Ludwig Institute for Cancer Research (LICR)

Statistical Analysis Plan

Protocol Number: LUD2015-008
Amendment 5 (19-June-2019)

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

SPONSOR

Ludwig Institute for Cancer Research Ltd.

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ACRONYMS

Below is the list of acronyms that will be used throughout this document.

Abbreviation	Definition
AE	Adverse Event
ATC-4	Anatomical Therapeutic Chemical level 4
CB	Clinical Benefit
CP	Clinical Progression
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DCB	Durable Clinical Benefit
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
IP	Intraperitoneally
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITT	Intent to Treat
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression-Free Survival
PP	Per Protocol
Q4W	Once every four weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VPs	Viral particles
WHO	World Health Organization

1 Introduction

This SAP describes the methods to be used in the analysis of study data from clinical protocol LUD2015-008 in order to answer the study objectives, and is based on Amendment 5 of the study protocol, dated 19June2019.

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the CSR for this trial. The SAP outlines any differences in data analysis methods relative to those planned in the study protocol. Any changes to the data analysis methods after the SAP is finalized will be described in the CSR.

2 Overall Study Design and Objectives

2.1 Study Objectives

2.1.1 Primary Objectives

Dose Escalation Phase:

Safety and Tolerability including:

- Recommended combination dose (RCD) of durvalumab and ONCOS-102
- Dose Limiting Toxicities (DLTs) according to Common Terminology Criteria for Adverse Events (CTCAE) 4.03

Expansion Phase:

- Clinical Benefit (CB) by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1, defined as the percentage of subjects who are not in progression at end of Week 24

2.1.2 Secondary Objectives

Dose Escalation and Expansion Phases (all subjects):

- Safety and Tolerability per AEs, SAEs, laboratory data, and vital sign data
- Clinical Efficacy by RECIST 1.1/ Immune-related Response Evaluation Criteria in Solid Tumors (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
    - Overall Response Rate (ORR) after 8 and 24 weeks
    - Progression Free Survival (PFS)
    - Overall Survival (OS)

2.2 Trial Design and Study Procedures

2.2.1 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-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.

ONCOS-102 will be administered intraperitoneal (IP) infusion at weekly intervals for 6 weeks. A bolus dose of 300 mg cyclophosphamide 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 RCD of ONCOS-102 when given with a fixed dose of durvalumab (1500 mg). Two dose levels of ONCOS-102 will be used: 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:

- Cohort 1 (OC): Platinum-resistant epithelial ovarian cancer
- Cohort 2 (CRC): Metastatic colorectal cancer

Simon's 2-Stage MINIMAX Design will be used in Phase 2 for Expansion Cohorts 1 (OC) and 2 (CRC). In the first stage, 18 subjects will be enrolled in Cohort 1 (OC) and 13 subjects in Cohort 2 (CRC), including the subjects who received RCD in Phase 1. If 5 or more subjects in Cohort 1 (OC), or one or more subjects in Cohort 2 (CRC), 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 (OC), and 14 additional subjects will be enrolled in Stage 2 of Cohort 2 (CRC).

2.2.2 Treatments and Assignment to Treatments

All subjects in the study will receive ONCOS-102 and durvalumab. A single dose of cyclophosphamide will be given prior to the first dose of ONCOS-102.

In the Phase 1, subjects will be enrolled and assigned treatment in parallel in a non-randomized, sequential manner, with competitive enrollment between study sites. The treatments for the 3 Phase 1 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.
- 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 20mg/kg Q4W as long as the body weight remains ≤ 30 kg.

Phase 2 will use the RCD of ONCOS-102 + durvalumab 1500 mg found in Phase 1.

2.3 Determination of Sample Size

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 (OC), and up to 27 subjects will be enrolled in Cohort 2 (CRC), for a total of up to 60 subjects.

The sample size rationale for Cohorts 1 (OC) and 2 (CRC) 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.

For Cohort 1, the null hypothesis for the clinical benefit rate (number of subjects who are not in progression) at end of Week 24 for Cohort 1 (OC) 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 (OC). If clinical benefit at end of Week 24 is seen in <5 of these subjects, the study of Cohort 1 (OC) 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.

For cohort 2 (CRC), 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 (CRC). If clinical benefit at end of Week 24 is seen in <1 of these subjects, the study of Cohort 2 (CRC) 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 General Analysis Conventions

3.1 Study Periods

The study will include screening, a treatment period for up to 12 cycles, On Study Follow-up phase for 90 days after the end of study drug administration, and Post Study Follow-up phase for up to 3 years from the start of treatment.

3.2 Visit Windows

The protocol visit windows are defined as shown in Table 1. Visits will be analyzed per the eCRF collection.

Table 1 Visit Windows

Visit	Window
Screening	Day -28 to -1
Cycle 1, Days 8, 15, 22 Cycle 2, Days 1, 8	+/- 2 day
Day 15 of Cycles 2, 3	+/- 3 days
Day 1 of Cycles 3, 5, 7	+/- 4 days
Day 15 of Cycles 4 - 12	+/- 7 days
On Study Follow-up	28 (+/-3) days post last dose 56 (+/-7) days post last dose 91 (+/-7) days post last dose
Post Study Follow-up	+/- 1 month

Note: Visit days are defined from baseline (Cycle 1, Day 1 visit).

It should be noted that summary tables will present only planned study visits, Unscheduled visit will not appear in the summary tables. However, all Unscheduled visits will appear in the listings. Also, if multiple assessments are performed during the same visit (i.e. multiple vital signs collected, repeat laboratory assessment taken) the first collection will be presented in summary tables but all data will be presented in listings.

3.3 Baseline

Unless specified otherwise, baseline measurements will be the most recent value prior to receiving the first dose of study medication.

3.4 Coding dictionaries

Medical history, adverse events, and concurrent procedures will be coded using Medical Dictionary for Regulatory Activities (MedDRA), Version 19 and Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary, Version WhoDrug_DDE_B2_201603.

4 Analysis Populations

4.1 Intent to Treat Population for Clinical Efficacy

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. All efficacy analysis will be performed on the ITT Population for Clinical Efficacy unless noted. Please note: the ITT population is identical to the Safety population as defined below.

4.2 Per Protocol Population for Clinical Efficacy

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 in escalation and both cohorts in expansion) over the first 2 cycles, as well as respective disease assessments, without major protocol violations. All efficacy analysis will be performed on the PP Population for Clinical Efficacy unless noted.

4.3 Per Protocol Population for DLT Assessment

The Per-Protocol (PP) Population for DLT Assessment is defined as all subjects who meet one of the two criteria:

- Experienced a DLT at any time during the DLT Evaluation Period.
- No DLT and received 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 deviations during the DLT Evaluation Period. The sponsor will define and provide all major protocol deviations that occur.

For Cohort A, the DLT Evaluation Period is the period from Day 1 of the study up to and including the Week 9 (Cycle 3 Day 1) study assessments.

For Cohorts B and C, the DLT Evaluation Period is the period from Day 1 of the study up to and including the Week 11 (Cycle 3, Day 15) pre-dose study assessments.

4.4 Safety Population

The Safety Population is defined as all subjects who receive at least one dose of durvalumab or ONCOS-102. The Safety population will be used for AEs, SAEs, laboratory data, and vital sign data.

5 Protocol Deviations

Protocol deviations are recorded in a written log. Any major protocol deviations will be described in the study report.

6 Subject Disposition

Subject disposition will be presented by cohort and overall. The number of subjects enrolled in each analysis population will be presented.

The following will be summarized:

- Number and percentage of Safety population
- number and percentage of PP for DLT Assessment subjects experiencing a DLT by cohort
- number and percentage of ITT for Clinical Efficacy subjects

- number and percentage of PP for Clinical Efficacy subjects
- number and percent of subjects discontinuing treatment (this would be < 12 cycles of therapy)
- Reasons for treatment discontinuation.
- Number and percentage of subjects completing study (completion is 12 months of therapy and on study follow-up)
- Reasons for study discontinuation

Descriptive statistics will also be presented for duration of time in study for subjects (start of therapy to last visit of follow-up). In addition to this, the duration of follow-up will be presented for overall survival in two ways using Kaplan-Meier methods: the first will be using the traditional "censor" and "event" flags as described in Section 8.2.4; the second will be constructed by reversing the "censor" and "event" flags (e.g. reverse Kaplan-Meier) to assess the length and completeness of follow-up.

7 Demographics and Baseline Characteristics

7.1 Demographic Characteristics

Demographic and baseline characteristics at study entry will be summarized for the Safety population, ITT for Clinical Efficacy Population and PP for Clinical Efficacy Population by cohort (within Phase 1 and Phase 2) and all cohorts overall.

Demographic and baseline variables to be summarized are:

- Continuous variables
  - Age (years) at time of consent
  - Height (cm)
  - Weight (kg)
- Categorical variables
  - Gender
  - Race
  - Ethnicity
  - Disease staging at initial diagnosis and study entry; MSI, MMR, KRAS NRAS status

7.2 Medical History

The number and percentage of subjects having a non-oncological medical condition in each MedDRA preferred term and lower level term as reported on the eCRF will be

summarized for the Safety population. Non-oncological medical history will be presented in a subject listing.

7.3 Oncological Treatment History

Frequencies and percentages will be tabulated for prior anti-cancer treatment use by lines of therapy for the Safety population overall. In addition, these summaries will be displayed by Phase 2 cohort (Ovarian and CRC). Prior oncological treatment, radiation and surgical history will be presented in subject listings.

8 Efficacy Analysis

8.1 Primary Efficacy Analysis for the Expansion Phase

The primary efficacy endpoint for the expansion phase is the Progression Free Survival rate at Week 24 (PFS 24) defined as percentage of subjects who are not in disease progression at the end of Week 24.

For Phase 2, the primary endpoint analyses of PFS 24 will be conducted as follows on the ITT and PP populations using RECIST 1.1:

- **Cohort 1:** The null hypothesis of PFS 24 = 20% will be tested against a one-sided alternative of PFS 24 = 40% at 0.05 level of significance based on Simon 2-stage Minimax criterion. The null hypothesis will be rejected if 11 or more of 33 subjects experience clinical benefit at end of Week 24.

- **Cohort 2:** The null hypothesis of PFS 24 = 5% will be tested against a one-sided alternative of PFS 24 = 20% at 0.05 level of significance based on Simon 2-stage Minimax criterion. The null hypothesis will be rejected if 4 or more of the 27 subjects experience clinical benefit at end of Week 24.

The number and percentage of subjects without progression will be presented. A 95% CI based on binomial distribution will be constructed for the estimated PFS 24.

The analysis of PFS 24 will be repeated using irRECIST for both the ITT and PP populations without the hypothesis testing.

8.2 Secondary Efficacy Analysis

8.2.1 Objective Response Rate (ORR)

ORR is defined as the percentage of subjects meeting criteria of Complete Response (CR) or Partial Response (PR). CR or PR must be confirmed at least 4 weeks after the date of the original CR or PR. For ovarian cancer subjects if the CA-125 is initially above the upper limit, the CA-125 value must normalize for a subject to be considered in CR for RECISIT 1.1. The number and percentage of these response categories will be presented.

The ORR rate at 8 and 24 weeks will be reported along with a 95% CI based on the exact binomial distribution. The ORR at 8 and 24 weeks will be based on the disease assessment scheduled at Week 9 and Week 25, respectively, with confirmation of response at least 4 weeks after the assessment. Subjects who drop out without a disease assessment will be considered a non-responder at the corresponding time point. These subjects will be included in the denominator when calculating the ORR.

Best Overall Response (BOR) will also be presented. In the determination of BOR, any subsequent scans on or after the date of a clinical progression will be ignored. .

The analysis will be performed on both the ITT and PP populations and using both RECIST 1.1 and irRECIST.

8.2.2 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 consecutive weeks. Visits with a non-evaluable assessment (or non-confirmed progression for irRECIST) will be not considered a break in the 24 consecutive weeks required for DCB as long as the assessment prior and after are SD or better. If a subject had clinical progression (CP), any recorded response (CR or PR) after the date of CP will be considered invalid.

The estimated DCB will be reported along with a 95% CI based on the exact binomial distribution.

The analysis will be performed on both the ITT and PP populations and using both RECIST 1.1 and irRECIST.

8.2.3 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), clinical progression (CP) or death whichever comes first. If progression or death did not occur, subjects will be censored at start of alternative therapy or the last available tumor assessment.

Descriptive analyses of PFS will include the following:

- Number and percentage of subjects that died or had a progressive disease or clinical progression,
- Number and percentage of subjects censored:
    - Number and percentage of subjects lost to follow up (unknown survival and/or progression status)
    - Number and percent of subjects survived without progression
    - Number and percentage of subjects missing tumor response assessment.

- Number and percentage of subjects who were offered alternative therapy

The analysis will be performed on both the ITT and PP populations and using both RECIST 1.1 and irRECIST.

8.2.4 Overall Survival (OS)

OS is defined as the time from date of first dose until date of death. The number and percentage of subjects who died, who were lost to follow up, and who survived will be summarized. Subjects who survived will be censored at the date of last contact/last data point collected in the CRF.

OS Rate and the corresponding 95% confidence intervals at 6 months and 12 months will be calculated based on Kaplan-Meier product limit estimates and will be displayed along with the corresponding number of subjects at risk at each time point.

The analysis will be performed on both the ITT and PP populations and using both RECIST 1.1 and irRECIST.

8.2.5 Duration of Response (DoR)

Duration of response (DOR) is defined as the time from the first documentation of RECIST- defined confirmed response (CR or PR) to the first date that recurrent or progressive disease is objectively documented, clinical progression or death whichever comes first. Censoring will be at the last available tumor scan if PD, CP or death did not occur.

The DoR analysis will be performed on only those subjects with a confirmed response (CR, PR). The analysis will be performed on both the ITT and PP populations and using both RECIST 1.1 and irRECIST.

8.2.6 Analysis of Time to Event (TTE) Variables

Progression Free Survival (PFS), OS and DoR will be analyzed using the Kaplan-Meier method. The Duration of follow-up (in months) will be analyzed using the Reverse Kaplan-Meier product limit estimation method.

For all time to event analysis the number of events, number censored, 25th percentile, median, 75th percentile, corresponding 95% CIs as well as the minimum and maximum survival time will be presented in tables. In addition, survival curves will be presented graphically.

9 Statistical/Analytical Issues

9.1 Handling of Dropouts or Missing Data

Algorithms for imputing partial or missing dates are shown below for adverse event (AE) start dates and defining concomitant medication based on missing start or stop dates. No other missing data will be imputed.

The following imputation rules will be used for missing or incomplete AE start dates:

- Missing AE start day:
  - If the partial date contains a different month from the date of first study dose, then impute it as the first day of the month.
  - If it contains the same month as the date of first dose, then impute it as date of first dose.
- Missing AE start day and month:
  - If the partial date contains a different year from the date of first dose, then impute the missing day and month as Dec 31.
  - If it contains the same year as the date of first dose, then impute the missing day and month as day and month of first dose.
- Completely missing AE date:
  - Impute the missing date as the date of first dose.

Defining concomitant medications for medications with missing start or stop dates:

- if both the start and stop dates of a particular medication are missing, that medication will be considered concomitant;
- if the start date of a medication is missing and the stop date of that medication falls on or after the first dose date, that medication will be considered concomitant;
- if the start date of a medication is missing and the stop date of the medication is prior to the first dose date, that medication is considered *not* concomitant;
- If the start date of a medication is prior to the first dose date and the stop date of the medication is missing, that medication is considered concomitant.

9.2 Multiple Comparisons/Multiplicity

There will be no adjustment for multiplicity.

9.3 Examination of Subgroups

No analysis of subgroups is planned.

9.4 Interim Analysis

Interim analyses will be performed at the end of Simon Stage 1 for Cohorts 1 and 2 as described in Section 8. Safety analyses will be performed to assess DLTs in the dose escalation cohorts.

9.5 Safety Monitoring and Study Stopping Rules

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.

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

10 Safety Analysis

10.1 Study Drug Exposure

For each subject, treatment duration and the total number of cycles treated will be calculated based on the expected treatments for that subject in accordance with their assigned cohort. Treatment duration (weeks) will be calculated for each subject as: ([date of last dose of any study drug received – date of first dose of any study drug received +1]/7).

Descriptive statistics for treatment duration and the total number of treatment cycles will be displayed. The number of doses and cumulative dose received will be summarized for durvalumab and ONCOS-102. Study drug administration will be presented in a by subject listing.

10.2 Adverse Events

All tables will only include treatment emergent adverse events (TEAEs), where TEAEs are defined as any AE that occurs on or after the day of the first dose of study drug and up to 90 days after the last dose of study drug or administration of alternate therapy. Listings will include all reported AEs flagging events that were TEAEs.

All adverse events will be coded using the Medical Dictionary of Regulatory Activities (MedDRA) and will be classified by MedDRA system organ class (SOC) and preferred term (PT).

The number and percentage of subjects who experienced at least one TEAE by PT as well as the number and percentage of subjects who experienced at least one TEAE within each specific SOC and PT will be presented overall and by Phase 2 tumor type and Phase

1 cohort. For the presentation of AE incidences, the SOCs will be sorted alphabetically, and within SOC, the preferred term (PT) will be presented by decreasing total frequency.

Adverse event toxicity grade will be classified using NCI-CTCAE Version 4.03 criteria. TEAEs will be presented by maximum CTCAE grade for each PT by cohort. For this analysis, if a subject has more than one occurrence of the same PT, then the PT will be counted only once for that subject under the maximum grade at which it was experienced. A missing toxicity grade will not be imputed.

10.2.1 Treatment Related Adverse Events

Adverse events with a relationship to study drug of "possibly," "probably" or "definitely" related will be classified as treatment related. The incidences of adverse events related to cyclophosphamide, durvalumab, ONCOS-102, and any of the study therapies will be summarized by SOC and PT.

10.2.2 Adverse Events TEAEs Leading to Study Drug Withdrawal

TEAEs leading to study drug withdrawal of durvalumab, ONCOS-102 or both will be presented by SOC and PT and will also be presented in a listing.

10.2.3 DLTs

DLTs will be presented in subject listings.

10.2.4 Serious Adverse Events

The incidences of serious adverse events will be summarized by SOC and PT and also will be presented in a listing.

10.3 Clinical Laboratory Data

Clinical Laboratory data (chemistry, hematology, coagulation, and urinalysis) will be collected as specified in the study flowchart in section 3.2 of the protocol. The Clinical lab tests are summarized in Table 2 below.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented by Phase 2 tumor types and overall Safety population for the shifts in these categories from baseline to selected post-treatment assessment time points (e.g., low to normal, low to high, high to low). Percentages for the shift tables will be calculated based on the number of subjects who had results for both baseline and the corresponding post-treatment assessment time point. Additionally, for continuous laboratory parameters, descriptive statistics will be presented for the changes from baseline to each selected post-treatment assessment time point.

The clinical lab data will be presented in tables and listings as follows:

- All laboratory results will be presented in the listings.

- Abnormal laboratory values with their clinical significance status will be presented in a listing.
- Urinalysis data, differentials (%), and RDW will be presented in listings only
- Magnesium, MCV, MCH, MCHC, MPV, differentials (absolute count), aPTT, PT, and INR will be presented in listings and summary tables but NOT in shift tables.
- The remaining analytes will be presented in listings, summary tables and shift tables

Table 2. Safety Laboratory Tests

Clinical Chemistry	Hematology	Coagulation	Urinalysis
Glucose Blood urea nitrogen (BUN) Creatinine Sodium Potassium Chloride Carbon Dioxide (CO_2) Calcium Magnesium Total protein Albumin Total bilirubin Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Lactate dehydrogenase (LDH) Amylase Lipase Free T_3 Free T_4	Hemoglobin Hematocrit Platelets White blood cell (WBC) count Red blood cell (RBC) count Mean cellular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC) Mean Platelet Volume (MPV) RBC Distribution Width (RDW) Differential (% and absolute count for each): • Eosinophils • Basophils • Neutrophils • Lymphocytes	Activated partial thromboplastin time (aPTT) Prothrombin time (PT) INR	Albumin Bilirubin Blood/Hemoglobin Glucose Ketones White Blood Cells Nitrite pH Protein Red Blood Cells Specific gravity Urobilinogen Color Turbidity

Clinical Chemistry	Hematology	Coagulation	Urinalysis
TSH CEA CA125	• Monocytes		

10.4 Vital Signs

Vital signs summaries will include temperature, heart rate, blood pressure, respiratory rate, and weight taken on the days ONCOS dosing is planned. Descriptive statistics will be presented for the changes in vital signs from baseline to each post-treatment assessment time point. Vital sign data will be presented in a listing.

10.5 ECOG performance status

ECOG performance status data will be presented in a listing.

10.6 Prior and Concomitant Medications and Procedures

A concomitant medication is defined as any drug or substance administered between the time of the first dose of study treatment and the time of the last study visit. This includes medications that were started prior to screening, if their use continued during or after dosing.

Concomitant medication use will be classified by Anatomical Therapeutic Class (ATC) level 4 and PT. For the presentation of concomitant medications, the ATC level 4 terms will be sorted alphabetically, and within ATC level 4 term, the PT will be used and presented by decreasing total frequency overall.

Frequencies and percentages of subjects using each concomitant medication will be presented for the Safety population overall as well as the Phase 2 cohorts (Ovarian and CRC). Prior and concomitant medications and concomitant procedures/surgeries will be presented in subject listings.

11 Quality Control

All data displays and analyses will adhere to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3).

The sponsor will review all tables, listings, and figures prior to final database lock. Final SAS datasets, programs and outputs will be transferred to the sponsor at project completion.

12 Tables and Listings Conventions

Data collected in this study will be documented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics (number of patients, mean, median, standard deviation, minimum, and maximum). Categorical variables will be summarized using frequencies and proportions. Time-to-event data will be summarized via Kaplan-Meier (KM) methodology using the 25th, 50th (median), and 75th percentiles with associated 2-sided 95% confidence intervals.

Mock-ups for statistical tables and listings will be provided. Final formats for the statistical tables and listings may deviate from these mock-ups upon agreement with the sponsor. Footnotes will be used as needed to clarify the information that is presented in the tables and listings. Unless otherwise requested by the sponsor, the term 'subject' will be used in all tables and listings, in accordance with CDISC standards. Basic demographic information (age/gender) will be presented along with subject id for each listing. Similar endpoints (e.g., all lab tests, all time to events endpoints etc.) should present in one listing or table for completeness or comparisons.

The general layout of tables and listings will be as follows:

Ludwig Institute for Cancer Research — Page x of y

Protocol: LUD2015-008 — Run Date: DDMMMYY_HH:MM

Clinical Study Report

Listing 16.2_x (or Table 14.x_x)

<Title>

<Population>

Col 1	Col 2	Col 3	etc.

<Any footnotes>

File Name: <pathname for SAS program>

All tables and listings will use landscape orientation. Margins will be at least 2.0 cm at the top and bottom and at least 0.8 cm on the left and right, excluding headers and footnotes, in accordance with electronic Common Technical Document (eCTD) guidelines. Font will be Courier, unless otherwise specified, with an 8-point font size in

most cases. Page numbering will be sequential within each table, listing, and figure. Column headers should be in initial capital letters. Units for numeric data will be included when appropriate.

Tables and data listings will be created from different SAS programs. A single program may produce multiple tables or multiple data listings from the same dataset (e.g. all clinical chemistry data listings may be generated by a single program).

12.1 Statistical Table Conventions

Mock-ups for statistical tables will include headers, title numbers, titles, column headers and footers, and a proposed layout for the display of data. The final decision on the precision (i.e. number of decimal places) for presentation of descriptive statistics will be made by the sponsor after review of draft statistical tables and before database freeze.

12.2 Data Listing Conventions

Mock-ups for data listings will include headers, title numbers, titles, column headers, and footnotes as appropriate. Data listings will provide all data collected on the corresponding eCRF page or provided by external vendors, unless otherwise indicated.

In general, data listings should include all subjects with data. However, if only subjects who meet a certain condition are listed (e.g., subjects with AEs) and no subjects meet the condition, the data listing will so indicate.

The sort order for data presented in data listings will be subject ID, unless otherwise requested by the sponsor. Within a subject, data will be listed in chronological order. Whenever possible, formatted values will be displayed (i.e., decoded). Where applicable, calendar date and study day of evaluations/events will be provided in the data listings.

13 References

None.

14 List of Statistical Tables, Listings and Figures to Be Programmed

The tables, figures, and listings displayed below represent the initial outputs planned. There may be minor variations to this output in the final summary package without updates to the lists displayed in this section.

14.1 Statistical Tables

Table 14.1.1	Subject Disposition, All Subjects
Table 14.1.2	Demographic and Baseline Characteristics, Safety Population
Table 14.1.3.1	Demographic and Baseline Characteristics, ITT Clinical Efficacy (CE) Population
Table 14.1.3.2	Demographic and Baseline Characteristics, Per Protocol Clinical Efficacy Population

Table 14.1.4 Non-Oncological Medical History, Safety Population
Table 14.1.5 Prior Anti-Cancer Therapies, Safety Population
Table 14.1.6 Treatment Exposure, Safety Population
Table 14.2.1.1 Progression Free Survival Based on RECIST v1.1 Criteria ITT CE Population
Table 14.2.1.2 Progression Free Survival Based on irRECIST Criteria ITT CE Population
Table 14.2.1.3 Progression Free Survival Based on RECIST v1.1 Criteria PP CE Population
Table 14.2.1.4 Progression Free Survival Based on irRECIST Criteria PP CE Population
Table 14.2.1.5 Progression Free Survival at Week 24 Based on RECIST v1.1 Criteria ITT CE Population
Table 14.2.1.6 Progression Free Survival at Week 24 Based on irRECIST Criteria ITT CE Population
Table 14.2.1.7 Progression Free Survival at Week 24 Based on RECIST v1.1 Criteria PP CE Population
Table 14.2.1.8 Progression Free Survival at Week 24 Based on irRECIST Criteria PP CE Population
Table 14.2.2.1 Summary of Response Rates and Durable Clinical Benefit Based on RECIST v1.1 Criteria ITT CE Population
Table 14.2.2.2 Summary of Response Rates and Durable Clinical Benefit Based on irRECIST Criteria ITT CE Population
Table 14.2.2.3 Summary of Response Rates and Durable Clinical Benefit Based on RECIST v1.1 Criteria PP CE Population
Table 14.2.2.4 Summary of Response Rates and Durable Clinical Benefit Based on irRECIST Criteria PP CE Population
Table 14.2.3.1 Summary of Duration of Response Based on RECIST v1.1 Criteria ITT CE Population
Table 14.2.3.2 Summary of Duration of Response Based on irRECIST Criteria ITT CE Population
Table 14.2.3.3 Summary of Duration of Response Based on RECIST v1.1 Criteria PP CE Population
Table 14.2.3.4 Summary of Duration of Response Based on irRECIST Criteria PP CE Population
Table 14.2.4.1 Overall Survival, ITT Clinical Efficacy Population
Table 14.2.4.2 Overall Survival, Per Protocol Clinical Efficacy Population
Table 14.3.1.1 Summary of Treatment-Emergent Adverse Events, Safety Population
Table 14.3.1.2 Summary of Treatment Related Adverse Events, Safety Population

Table 14.3.2 Incidence of Treatment Emergent Adverse Events by MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.3.3 Incidence of Treatment Emergent Adverse Events by MedDRA Preferred Term, Safety Population

Table 14.3.4 Incidence of Treatment Emergent Adverse Events by Maximum CTCAE Grade, MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.3.5.1 Incidence of ONCOS-102 Related Adverse Events by MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.3.5.2 Incidence of Cyclophosphamide Related Adverse Events by MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.3.5.3 Incidence of Durvalumab Related Adverse Events by MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.3.5.4 Incidence of Adverse Events related to any component of study therapy by MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.3.6.1 Incidence of Treatment Related Adverse Events Leading to ONCOS-102 Withdrawal by MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.3.6.2 Incidence of Treatment Related Adverse Events Leading to Durvalumab Withdrawal by MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.3.7 Incidence of Serious Adverse Events by MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.3.8 Incidence of Adverse Events related to any component of study therapy by Maximum CTCAE Grade, MedDRA System Organ Class and Preferred Term, Safety Population

Table 14.4.1 Hematology Parameters – Change from Baseline by Visit, Safety Population

Table 14.4.2 Hematology Parameters – Shift from Baseline by Visit, Safety Population

Table 14.4.3 Chemistry Parameters – Change from Baseline by Visit, Safety Population

Table 14.4.4 Chemistry Parameters – Shift from Baseline by Visit, Safety Population

Table 14.4.5.1 Vital Signs – Change from Baseline by Visit, Safety Population

Table 14.4.6 Concomitant Medications, Safety Population

14.2 Figures

Figure 1 KM Estimate of Progression-free Survival based on RECIST v1.1, ITT

Clinical Efficacy Population
Figure 2 KM Estimate of Progression-free Survival based on irRECIST, ITT Clinical Efficacy Population
Figure 3 KM Estimate of Progression-free Survival based on RECIST v1.1 by Cohort, Per Protocol Clinical Efficacy Population
Figure 4 KM Estimate of Progression-free Survival based on irRECIST by Cohort, Per Protocol Clinical Efficacy Population
Figure 5 KM Estimate of Overall Survival by Cohort, ITT Clinical Efficacy Population
Figure 6 KM Estimate of Overall Survival by Cohort, Per Protocol Clinical Efficacy Population

14.3 Data Listings

Listing 16.2.1 Inclusion and Exclusion Criteria Not Met
Listing 16.2.2 Study Disposition
Listing 16.2.3 Demographic Characteristics
Listing 16.2.4 Baseline Disease Characteristics
Listing 16.2.5 Non-Oncological Medical History and Procedures
Listing 16.2.6 Other Prior Cancer History
Listing 16.2.7 Prior Oncological Treatment History
Listing 16.2.8 Prior Oncological Radiation History
Listing 16.2.9 Prior Oncological Surgical History
Listing 16.2.10 Study Drug Exposure
Listing 16.2.11 Target Lesions
Listing 16.2.12 Non-Target Lesions
Listing 16.2.13 RECIST 1.1 Tumor Response by Visit
Listing 16.2.14 irRECIST Tumor Response by Visit
Listing 16.2.15 CA-125 and CEA Tumor Markers
Listing 16.2.16 RECIST 1.1 Progression-free Survival and Overall Survival
Listing 16.2.17 irRECIST Progression-free Survival
Listing 16.2.18 Prior and Concomitant Medications
Listing 16.2.19 Concomitant Procedures/Surgeries
Listing 16.2.20 Treatment Emergent Adverse Events
Listing 16.2.21 Serious Adverse Events
Listing 16.2.22 Adverse Events Leading to Study Drug Interruption or Discontinuation
Listing 16.2.23 Adverse Events Leading to Treatment Withdrawal
Listing 16.2.24 Dose-Limiting Toxicities
Listing 16.2.25 Deaths
Listing 16.2.26 Hematology Laboratory Results
Listing 16.2.27 Chemistry Laboratory Results
Listing 16.2.28 Urinalysis Laboratory Results
Listing 16.2.29 Coagulation Laboratory Results

Listing 16.2.30 Endocrine, Amylase, Lipase Laboratory Results
Listing 16.2.31 Vital Signs
Listing 16.2.32 ECOG Performance Status
Listing 16.2.33 Physical Examination, ECG, and Weight

15 Change history

Version	Date	Description of Changes
1	04APR2019	Original Approved Document
2.0	15MAY2020	Revised to enhance clarity of the efficacy sections including the corresponding TFL mock shells. The following sections were updated: I. Section 8.2.3: Section rephrased to emphasize the criteria for censoring in the analysis. II. Section 8.2.3: PFS at the End of Week 24 added since subjects without progression at week 24 is a primary end point III. Section 8.2.4 (Overall Survival (OS)) rephrased to define censoring more clearly. The analysis populations to be analyzed for OR were inserted IV. Section 8.2.5 (Duration of Response (DoR) added including how it will be analyzed V. Section 8.2.6 (Analysis of Time to Event (TTE) Variables added to indicate how these variables will be analyzed VI. Table 14.2.2.1 split into 2 tables: Table 14.2.2.1 Summary of Response Rates and Durable Clinical Benefit Based on RECIST v1.1 Criteria and Table 14.2.3.1 Summary of Duration of Response Based on RECIST v1.1 Criteria VII. List of Tables in SAP updated to align with current table shells
3.0	10SEP2020	Section 10.3 (Clinical Laboratory Data) revised to reflect intended analysis
4.0	19FEB2021	Section 8.2.5 (Duration of Response) revised. Clinical Progression (CP) removed from documented response options to assess DoR. The updated text reads as follows: 'The DoR analysis will be performed on only those subjects with a documented response (CR, PR)'. First paragraph in the section rephrased to reflect this change
4.0	23FEB2021	Section 8.2.5: 'The DoR analysis will be performed on only those subjects with a documented response (CR, PR)'. The Word documented in this sentence was replaced with 'confirmed'