-related toxicities:

1. Isolated fever or pain may be treated with acetaminophen, NSAIDS, opioids, or as determined by the Investigator.
2. For more severe reactions, aggressive symptomatic treatment may be administered, which may include fluids, oral or IV antihistamine, anti-pyretics, bronchodilators, pressors, and oxygen as indicated. Glucocorticoids may be administered for refractory symptoms according to the judgment of the Investigator.

All adverse events (AEs), including clinically significant changes in vital signs and temperature, that occur during this observation period should be documented in the source and eCRF. Refer to Section 7.1.5 for details on reporting AEs and Section 7.1.6 for details on reporting serious AEs.

Based on the safety data from the dose escalation phase, the internal data safety monitoring panel (as defined in Section 3.1.14) will decide if an observation period will be required for the expansion phase. The safety review for the dose escalation phase was conducted, and it was agreed that the observation period would be shortened for the expansion phase. See note above for expansion phase requirements, per Amendment 5.

6.5 Drug Overdose Management

There are no known antidotes available for durvalumab or ONCOS-102. Any overdoses with these drugs should be managed symptomatically. 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 .

7 Administrative, Legal and Ethical Requirements

7.1 Documentation and Reporting of Adverse Events

7.1.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient/subject or clinical investigation subject administered a pharmaceutical product and which 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 Ludwig Institute for Cancer research (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.

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 6.5).
3. Hepatic function abnormality (as defined in Section 7.1.8)
4. New cancers
5. Deaths

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.

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 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 final dose of investigational product.

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 6.5) of a study subject, 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 ONCOS-102. The Investigator will use clinical judgment to treat any overdose. See Section 6.5 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 MedImmune/AstraZeneca.

7.1.2.4 New Cancers

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

7.1.2.5 Deaths

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

- Death clearly resulting from disease progression should be reported to the Study Monitor/Physician at the next monitoring visit and should be documented in the eCRF. It should be reported as an SAE if it meets SAE reporting criteria per Section 7.1.6.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Monitor/Physician as an SAE within 24 hours. It should also be documented in the eCRF.

- The report should contain a comment regarding the co involvement of PD, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. It should also be documented in the eCRF.
- A post mortem may be helpful in the assessment of the cause of death, and if performed, a copy of the post-mortem results should be forwarded to LICR within the usual timeframes.

Deaths occurring after the protocol-defined safety follow-up period after the administration of the last dose of study drug should be documented only in the Post Study Follow-up eCRF form. If the death occurred as a result of an event that started after the defined safety follow-up period and the event is considered to be due to a late onset toxicity to study drug, then it should also be reported as an SAE.

LICR and AstraZeneca retain the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

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 AEs to the investigational agent(s) will be determined by the Investigator on the basis of his/her 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 severity or 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 90 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 90 days after the last dose of the last study treatment (regardless of initiation of another therapy).

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 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 (see contact information below). SAEs should be reported via the Medidata RAVE data capture system (which utilizes "Safety Gateway"), 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. In the event that the SAE cannot be reported via Medidata RAVE, the SAE should be reported using the "Initial Serious Adverse Event Report Form," provided by the Sponsor.**

Note: If an SAE cannot be reported via Medidata RAVE or the "Initial Serious Adverse Event Report Form" 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 through Medidata RAVE or an "Initial Serious Adverse Event Report Form" within one working day of the event.

If the "Initial Serious Adverse Event Report Form" is being used, 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 Medidata RAVE (and the "Safety Gateway"), built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to Medidata RAVE and "Safety Gateway" procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact (see table below for contact information).

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

Drug Safety Contact:	*Primary Sponsor Contact:*
[redacted]	[redacted]
Senior Manager, Drug Safety	Senior Director
Clinical Trials Management	Clinical Trials Management
Ludwig Institute for Cancer Research	Ludwig Institute for Cancer Research
600 3rd Ave, 32nd Floor	600 3rd Ave, 32nd Floor
New York, New York 10016	New York, New York 110016
[redacted]	[redacted]

Serious adverse events must also be reported by the Principal Investigator to the respective Institutional Review Board after being assigned an SAE tracking number by the Sponsor. Institutional Review Boards may have specific rules on which AEs need to be reported expeditiously, as well as, the time frames for such reporting.

Serious Adverse Event 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 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.

7.1.8 Adverse Events of Special Interest (AESIs)

An adverse event of special interest (AESI) is an event 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.

7.1.8.1 AESIs for Durvalumab

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. 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 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 version of the durvalumab (MEDI4736) Investigator's Brochure (IB). Guidelines for the management of subjects experiencing toxicities for durvalumab can be found in Section 8.3 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 are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAbs.(57) Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Hepatic function abnormalities (Hepatitis / transaminase increases)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies.(58) 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 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 ≥3xULN **or** total bilirubin ≥ 2xULN 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 hypophysitis/hypopituitarism, adrenal insufficiency, Type 1 diabetes mellitus, and hyper- and hypothyroidism.

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 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, haematological 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.(58) As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (immunoglobulin E-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.

7.1.8.2 Additional AESI for ONCOS-102

7.1.8.2.1 Fever

Temporary fever was observed in all subjects after the ONCOS-102 administrations in the Phase 1 study. The addition of durvalumab could theoretically exacerbate the fever. Paracetamol may be given at the discretion of the Investigator.

Guidelines for the management of subjects experiencing the toxicities for ONCOS-102 can be found in Section 8.4.

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

7.2 Administrative Sponsor Requirements

7.2.1 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.

7.2.2 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 Investigator will sign and date the completed eCRF sections. This signature will indicate a thorough inspection of the data in the CRF and will certify its content.

7.2.3 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.

7.2.4 Monitoring

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site qualification, 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 Institutional Review Board review, and regulatory inspection/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 CRFs at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to GCP guidelines. The Clinical Monitor should have access to subject charts, laboratory reports, and other subject records needed to verify the entries on the CRFs ("source data verification").

7.2.5 Protocol Amendments

Protocol amendments may be implemented only after approval by the Investigator, Sponsor, Institutional Review Board 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 that do not affect the safety of the subjects usually do not require prior Institutional Review Board approval, just notification.

When immediate deviation from the protocol is required to eliminate 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.

7.2.6 Premature Subject Withdrawal from Treatment or from Study

A subject may withdraw from study 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 criteria are listed in Section 3.1.10. Should a subject (or a subject's legally authorized representative) decide to withdraw from study treatment or from the study, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

For all subject withdrawals, a complete final evaluation should be made at the time of 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.

7.2.7 Early Trial Termination

The Study 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 Institutional Review Board accordingly.

7.2.8 Study Drug Shipments and 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; see Note for ONCOS-102)
- 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 seeing to it that all used and unused trial supplies are accounted for. 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 by a second person. At the end of the study, the Clinical Monitor will collect the original drug disposition logs.

Additional Note for ONCOS-102:
During the course of the clinical trial, the ONCOS-102 remaining after dilution (i.e., used vials and unused extra vials) will be destroyed at the site according to hospital practice for Biosafety Level 2 agents or according to guidance provided by Targovax; the guidance will be provided to the sites by the Sponsor. Please refer to the ONCOS-102 Handling Guideline for specific details regarding drug accountability and disposal. The drug disposition log will be maintained as stated above.

7.3 Regulatory, Legal and 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 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 Institutional Review Board

The Investigator must obtain written approval from the appropriate Institutional Review Board 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 SAEs to the appropriate Institutional Review Board in accordance with the Institutional Review Board's 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 Institutional Review Board throughout the duration of the study. If so required by the Institutional Review Board, the Investigator must provide study reports on an annual basis and upon completion of the study.

All correspondence with, and reports to, the Institutional Review Board 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 CRFs 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: Final, 19-OCT-2016** **Summary of Changes:** not applicable
Original Issue 0.1 **Issue Date: Final, 01-NOV-2016** **Summary of Changes: The IND # was added to the cover page. This was done as an administrative change.**
Amendment 1 **Issue Date: Final, 09-FEB-2017** **Summary of Changes:** Per FDA request, clarification was provided for Inclusion Criterion #1. Other changes were made for consistency with the language in Inclusion Criterion #1. 1. Synopsis and Section 3.1, Study Design: Paragraph 1 was changed **FROM**: "This is a two-part Phase 1/2 dose escalation and dose expansion study of the GMCSF-encoding adenovirus, ONCOS-102, in combination with anti-programmed death ligand-1 (PD-L1) antibody, durvalumab, in adult subjects with peritoneal disease who have failed prior standard chemotherapy and have histologically confirmed platinum-resistant or refractory epithelial ovarian cancer or colorectal cancer." **TO:** "This is a two-part Phase 1/2 dose escalation and dose expansion study of the GMCSF-encoding adenovirus, ONCOS-102, in combination with anti-programmed death ligand-1 (PD-L1) antibody, durvalumab, in adult subjects with peritoneal disease who have histologically confirmed epithelial ovarian cancer or metastatic colorectal cancer and have failed prior standard therapies." 2. Synopsis: The following changes were made (changes in bold): Phase 2 of the study is the dose expansion phase, which will further explore the safety and anti-tumor activity for the RCD in 2 expansion cohorts **with peritoneal disease**: • Platinum-resistant epithelial ovarian cancer • **Metastatic ~~C~~c**olorectal cancer 3. Section 3.1, Study Design: The following changes were made (changes in bold): **In Phase 2, there are ~~The~~** 2 expansion cohorts **with peritoneal disease ~~in Phase 2 are the following~~**: • Cohort 1: Platinum-resistant epithelial ovarian cancer • Cohort 2: **Metastatic ~~C~~c**olorectal cancer 4. Section 3.1.4, Subject Population was changed **FROM:** "Subjects with peritoneal disease who have failed prior standard chemotherapy and have histologically confirmed platinum-resistant or refractory epithelial ovarian cancer or colorectal cancer will be enrolled. Platinum resistance is defined as relapse within 6 months of last platinum-based chemotherapy or progression while on platinum-based therapy. Co-existing distant metastases and parenchymal organ metastases will be allowed. Details on subject eligibility are found in Section 5."

TO: "Subjects with peritoneal disease who have histologic confirmation of epithelial ovarian cancer or metastatic colorectal cancer (CRC) will be enrolled. Subjects with ovarian cancer must have either received one line of platinum based therapy and have progressed within 6 months (defined as platinum resistant) or have received 2 or more lines of standard therapy. Subjects with CRC must have at least failed two lines of fluropyrimidine based therapies, oxaliplatin or irinotecan based therapies with or without anti-VEGF component, or for RAS wild-type, with or without anti-EGFR therapy. Co-existing distant metastases and parenchymal organ metastases will be allowed. Subjects may have received prior intraperitoneal therapy. Details on subject eligibility are found in Section 5.*"*

5. Section 3.1.7.2, Dose Expansion Phase: The following changes were made (changes in bold): ~~**The following cohorts will be enrolled:**~~ I**n Phase 2, there are 2 expansion cohorts with peritoneal disease**:
   - Cohort 1: Platinum-resistant epithelial ovarian cancer
   - Cohort 2: **Metastatic c**~~**C**~~olorectal cancer
6. Section 5.1: Inclusion Criterion #1 was changed

FROM: "Subjects with peritoneal disease who have failed prior standard chemotherapy and have histologic confirmation of platinum-resistant or refractory epithelial ovarian cancer or colorectal cancer will be enrolled. Platinum resistance is defined as relapse within 6 months of last platinum-based chemotherapy or progression while on platinum-based therapy. Co-existing distant metastases and parenchymal organ metastases will be allowed."

TO: "Subjects with peritoneal disease who have histologic confirmation of epithelial ovarian cancer or metastatic colorectal cancer (CRC) will be enrolled. Subjects with ovarian cancer must have either received one line of platinum based therapy and have progressed within 6 months (defined as platinum resistant) or have received 2 or more lines of standard therapy. Subjects with CRC must have at least failed two lines of fluropyrimidine based therapies, oxaliplatin or irinotecan based therapies with or without anti-VEGF component, or for RAS wild-type, with or without anti-EGFR therapy. Co-existing distant metastases and parenchymal organ metastases will be allowed. Subjects may have received prior intraperitoneal therapy."

Amendment 2

Issue Date: Final, 18-JAN-2018

Summary of Changes:

1. Section 1.3.2 (ONCOS-102): For Clinical Study ONCOS C1, a clarification was provided that the ONCOS injections were given intratumorally. In addition, paracetamol was deleted in the last paragraph, as acetaminophen is sufficient description for the US sites.
2. Section 2.1.3 (Fixed dosing for Durvalumab): Based on Medimmune recommendations, a clarification was provided to indicate that: "If a subject's body weight drops to ≤ 30 kg while on the study, the durvalumab dose will be weight based as long as the body weight remains ≤ 30 kg." This was changed from 600 mg Q4W fixed dose for subjects≤ 30 kg. A reference to Section 6.1.3 was provided for additional details.
   a. This change was also implemented in Sections 3.1 (Study Design), 3.1.7 (Treatment Arms and Treatment Schema), and 3.1.7.1 (Dose Escalation Phase).
3. Section 3.1.7 (Treatment Arms and Treatment Schema): Treatment with ONCOS-102, third paragraph was modified to provide clarification for the ONCOS-102 infusion (changes in bold):

"After accessing the IP port and aspirating any ascites, if present, the ~~**reconstituted**~~ ONCOS-102 will be infused in a total volume of 500 mL saline (0.9 mg/mL NaCl in water for injection) **by gravity feed or per institutional procedures for IP infusions. The infusion should be given as soon as possible after preparation of the infusion solution. It is recommended that the total infusion time not exceed 2 hours.** ~~over a period of approximately **1 hour**~~. **To ensure uniform distribution of ONCOS-102 in the peritoneal cavity** during infusion, **it is recommended that** the subjects are rotated every 30 minutes, **or institutional procedures may be followed.** See Section 6.2.3 regarding administration of ONCOS-102."

   a. This modification was also implemented in Section 6.2.3.

4. Section 3.1.7.1 (Dose Escalation Phase) change from overnight stay to an observation period of 8 to 12 hours after each ONCOS-102 infusion was implemented.
5. Section 3.1.9 (DLT and MTD/RCD): 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 8.3.1 dose modifications."
6. Section 3.1.16.1 (End of Study Visit): The following clarification was added to the first paragraph (changes in bold): "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.**
7. Section 3.2 (Flowchart): the following changes/additions were made based on updated recommendations from the Investigators and/or corrections:
   a. Previous Row 35 (Blood for Tumor markers in serum) was moved below Disease Assessment Row, and renamed as: "Blood for CA-125 for ovarian or CEA for CRC (must be at same time points as disease assessments; test will be performed by local lab)[h]" The assessment on Cycle1/Day1 was moved Screening/Baseline to correspond with the disease assessments.
   b. Day 1 of Cycles 3, 5, and 7- visit window was changed from ±2 to ±4.
   c. Window of ±1 month was added for Post Study Follow-up visits. Note: this window was also added to Section 3.1.16.
   d. Window of ±1 week was On Study Follow-up visits for disease assessments and tumor markers
   e. Footnote a was clarified changes in bold): "pre-dose (if applicable). Note: It is strongly recommended that test results are reviewed before dosing for hematology, chemistry **(including amylase, lipase, and thyroid pre durvalumab)** and pregnancy (when applicable)."
   f. Footnote b was updated to correspond with changes to observation period in Section 6.4.2 (changes in bold): "pre-ONCOS-102 dose, 4-6 hours after ONCOS-102 dose, and prior to discharge ~~**the following morning.**~~
   g. Footnote f was updated (changes in bold): "Six CPT tubes per time point (pre-dose) -> PBMC isolation; **used for banking PBMCs and plasma** (* Only one CPT tube is required on Day 1 -> PBMC isolation for assessment of T regs)
   h. Footnote h was clarified (changes in bold): "Collected ~~**as part of**~~ **together with** routine lab assessment blood draw (pre-dose, **if applicable**)
   i. Footnote i was added for Cycle 1/Day 1 Physical Exam: "The physical exam on Cycle1/Day1 does not need to be repeated if it was performed on Day -1, prior to the cyclophosphamide injection."

j. Footnote J was added for Cycle 1/Day1 for all routine lab procedures: "The Cycle1/Day 1 lab assessments may be done on Day -1."
k. Row labeled Long Term Follow-up was corrected to Post Study Follow-up.
l. The following routine lab procedures were deleted as they were inadvertently included in the previous versions:
    i. Thyroid tests on Cycle 5/Day1
    ii. Amylase/Lipase tests on Cycle 1/Days 8 and 22, Cycle 2/Days 1 and 8, Cycle 3/Day 1, Cycle 5/Day 1, and Cycle 7/Day 1.
    iii. Coagulation for Cycles 3 to 12 and 2nd/3rd on study follow-up visits. (For durva, coag is needed at screening and as clinically indicated; however, it is required during ONCOS-102 administration.)

8. Section 4.3.1 (Biological Activity, Endpoints and Assessment Methods): Table 2 was changed as follows to provide clarification of intended meaning (changes in bold):
    a. Fifth row: Pre-treatment and on treatment ~~**serum**~~ **plasma (from PBMC collection tubes)**
    b. New sixth row was added: "Blood for cytokines in serum"
    c. Last row: "**Blood for CA-125 for ovarian or CEA for CRC (must be collected at same time points as disease assessments; test will be performed by local lab)**. ~~**Tumor markers – part of routine lab assessment blood draw.**~~
9. Section 5.1 (Inclusion Criteria):
    a. Criterion #1. The following note was added for clarification: "Note: the CRC cohort may include subjects with cancer originating from the appendix." Rationale: The treatment paradigm for appendiceal cancer is essentially the same as CRC; in many studies, they are grouped together.
        - This note was also added to the description of the population in the Synopsis.
    b. Criterion #1, the CRC paragraph was modified as follows (changes in bold): "Subjects with CRC must have at least failed two lines of **therapy (e.g.,** fluropyrimidine based therapies, oxaliplatin or irinotecan based therapies with or without anti-VEGF component, or for RAS wild-type, with or without anti-EGFR therapy.**)**
    c. Previous Inclusion Criterion #4 was changed as follows for clarification of the intended meaning (changes in bold): "**Subjects should have failed prior treatment** ~~**Previously treated**~~ for advanced cancer **and deemed by the Investigator to no longer be eligible for or have reasonable standard of care alternatives, which are felt to have a clinically meaningful impact on their** ~~**with no additional therapy options available known to prolong**~~ survival."
    d. The re-worded criterion 4 was added to text of Inclusion criterion #1. All other inclusion criteria were re-numbered, as appropriate.
    e. The changes made to inclusion criterion #1 were also made to Section 3.1.4 (Subject Population).
10. Section 6 (Study Drug Preparation an Administration): The following change was made to provide clarification of the intended meaning (changes in bold): "When durvalumab and ONCOS-102 are administered on the same day, durvalumab is administered first, **and there should be at least 1 hour between the end of infusion of the durvalumab and the start of the infusion of ONCOS-102.**
11. Section 6.1 (Durvalumab):
    a. The entire section and sub-sections were updated and reorganized according to current language from Medimmune.
    b. In Section 6.1.3 (Durvalumab Preparation):

i. The following note was added based on current Medimmune recommendations: "NOTE: if a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing equivalent to 20 mg/kg of durvalumab as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of durvalumab 1500 mg." The note stating that the fixed dosing for subjects who weigh ≤ 30 kg will be 600 mg Q4W was deleted.

ii. The following clarification was added for sub-section Dose preparation (changes in bold): "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."

12. Section 6.2.1 (ONCOS-102 Study Drug Information): Stability of diluted solution was updated based on current recommendations from updated IB (changes in bold):

Stability after ~~reconstitution~~ **addition to the infusion bag**	~~5~~ **8** (changed from 5 to 8) hours at ~~0~~ +**15 to** +25 °C **Note: this is from the time the ONCOS-102 is added to the infusion bag to the end of infusion.**

Note: term "reconstitution" was changed to "dilution or preparation" throughout the document, as it more accurately reflects the preparation of ONCOS-102.

13. Section 6.2.2 (ONCOS-102 Preparation): The fifth paragraph was modified to reflect the changes noted above for stability of the diluted ONCOS-102 (changes in bold): "The dose of ONCOS-102 will be ~~reconstituted~~ **diluted** with saline i**n a 500-mL infusion bag** prior to administration. The ~~reconstituted~~ **diluted** product is stable for treatment at a temperature of ~~+2~~**+15** to +25°C for a maximum of ~~5~~ **8** hours (**from the time the ONCOS-102 is added to the infusion bag to the end of infusion**). The ~~reconstitution~~ **dilution** must be performed within a biosafety cabinet with a Closed System Transfer Device to reduce the risks posed by the possibility of generation and inhalation of aerosols."
14. Section 6.2.3 (ONCOS-102 Administration): the section was updated based on updated recommendations from the Investigators (changes in bold): "ONCOS-102 will be delivered by intraperitoneal (IP) infusion via a peritoneal Hickmann catheter (or institutionally preferred alternative). ~~Reconstituted~~ **The** ONCOS-102 will be infused in a total volume of 500 mL saline (0.9 mg/mL NaCl in water for injection) ~~over a period of approximately 1 hour~~ **by gravity feed or per institutional procedures for IP infusions. The infusion should be given as soon as possible after preparation of the infusion solution. It is recommended that the total infusion time not exceed 2 hours**. To ensure uniform distribution of ONCOS-102 in the peritoneal cavity during the infusion, **it is recommended that t**he subjects are rotated every 30 minutes, **or institutional procedures may be followed**. ONCOS-102 will be administered weekly for a total of 6 weeks (see separate ONCOS-102 Handling Guideline for additional details).
15. Section 6.4.2 (Monitoring for ONCOS-102 Administration): the following changes were made based on updated recommendations and/or clarifications. (changes in bold): "All subjects in the dose escalation phase will remain in the facility ~~overnight~~ for observation **for 8 to 12 hours** after each ONCOS-102 infusion. ~~This is not a 24-hour stay, as they can leave the~~

~~following morning~~. **During this period, subjects should be monitored according to institutional policy. Further guidance is provided below.**
It is suggested that vital signs and temperature are taken every 4 hours. Discharge or admission for further observation are at the discretion of the Investigator. Subjects are expected to develop fever. Fever without associated other symptoms, such as hemodynamic instability, is generally not a reason for admission.
The following suggested guidelines may be used for the management of ONCOS-102-related toxicities: (1) Isolated fever or pain may be treated with acetaminophen, NSAIDS, opioids, or as determined by the Investigator. (2) For more severe reactions, aggressive symptomatic treatment may be administered, which may include fluids, oral or IV antihistamine, anti-pyretics, bronchodilators, pressors, and oxygen as indicated. Glucocorticoids may be administered for refractory symptoms according to the judgment of the Investigator.
All adverse events (AEs), including clinically significant changes in vital signs and temperature, that occur during this observation period should be documented in the source and eCRF. Refer to Section 7.1.5 for details on reporting AEs and Section 7.1.6 for details on reporting serious AEs.
Based on the safety data from the dose escalation phase, the internal data safety monitoring panel (as defined in Section 3.1.14) will decide if an ~~**overnight stay**~~ **observation period** will be required for the expansion phase."

a. The change from overnight stay to an observation period of 8 to 12 hours was also implemented in Section 3.1.7.1 (Dose Escalation Phase).

16. Section 7.1.8.1 (AESIs for Durvalumab): The entire section was updated and reorganized based on updated recommendations from Medimmune in the updated IB. Specifically, the following changes or additions were implemented (changes in bold):

Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis/**hypopituitarism,** adrenal insufficiency, **Type 1 diabetes mellitus**, and hyper- and hypothyroidism.

Dermatitis/Rash

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

Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, **(or labs suggestive of pancreatitis - increased serum lipase, increased serum amylase)** ~~**and lipase/amylase elevation**~~

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).

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

17. Section 8.3.1 (Durvalumab 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.
18. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

Amendment 2.1
Issue Date: Final, 05-MAR-2018
Summary of Changes:
Inclusion Criterion for laboratory parameters was updated to remove the requirement that the lymphocyte count should be ≥ LLN. Rationale: A follow-up discussion indicated that a specific target of LLN for lymphocyte count has not been found to be associated with response to checkpoint inhibitors. Thus, the decision was made to remove the criterion.
This discussion occurred after Amendment 2 was finalized but before it was distributed to the sites. A temporary change (TC-2018-02) was written to allow the notation of Amendment 2.1 for the updated amendment.

Amendment 3
Issue Date: Final, 04-MAY-2018
Summary of Changes:
1. Synopsis; The following sentence in the last paragraph was edited for clarification (changes in bold): "Simon's 2-Stage MINIMAX Design will be used in Phase 2 for Expansion Cohorts 1 and 2 (see Section 3.1.6 for sample size considerations). In the first stage, 18 subjects will be enrolled in Cohort 1 and 13 subjects in Cohort 2 **(including the 6 subjects at the RCD from the dose escalation phase)**. This clarification was also added to Section 3.1.2 (Enrollment).
2. Section 3.1 (Study Design), Phase 1: The following note was added for Cohort A:
   "(**NOTE:** Upon agreement between Investigator and Sponsor, if a subject in Cohort A has tolerated the ONCOS treatment well but is starting to get symptomatic, the first dose of durvalumab may be given on Day 43 (Cycle 2/Day15); durvalumab dosing will then continue per flowchart in Section 3.2)."
   Rationale: This was based on an exception that was provided per Note to FILE, LUD2015-008_017_Correspondence_12Apr2018_017-002-YRE Durvalumab Start_revised.
   References to this note were added to Section 3.1.2 (Enrollment); Section 3.1.7.1 (Dose escalation phase), Table 1 and Figure 3.
3. Section 5.1 (Inclusion Criteria): The following criterion was added as #3:
   "Availability of microsatellite instability (MSI) status for all subjects (OC and CRC)
   Availability of KRAS and NRAS status for subjects with CRC."
   Subsequent inclusion criteria were re-numbered, as appropriate.
4. Section 5.2 (Exclusion Criteria):

a. # 19 was changed **FROM:** "Other invasive malignancy within 5 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin or ductal carcinoma in situ of the breast that has/have been surgically cured." **TO: "**Active or prior malignancy except for history of other prior malignancy treated with curative intent which, in the opinion of the treating investigator and the Sponsor, has minimal risk of interfering with safety or efficacy endpoints of the study."
   Rationale: The language was updated to be consistent with current standards.
b. #21 was clarified as follows (changes in bold):
   Any condition that, in the clinical judgment of the treating physician, is likely to **interfere with the interpretability of the data or** prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.

5. Section 8.8 (Abbreviations): MSI was added
6. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

Amendment 4
Issue Date: Final, 08-JAN-2019
Summary of Changes:

1. The requirement for a 4-week waiting period between the first study drug administration for the first and second subjects in Cohort C in the dose escalation phase was removed.
   This was based on the completion of the safety reviews for Cohort B (ONCOS-102 $1x10^{11}$ VP +1500 mg durvalumab) and Cohort A (ONCOS-102 $1x10^{11}$ VP +delayed 1500 mg durvalumab which started after completion of the 6 weekly doses of ONCOS-102).
   Changes are reflected in Section 3.1.2 (Enrollment) and Section 3.1.7.1 (Dose Escalation Phase).
2. Section 5.1 (Inclusion Criteria)
   a. #1 – the second paragraph was clarified as follows:
      Subjects·with·CRC·must·have·~~at·least·~~failed·~~two·lines·of·~~prior·therapy·~~(e.g.,·~~
      containing·fluropyrimidine·~~based·therapies~~,·oxaliplatin·~~or·~~and·irinotecan,·~~based·~~
      ~~therapies~~·with·or·without·anti-VEGF·component,·or·for·RAS·wild-type,·with·or·
      without·anti-EGFR·therapy.~~)~~¶
   b. #3 was clarified as follows:
      Availability·of·microsatellite·instability·(MSI)/MMR·status·for·all·subjects·(OC·and·CRC)¶
      Availability·of·KRAS·and·NRAS·status·for·subjects·with·CRC.·NOTE:·if·these·results·are·
      not·available,·the·testing·may·be·done·on·archival·tissue·or·on·tissue·that·is·obtained·
      pre-treatment.¤
      This clarification was also added as footnote K to the Flowchart in Section 3.2.
3. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable

Amendment 5
Issue Date: Final, 19-JUN-2019
Summary of Changes:

1. Optional durvalumab treatment extension beyond the initial 12-cycle treatment period (Core Study) was added. Sections impacted were as follows:
   a. Synopsis, Section 3.1.7 (Treatment Arms and Treatment Schema), Section 3.1.12 (Optional Study Treatment Extension) . The following paragraph was added: "Per Amendment 5, optional durvalumab treatment extension beyond the initial 12-cycle treatment period (Core Study) will be available for subjects who complete the Core Study with Stable Disease or better. The optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator, and it may continue until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Section 8.8 for details."
   b. Section 3.1.15 (Duration of Study) and Section 3.1.16 (On Study and Post Study Follow-up). The following statement was added: "See Section 3.1.12 for optional durvalumab treatment extension."
   c. Section 8.8 (Details for Subjects who Continue Durvalumab Treatment Beyond the Core Study) was added (including flowchart).
2. Section 3.1.10.1 (Treatment Beyond Progression). The second paragraph was clarified to indicate that irRECIST would be used to assess progression in agreement with other ongoing protocols. Changes in bold.
   "Subjects meeting criteria for progression by **irRECIST** ~~**RECIST 1.1**~~ (Section 8.5) will be allowed to continue on therapy until confirmation of progression **by irRECIST** if the subject agrees and signs an appropriate informed consent form regarding continuation of treatment and as long as the following criteria are met at the discretion of the Investigator:
   - Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression;
   - No significant decline in ECOG performance status;
   - Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention."
3. The observation period post ONCOS-102 was shortened for the expansion phase. Sections impacted were as follows:
   a. Section 3.1.7.1 (Dose Escalation Phase). Last paragraph was updated (changes in bold): "Based on the safety data from the dose escalation phase, the internal data safety monitoring panel (as defined in Section 3.1.14) will decide if an observation period will be required for the expansion phase. **The safety review for the dose escalation phase was conducted, and it was agreed that the observation period would be shortened for the expansion phase. See note below for expansion phase requirements, per Amendment 5.**
   Note: Per Amendment 5, all subjects in the expansion phase will remain in the facility for observation for a minimum of 6 hours after the first dose of ONCOS-102 infusion; for subsequent doses, the observation period will be a minimum of 4 hours, but it may be longer based on Investigator's discretion. See Section 6.4.2 for additional details."
   b. Section 3.1.7.2 (Dose Expansion Phase). The following statement was added "See Section 6.4 for monitoring details before/during/after drug administration."
   c. Section 6.4.2 (Monitoring for ONCOS-102 Administration). The following note was added after the first paragraph: "NOTE: Per Amendment 5, all subjects in the expansion phase

will remain in the facility for observation for a minimum of 6 hours after the first dose of ONCOS-102 infusion; for subsequent doses, the observation period will be a minimum of 4 hours, but it may be longer, based on Investigator's discretion.

d. Section 6.4.2 (Monitoring for ONCOS-102 Administration). The last paragraph was updated (changes in bold): "Based on the safety data from the dose escalation phase, the internal data safety monitoring panel (as defined in Section 3.1.14) will decide if an observation period will be required for the expansion phase. **The safety review for the dose escalation phase was conducted, and it was agreed that the observation period would be shortened for the expansion phase. See note above for expansion phase requirements, per Amendment 5."**
e. Section 3.2 (Study Flowchart). For Footnote b, the following note was added: "(Note: the cytokine collection prior to discharge is for dose escalation phase only).

Amendment 6, dated 14-JAN-2022, was not issued. The following clarification was made, and all changes were incorporated into Amendment 6.1 **(changes in bold):**
"By the date of implementation of this amendment, all subjects will have completed treatment and applicable On Study Follow-up, with the exception of one subject in optional treatment extension who will complete treatment **and On Study Follow-up** by 30 June 2022 ~~**or before**~~. 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."

Amendment 6.1
Issue Date: Final, 10-MAR-2022
Summary of Changes:

1. By the date of implementation of this amendment, all subjects will have completed treatment and applicable On Study Follow-up, with the exception of one subject in optional treatment extension who will complete treatment and On Study Follow-up by 30 June 2022. 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. (The preceding note was added to the Synopsis and Section 8.8 [Details for Subjects Continuing Durvalumab Treatment Beyond the Core Study].)
    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 4.2.1.5 (Overall Survival): "NOTE: Per Amendment 6.1, 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 6.1).
    b. Section 3.2 (Study Flowchart) and Section 8.8.1 (Study Flowchart for Subjects Who Continue Durvalumab Treatment Beyond the Core Study): Footnotes L and e, respectively, were added, "Per Amendment 6.1, all post study follow-up for the collection of survival data will be discontinued as of 30 June 2022 (see Section 8.1, Amendment 6.1)"
2. AstraZeneca provided updated language for Section 7.1.2 (Additional expedited reporting requirements for this study). Section 7.1.2.4 (New Cancers) and Section 7.1.2.5 (Deaths) were added.
3. Section 7.1.6 (Expedited SAE Reporting Requirements): updated address for Drug safety Contact and Primary Sponsor Contact due to office move, and updated the title of the

primary Sponsor Contact.
~~666~~ 600 3rd Ave, ~~28th~~ 32nd Floor
New York, New York ~~10017~~ 10016

8.2 Participating Study Sites, Investigators and Staff, Laboratories, and Sponsor Information

This information is maintained in the Clinical Study File

8.3 Dose Adjustments and Delays for Durvalumab

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3. or 8.4, 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.

8.3.1 Durvalumab (MEDI4736) Dose Modification Due to Toxicity

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

Additional information and guidance regarding dose modification due to toxicity are provided from Medimmune in the following 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*)".

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

Durvalumab (D) Dose Modification Due to Toxicity
Note: If D 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 D depicted below, <u>permanently discontinue D</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 D dosing as clinically appropriate and during diagnostic work-up for other etiologies.

Grade 2

- In general, hold D until resolution to ≤ Grade 1 and after the end of any steroid taper, and discontinue D permanently if such resolution does not occur within 60 days (30 days for neurotoxicities). Criteria for temporary hold or permanent discontinuation of D may differ by event as detailed below.
- For *myositis/polymyositis*, hold D until resolution to ≤ Grade 1; permanently discontinue D 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 D 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 D 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 subjects may be retreated if the endocrinopathy is controlled and the subject 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 D is at the discretion of the Investigator.
- For *elevated creatinine* or *rash*, D 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 D until resolution to ≤ Grade 1, and after the end of any steroid taper, and discontinue D permanently if such resolution does not occur within 60 days (30 days for neurotoxicities and rash). Criteria for permanent discontinuation of D 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 D 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 D permanently.
- For *asymptomatic increases of amylase or lipase* levels, hold D, and if complete work up shows no evidence of pancreatitis, D may be continued.
- For *hepatitis*, discontinue D 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 × ULN, or (3) any case meeting Hy's law criteria (as defined in FDA Guidance Document "Drug-Induced Liver Injury").
- For *rash*, D should be held until resolution to ≤ Grade 1 or baseline.

Grade 4

- In general, discontinue D permanently.

Durvalumab (D) Dose Modification Due to Toxicity
• For *endocrinopathies,* follow Grade 2 instructions above. • For *asymptomatic increases of amylase or lipase* levels, hold D, and if complete work up shows no evidence of pancreatitis, D may be continued.
Infusion-related Reactions **Grade 1** • The infusion rate of D 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** immediately 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 D until resolution to ≤ Grade 1 or baseline, and discontinue D permanently if such resolution does not occur within 60 days. **Grade 3** • Hold D. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume D administration at next scheduled dose. Otherwise, discontinue D permanently. **Grade 4** • In general, discontinue D 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.

8.3.2 Durvalumab Dose Modification Not Due to Treatment-related 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 21 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.

8.4 Dose Modifications and Delays for ONCOS-102

If a toxicity occurs that requires toxicity management in accordance with Sections 8.3. or 8.4, 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.

8.4.1 Dose Modifications

With a rapidly replicating virus, dose modifications are unlikely to be relevant or have any significant impact on the resulting production of virus particles. Thus, intra-subject dose reductions are not permitted. If a subject has an ONCOS-102 related toxicity, the subject should discontinue treatment.

Subjects must be discontinued from ONCOS-102 treatment for deterioration of serum bilirubin, international normalized ratio (INR), aspartate aminotransferase (AST), alanine aminotransferase (ALT), or creatinine by an increase of National Cancer Institute, common terminology criteria for adverse events (NCI CTCAE) toxicity Grade ≥2 from the baseline value:

Laboratory variable	Baseline value (predose on Day 1)	CTCAE Grade after Day 1 - continue to treat	CTCAE Grade after Day 1 - withdraw from treatment
Bilirubin, INR	Normal	Grade 1	Grade 2 or higher
AST, ALT, creatinine	Normal	Grade 1	Grade 2 or higher
	Grade 1	Grade 2	Grade 3

8.4.2 Dose Delays Not Due to Toxicities

For the administration of ONCOS-102, there will be a dosing window of ±2 days. If there is a delay of > 2 days, the dose should be skipped and the next scheduled drug administration should be performed. The respective protocol deviation should be documented.

8.5 Guidelines for RECIST 1.1 and irRECIST

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were revised in 2009 as RECIST 1.1.(59) 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.(54) 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.(60) 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).(61) 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 (59) 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 subject, 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 subject 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.(62-64) 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.(65)

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:

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
2. 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.
3. 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 subject 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 subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

1. For Subjects 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: Subjects 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 Subjects 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. (61) 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 (TA), 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

8.6 ECOG Performance Status

ECOG Performance Status: Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair.(66)

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

8.7 Exploratory Assessment of Correlative Immunologic Research

Please refer to Section 4.3 for information on correlative testing and refer to the Study Laboratory Manual for instructions on specimen handling and logistics.

8.8 Details for Subjects who Continue Durvalumab Treatment beyond the Core Study

According to Section 3.1.12, optional durvalumab treatment extension beyond Core Study is available for subjects who complete the Core Study with Stable Disease or better. The optional treatment extension will be permitted upon agreement with the subject, Sponsor and Investigator, and it may continue until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

The flowchart for optional treatment extension in Section 8.8.1 will be followed.

Preparation and administration of durvalumab will proceed according to Section 6.1.

Collection and reporting of AEs/SAEs will be performed according to the protocol requirements (Section 7.1) and until disease progression is documented. For AEs/SAEs that may be ongoing at the time of disease progression, follow-up will be performed until resolution or stabilization of the events or up to 90 days after the last dose of durvalumab.

Per Amendment 6.1:
By the date of implementation of this amendment, all subjects will have completed treatment and applicable On Study Follow-up, with the exception of one subject in optional treatment extension who will complete treatment and On Study Follow-up by 30 June 2022. 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.

8.8.1 Study Flowchart for Subjects who Continue Durvalumab Treatment beyond the Core Study

LUD2015-008 - Study Flowchart for Subjects who Continue Optional Durvalumab Treatment after Core Study	Optional Study Treatment (Q4W following Cycle 12 study treatment dose)	On Study Follow-up			Post Study Follow-up[e]
		Last Study Drug Dose +28 (±3) days	Last Study Drug Dose +56 (±7) days	Last Study Drug Dose +91 (±7) days End of Study	Every 6 months (± 1 month) for 3 years from initiation of treatment
Study Drug Administration					
Durvalumab (IV)	1500 mg Q4W				
Tumor and Disease Assessments					
Disease Assessment by RECIST 1.1/irRECIST (see Sections 4.2 and 8.5 for details on scans and confirmation)	SOC	If subject has not progressed, one tumor/disease assessment should be done, either at treatment discontinuation or at some point during on study follow-up			
Blood for CA-125 for ovarian or CEA for CRC (must be at same time points as disease assessments; test will be performed by local lab)[c]	SOC	If subject has not progressed, one tumor/disease assessment should be done, either at treatment discontinuation or at some point during on study follow-up			
Study Procedures and Examinations					
Physical Exam (incl. weight and ECOG Perf Status)	Q4W	x	x	x	
12-Lead ECG[a]	At first optional treatment visit, then every 6 months	x			
Vital Signs (T, HR, BP, RR) - pre dose	Q4W	x	x	x	
Concomitant Medication / Procedure (name, indication, dose, route, start & end dates)	Q4W	x	x	x	
Adverse Events (starting or worsening after IC)[b]	Q4W	x	x	x	
Specimens for Routine Laboratory Procedures					
Blood Hematology (CBC, differential, platelets)[a]	At first optional treatment visit, then Q12W	x	x	x	
Chemistry (glucose, BUN, creat., Na, K, Cl, CO_2, Ca, Mg, protein, alb, TBili, AST, ALT, ALP, LDH)[a]	At first optional treatment visit, then Q12W	x	x	x	
Chemistry Cont. (Free T_3, Free T_4, TSH)[a]	At first optional treatment visit, then Q12W	x	x	x	
Chemistry Cont. (amylase, lipase)[a]	At first optional treatment visit, then Q12W	x	x	x	
Urinalysis[a]	At first optional treatment visit, then Q12W	x	x	x	
Coagulation parameters (PT, aPTT, INR)[a]	At first optional treatment visit, then every 6 months	x			
Serum pregnancy test[a]	At first optional treatment visit, then Q12W	x		x	
Specimens for Biological Markers and Correlative Studies					
Blood for PBMC Collection and Banking[d]	At first optional treatment visit, then every 6 months	x			
Blood for Th1/Th2/Th17 cytokines in serum	At first optional treatment visit, then every 6 months	x			
Post Study Follow-up[e]					
Overall Survival					x[e]
Progression Free Survival					x[e]

a - Collected pre-dose (if applicable). Note: It is strongly recommended that test results are reviewed before dosing for hematology, chemistry (including amylase, lipase, and thyroid pre durvalumab) and pregnancy (when applicable).

b - See section 7.1.5 of protocol for details regarding collection of AEs for 90 days after last study drug administration

c - Collected together with routine lab assessment blood draw (pre-dose, if applicable)

d - Six CPT tubes per time point (pre-dose if applicable) -> PBMC isolation; used for banking PBMCs and plasma

e - Per Amendment 6.1, all post study follow-up for the collection of survival data will be discontinued as of 30 June 2022 (see Section 8.1, Amendment 6.1)

Q4W = every 4 weeks; Q12W = every 12 weeks; SOC = standard of care

8.9 List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATAP	Advanced Therapy Access Program
AUC	area under the concentration time curve
BSA	Body surface area
BSL-2	Biosafety level 2
CBC	Complete Blood Count
CB	Clinical benefit
CD	Cluster of differentiation
Cmax	peak concentration
Cmin	trough concentration
CPO	cyclophosphamide
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte Antigen 4
DCB	Durable clinical benefit
DL	Dose level (or starting dose level)
DLT	Dose-limiting Toxicity
EC	Ethics Committee
eCRF	Electronic Case Report Form
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
GMCSF	granulocyte-macrophage colony stimulating factor
GMM	genetically modified micro-organism
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICD	Immunogenic cell death
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IgG2	immunoglobulin G2
IHC	Immunohistochemistry
INR	International normalized ratio
IP	intraperitoneal
IRB	Institutional Review Board
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
ITT	Intent to treat
IV	intravenous
LICR	Ludwig Institute for Cancer Research
LLN	Lower limit of normal
mAb	Monoclonal antibody
MDSC	Myeloid derived suppressor cells
MSI	Microsatellite instability
NCI CTCAE	National Cancer Institute, common terminology criteria for adverse events
ORR	Objective response rate
OS	Overall survival
OV	Oncolytic virus
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand-1
PFS	Progression-free survival
PP	Per protocol
PR	Partial response
PSDSS	peritoneal surface disease severity score
Q4W	Every 4 weeks
Q8W	Every 8 weeks
RCD	Recommended combination dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SD	Stable disease
TEAE	treatment-emergent adverse events
T-VEC	talimogene laherparepvec
TMTB	Total measured tumor burden
ULN	Upper limit of normal
VP	Viral particle
WFI	Water for injection
w/v	Weight/volume

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