THERADEX ONCOLOGY

Reporting and Analysis Plan
For Phase I Study
Signature Page

Final Version 2.0
Date: 17 January 2019

A Phase I, Open Label, Dose Escalation Study of Immunoconjugate L-DOS47 in Combination with Standard Doublet Therapy of Pemetrexed/Carboplatin in Patients with Stage IV (TNM M1a and M1b) Recurrent or Metastatic Non-Squamous Non-Small Cell Lung Cancer

Protocol No. LDOS001

Prepared by: Dailan Danforth Date: 22 Jan, 2019
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Associate Director, Biostatistics
Theradex Systems, Inc.

Reviewed by: Date: 22 JAN 2019
Richard S. Ungerleider, MD
Senior Vice President, Clinical Research Affairs
Theradex Systems, Inc.

Date: 22 Jan 2019
Jose Mejias, B.S.
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Helix BioPharma Corp.

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Helix BioPharma Corp.

Introduction to the Reporting and Analysis Plan

This Reporting and Analysis Plan (RAP) outlines the structure and content of the Clinical Study Report (CSR) including the statistical issues associated with the analysis of the safety and efficacy findings of this study.

This was a Phase I, open label, multicenter, dose-escalation study to evaluate the safety and tolerability of ascending doses of L-DOS47 in combination with standard doublet chemotherapy of pemetrexed/carboplatin in patients with Stage IV (TNM M1a and M1b) non-squamous non-small cell lung cancer. Initially, cohorts of 3 to 6 patients were to be enrolled in ascending dose cohorts until the maximum tolerated dose (MTD) was reached; as of Amendment 3, an accelerated dose design was implemented to permit cohorts of 1 patient up to the L-DOS47 dose level of 6µg/kg, followed by cohorts of 3 to 6 patients for the final two L-DOS47 dosing cohorts of 9 and 12 µg/kg. The MTD was defined as the highest dose level at which ≤ 1 of 6 patients experienced a dose-limiting toxicity (DLT) during the first treatment cycle. Once the MTD was defined, a confirmation cohort of approximately 10 patients was planned for enrollment at the MTD to determine the recommended Phase II dose for the combination treatment.

The starting dose of L-DOS47 was 0.59 µg/kg administered by intravenous infusion over 30 minutes. The standard of care doses of pemetrexed [500 mg/m^2 administered over 10 minutes] and carboplatin [AUC_6 mg/mL administered over 30 minutes], respectively, administered in combination with L-DOS47, remained constant across cohorts. A treatment cycle was 21 days with patients receiving L-DOS47 on Days 1, 8, and 15 and pemetrexed/ carboplatin on Day 1 of each treatment cycle for up to 4 cycles. Patients who tolerated treatment could continue L-DOS47 treatment for additional cycles.

Safety data, including laboratory parameters and adverse events, were collected for all patients. Adverse events were classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Efficacy was assessed after every 2 cycles of treatment using the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) guidelines. Pharmacokinetic parameters for L-DOS47 were determined from plasma samples collected from all patients at protocol-defined time points at predose, during the infusion and post infusion during Cycles 1 through 4. Patients could continue study treatment in the absence of unacceptable toxicity or until disease progression was documented. Continuation of treatment was to be determined by the clinical judgment of the Investigator.

The following documents were used in the preparation of this RAP:

Protocol	Version Date
Original	March 5, 2014
Version 1.1*	April 22, 2014
Amendment 1	June 2, 2015
Amendment 2	September 28, 2016
Amendment 3	August 10, 2017

* The first patient was enrolled and treated in accordance with Version 1.1 of the protocol.

CRF	Version Date
1068 Annotated Layouts	February 20, 2018

HELIX BIOPHARMA

CLINICAL STUDY REPORT

A Phase I, Open Label, Dose Escalation Study of Immunoconjugate L-DOS47 in Combination with Standard Doublet Therapy of Pemetrexed/Carboplatin in Patients with Stage IV (TNM M1a and M1b) Recurrent or Metastatic Non-Squamous Non-Small Cell Lung Cancer

Protocol No. LDOS001

Sponsor: Helix BioPharma Corp.
9120 Leslie Street, Suite 205
Richmond Hill, ON L4B 3J9
Canada

Investigators:

Sarina Piha-Paul, MD
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Chandra Belani, MD
Penn State Hershey Cancer Institute
500 University Drive, MC CH72
Hershey, PA 17033

Medical Monitor: Theradex Oncology
4365 US-1, Suite 101
Princeton, NJ 08540

Study Initiation Date: 20Apr2015
(First Patient On-Study)

Study Completion Date:
(Last Patient Off-Study)

Date of Study Report:

This study was performed in compliance with good clinical practice (GCP) including the archiving of essential documents.
This report complies with ICH Guideline E3.

Helix BioPharma Corp.

CLINICAL STUDY REPORT
Signature Page

A Phase I, Open Label, Dose Escalation Study of Immunoconjugate L-DOS47 in Combination with Standard Doublet Therapy of Pemetrexed/Carboplatin in Patients with Stage IV (TNM M1a and M1b) Recurrent or Metastatic Non-Squamous Non-Small Cell Lung Cancer

Protocol No. LDOS001

Sponsor Representative:	_____ Brenda Lee, M.Sc. Clinical Research Consultant to Helix Biopharma Corp. Helix BioPharma Corp.	_____ Date
Medical Monitor:	_____ Richard S. Ungerleider, MD Senior Vice President, Clinical Research Affairs Theradex Systems, Inc.	_____ Date
Biostatistician:	_____ Dailan Danforth Associate Director, Biostatistics Theradex Systems, Inc.	_____ Date
Medical Writer:	_____ Janet S. Johnson Senior Medical Writer / Regulatory Affairs Theradex Systems, Inc.	_____ Date

2.0 Synopsis

<table>
<tr><td>Name of sponsor:
Helix BioPharma Corp.</td><td rowspan="3">Individual study table referring to part of the dossier

Volume:

Page:</td><td rowspan="3">(For national authority use only)</td></tr>
<tr><td>Name of finished product:
L-DOS47</td></tr>
<tr><td>Name of active ingredient:
L-DOS47 is an immunoconjugate drug composed of single chain antibody molecules specific for carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), cross-linked with a purified urease derived from the Jack-Bean plant.</td></tr>
<tr><td colspan="3">Title of the study: A Phase I, Open Label, Dose Escalation Study of Immunoconjugate L-DOS47 in Combination with Standard Doublet Therapy of Pemetrexed/Carboplatin in Patients with Stage IV (TNM M1a and M1b) Recurrent or Metastatic Non-Squamous Non-Small Cell Lung Cancer [Protocol No. LDOS001]</td></tr>
<tr><td colspan="3">Investigators and study centers:
Sarina Piha-Paul, MD [Site 002]
UT MD Anderson Cancer Center
Department of Investigational Cancer Therapeutics
1515 Holcombe Boulevard, Unit 455
Houston, TX 77030

Afshin Dowlati, MD [Site 003]
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Cleveland, OH 44106

Chandra Belani, MD [Site 001]*
Penn State Hershey Cancer Institute
500 University Drive, MC CH72
Hershey, PA 17033

*Site 001 enrolled and treated 1 patient in 2015, then was closed on 18Aug2017 while the study was ongoing.</td></tr>
<tr><td colspan="3">Publication (reference):
Not applicable.</td></tr>
<tr><td colspan="2">Study period (years): 2015 - ____
First patient enrolled: 20Apr2015
Last patient completed:</td><td>Clinical phase: I</td></tr>
<tr><td colspan="3">Objectives:
Primary Objectives:
• Safety and tolerability of L-DOS47 in combination treatment with pemetrexed/carboplatin
• Determination of dose limiting toxicity of L-DOS47 in combination treatment with pemetrexed/carboplatin
• Determination of maximum tolerated dose (MTD) and recommended Phase II dose of</td></tr>
</table>

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L-DOS47 in combination treatment with pemetrexed/carboplatin

Secondary Objectives:

- Objective response rate of the combination treatment according to RECIST 1.1
- Evaluation of clinical benefit, defined as the percentage of patients who have achieved complete response, partial response, and stable disease following combination treatment with L-DOS47 + pemetrexed/ carboplatin. For patients to be evaluable for stable disease, the duration of stable disease must be at least 42 days from the first dose of study treatment.

Exploratory Objectives:

- Evaluation of the pharmacokinetics of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Evaluation of the immunogenicity of L-DOS47

Methodology:

This was a Phase I, open label, multicenter, dose-escalation study to evaluate the safety and tolerability of ascending doses of L-DOS47 in combination with standard doublet chemotherapy of pemetrexed/carboplatin in patients with Stage IV (TNM M1a and M1b) non-squamous non-small cell lung cancer. The study initially utilized a standard "3 + 3" design of dose escalation. Patients were recruited into cohorts of L-DOS47 escalating doses, with a minimum of 3 and a maximum of 6 patients per cohort. As of Amendment 3, the study implemented an accelerated "1 + 2" design up to 6 µg/kg and the standard "3 + 3" design for the final two dosing cohorts. The starting dose of L-DOS47 was 0.59 µg/kg administered by intravenous infusion over 30 minutes. The standard of care doses of pemetrexed [500 mg/m^2 administered over 10 minutes] and carboplatin [AUC_6 mg/mL administered over 30 minutes], respectively, administered in combination with L-DOS47, remained constant across cohorts. As of Amendment 2, the L-DOS47 infusion could be increased from 30 minutes to 60 minutes in the event of a mild infusion reaction.

All patients at a given dose level had to complete Cycle 1 before escalation in subsequent patients could proceed. The decision for escalation to the next dose level was made after safety data were reviewed by a Safety Review Committee, which consisted of the Investigators, the Medical Monitor, and the Sponsor. Dose escalation was based on dose limiting toxicities (DLTs) occurring during the first cycle of treatment.

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The sequence of administration of the combination therapy on Day 1 of each treatment cycle was:

1) pemetrexed intravenous infusion over 10 minutes;
2) approximately 30 minutes after the end of the pemetrexed infusion, carboplatin intravenously infused over 30 minutes;
3) approximately 30 minutes after the end of the carboplatin infusion, L-DOS47 intravenously infused over 30 minutes.

A treatment cycle was 21 days with patients receiving L-DOS47 on Days 1, 8, and 15 and pemetrexed/ carboplatin on Day 1 of each treatment cycle.

Patients were to receive 4 cycles of combination treatment with L-DOS47 + pemetrexed/carboplatin. Patients who did not progress following the 4 cycles of combination treatment and who did not experience unacceptable toxicity had the opportunity to continue to receive additional cycles of L-DOS47 treatment for as long as there was clinical benefit and it was well-tolerated, in the opinion of the Investigator, until disease progression. Patients who were unable to complete 4 cycles of L-DOS47 + pemetrexed/carboplatin combination treatment due to pemetrexed/carboplatin toxicity had the opportunity to continue receiving L-DOS47 treatment following discontinuation of pemetrexed/carboplatin, for as long as there was clinical benefit and it was well-tolerated, in the opinion of the Investigator, until disease progression.

Patient safety was monitored throughout the study and for a minimum of 30 days after last dose of study drug. Long-term follow-up for disease progression was conducted by radiologic assessments every 6 weeks (±7 days) until disease progression, the patient initiated non-study cancer treatment, the patient withdrew consent or became lost-to-follow-up. Survival data was captured by telephone call every 30 days (±7 days) and patients were followed until death. Severity of adverse events and laboratory abnormalities were reported according to NCI CTCAE version 4.0. Response to treatment was assessed after every 2 cycles using RECIST version 1.1.

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The following table shows the planned dose levels for L-DOS47 treatment:

Cohort	L-DOS47 Dose in µg/kg
-1*	0.46
1	0.59
2	0.78
3	1.5
4	3.0
5	6.0
6	9.0
7	12.0

*If the starting dose level resulted in DLT, patients were to be treated at the -1 dose level.

Enrollment in each dose cohort proceeded in the standard "3+3" schema where 3 patients were initially enrolled per cohort (see note above regarding implementation of accelerated dosing as of Amendment 3). The decision to escalate to the next dose level was based on the observation of DLT during Cycle 1. If 0 of 3 patients had DLT, escalation could proceed to the next cohort. If, however, DLT was observed in 1 of the 3 patients, an additional 3 patients were to be enrolled at that dose. In a cohort of 6, if one patient had DLT, then dose escalation could proceed; if 2 or more patients had DLT, then that dose would be declared the maximally administered dose and dose escalation would cease. Three additional patients were to be entered at the next lowest dose level if only 3 patients had been treated previously at that dose. The MTD/RD was defined as the highest dose level at which ≤ 1 of 6 patients experienced a DLT during the first treatment cycle.

MTD Confirmation Cohort:

Once the MTD was defined, a confirmation cohort of approximately 10 patients was planned for enrollment at the MTD to determine the recommended Phase II dose for the combination treatment.

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Dose-limiting toxicity (DLT):

DLT was defined as the occurrence of any of the following events (according to NCI CTCAE version 4.0) that occurred within 21 days after commencing study drug treatment and was considered to be possibly, probably, or definitely related to study drug treatment by the Investigator:

- Hematologic adverse events ≥ grade 4
- Non-hematologic adverse events ≥ grade 3
- One instance each of two unique grade 2 adverse events (accelerated dose cohorts only)

For the purpose of cohort evaluation, if a patient did not receive all of his/her scheduled L-DOS47 doses in Cycle 1 due to toxicity, this was considered a DLT. Patients experiencing a DLT during the first treatment cycle were to be withdrawn from the study.

Number of patients:

Enrollment in the study was planned for up to 37 patients (estimation based on 3 patients per cohort for 5 dose escalation cohorts, 6 patients per cohort for 2 dose escalation cohorts and 10 patients in the MTD expansion cohort).

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

Patients had to fulfill all of the following criteria to be eligible for the study:

1. Male or female patient ≥ 18 years of age;
2. Histologically or cytologically confirmed non-squamous NSCLC, classified as:
   - Chemotherapy-naive Stage IV (TNM M1a or M1b) non-squamous NSCLC for whom pemetrexed/carboplatin would be appropriate therapy
   - Stage IV (TNM M1a or M1b) non-squamous NSCLC recurrent following prior surgery, radiation and/or adjuvant chemotherapy, for whom pemetrexed/carboplatin would be appropriate therapy
   - Staging of non-squamous NSCLC had to be assessed according to TNM, 7th edition and based on computed tomography (CT) scan;
3. EGFR-mutation positive patients had to have progressed on or had intolerance to an EGFR small molecule tyrosine kinase inhibitor. The washout period for patients treated with an EGFR tyrosine kinase inhibitor was 7 days;
4. Patients whose tumors harbored an anaplastic lymphoma kinase (ALK) translocation had to have progressed on or had intolerance to an ALK inhibitor. The washout period for patients

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treated with an ALK inhibitor was 7 days;

5. No prior adjuvant chemotherapy within 6 months of the first treatment day if there was recurrent disease;
6. At least 1 site of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and minimum life expectancy of ≥ 3 months;
8. Adequate bone marrow function defined as: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, hemoglobin ≥ 9 g/dL, and platelet count ≥ 100 x 10^9/L;
9. Adequate renal function defined as creatinine ≤ 1.5 x institutional upper limit of normal (ULN);
10. Adequate liver function defined as: total bilirubin ≤ 1.5 x institutional ULN and not increasing more than 25% within the last 4 weeks, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x institutional ULN, or < 5 x ULN if liver abnormalities were due to underlying malignancy;
11. Male or female patients of child-producing potential had to agree to use an effective method of contraception during the study and for 90 days after the last day of treatment;
12. Females of childbearing potential had to have a negative serum pregnancy test;
13. Females had to not be breastfeeding;
14. Ability to understand study procedures and provision of signed and dated written informed consent prior to any study specific procedures;
15. Patients with treated and stable brain metastases as documented by repeat MRI showing stabilization one month after definitive response. Patients had to be off steroids and not taking antiepileptics for brain metastases.

Exclusion Criteria:

Patients would not be entered in the study for any of the following reasons:

1. Histologic evidence of predominantly squamous cell NSCLC;
2. Patients with brain metastasis unless asymptomatic, not requiring steroids or antiseizure medications, and treated and stable for at least 4 weeks prior to start of study treatment;
3. Peripheral neuropathy > CTCAE grade 1;
4. Possibility of a curative local treatment (surgery and/or radiotherapy);
5. Previous chemotherapy except adjuvant treatment with progression of disease documented ≥ 6 months after end of adjuvant treatment (prior to Amendment 2, ≥ 12 months);

Name of sponsor: Helix BioPharma Corp. **Name of finished product:** L-DOS47 **Name of active ingredient:** L-DOS47 is an immunoconjugate drug composed of single chain antibody molecules specific for carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6), cross-linked with a purified urease derived from the Jack-Bean plant.	Individual study table referring to part of the dossier Volume: Page:	*(For national authority use only)*

6. Received treatment in another clinical study within the 30 days prior to commencing study treatment or having side effects of a prior study drug that were not recovered to grade ≤ 1 or baseline, except for alopecia;
7. Concurrent chronic systemic immunotherapy, chemotherapy or hormone therapy;
8. Chronic treatment with systemic steroids (other than inhalers or topical steroids) or other medications to suppress the immune system; acute steroid use was permissible;
9. Significant cardiac disease including heart failure that met New York Heart Association (NYHA) class III and IV definitions, history of myocardial infarction within six months of study entry, uncontrolled dysrhythmias or poorly controlled angina;
10. Sustained QTc (the QT interval corrected for heart rate) with Fridericia's correction > 470 ms at screening or a history of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome);
11. Known positive human immunodeficiency virus (HIV), known hepatitis B surface antigen positivity, or hepatitis C antibody positivity;
12. Previous malignancy within the last 5 years (except history of basal cell carcinoma of skin or pre-invasive carcinoma of the cervix with adequate treatment);
13. Serious uncontrolled medical condition, other Life threatening illness, significant organ dysfunction, or clinically significant laboratory abnormality, which in the opinion of the Investigator, would either compromise the patient's safety or interfere with evaluation of the safety of the study treatment;
14. History of severe psychiatric illness;
15. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent or compliance with the requirements of the protocol;
16. Life expectancy of < 3 months;
17. Known hypersensitivity reaction to any of the components of the study treatment;
18. Pregnancy (absence to be confirmed by ß-hCG test) or breastfeeding;
19. History of hepatic encephalopathy;
20. Presence of interstitial pneumonitis.

Test product, dose and mode of administration, batch number:

L-DOS47 drug product was provided by Helix BioPharma Corp. as a lyophilized cake in 3 mL stoppered and crimped Type I glass vials intended for reconstitution for i.v. infusion in normal saline (0.9% NaCl) solution with 0.02% polysorbate 80. L-DOS47 was stored at 2-8°C. The lot numbers used in the study were OBP-801-001 and OBP-801-003.

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L-DOS47 Administration:
L-DOS47 was administered at a starting dose of 0.59 µg/kg by intravenous infusion over 30 minutes. As of Amendment 2, the L-DOS47 infusion time could be increased to 60 minutes in the event of a mild infusion reaction.

Doublet Chemotherapy:
Carboplatin was prepared per the drug package insert and administered by intravenous infusion at a dose of AUC_6 mg/mL over 30 minutes.

Pemetrexed was prepared per the prescribing information sheet and administered by intravenous infusion at a dose of 500 mg/m^2 over 10 minutes.

Pemetrexed pre-medication:

- Vitamin Supplementation: patients were instructed to initiate folic acid 400 µg to 1000 µg orally once daily beginning 7 days before the first dose of pemetrexed and continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Vitamin B12 1 mg was administered intramuscularly 1 week prior to the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B12 injections could be given the same day as treatment with pemetrexed.
- Corticosteroids: Dexamethasone 4 mg orally was administered twice daily the day before, the day of, and the day after pemetrexed administration.

Duration of treatment:
Patients were to receive 4 cycles of combination treatment with L-DOS47 + pemetrexed/carboplatin. After 4 cycles, patients could continue to receive additional cycles of L-DOS47 alone until disease progression as long as there was clinical benefit and it was well-tolerated. Patients who were unable to complete 4 cycles of combination treatment due to pemetrexed/carboplatin toxicity could receive additional cycles of L-DOS47 alone until disease progression as long as there was clinical benefit and it was well-tolerated.

Reference therapy, dose and mode of administration, batch number:
Not applicable.

Criteria for evaluation:
Safety: Safety data including vital signs, laboratory parameters, and adverse events, etc. were collected for all patients. All patients who received any amount of L-DOS47 were included in the

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safety analysis. Safety parameters evaluated include adverse events, vital signs, and clinical laboratory results, etc. Adverse events were classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0.

Efficacy: Although response was not the primary endpoint of this study, patients with measurable disease were assessed using RECIST version 1.1. Objective response assessment was performed at baseline, after every 2 cycles, and at off-study using the same method of radiologic imaging at each assessment. For patients with less than 2 cycles of study therapy, there had to be clear evidence of clinical progression to be considered eligible for the efficacy evaluation.

Exploratory:
Pharmacokinetic parameters for L-DOS47 were determined from plasma samples collected from all patients at protocol-defined time points at predose, during the infusion and post infusion during Cycles 1 through 4.

Tumor antigen (CEACAM6) assessment: blood samples were to be drawn from patients twice during the study at protocol-defined time points for assessment of tumor antigen.

Immunogenicity of L-DOS47 was assessed from serum samples collected from patients at protocol-defined time points prior to L-DOS47, during the study, at the end of treatment, and at the follow-up visit 30 days after last study dose.

Statistical methods:
The primary endpoint of this study was to assess the toxicity of L-DOS47 by determining the dose level at which DLTs were observed. The MTD and RP2D were to be determined during the course of the study and not during the statistical analysis phase. Safety data were tabulated for all patients, include laboratory parameters, vital signs, and AEs. AEs were tabulated by body system, preferred term, severity, and relationship to treatment. AEs were arranged by decreasing frequency of AEs. Laboratory data was graded according to NCI CTCAE (Version 4.0) and tabulated based on maximum grade. AEs were coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA®) Version 17.1.

Secondary endpoints of this study were to examine the efficacy and pharmacokinetics of L-DOS47. For efficacy analysis, best overall response was assessed using RECIST version 1.1. The

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objective antitumor response rate [complete response (CR) or partial response (PR)] and 95% confidence interval were calculated based on the proportion of patients with responsive disease (CR + PR). The clinical benefit rate (CR+PR+SD) and 95% CI were calculated. Duration of response (CR or PR) was evaluated using Kaplan-Meier methodology and the 95% confidence interval for the median progression-free time was provided. Pharmacokinetic analysis was performed to establish C_{max}, T_{max}, half-life, AUC, CL, and V_d.

Summary - Conclusions:

Demographics Summary:
[Insert demographics summary here]

Safety Summary:
[Insert safety summary here]

Efficacy Summary:
[Insert efficacy summary here]

Pharmacokinetics Summary:
[Insert PK summary here, or "The PK results is presented in a separate report."]

Conclusions:
[Insert overall discussion and conclusions here]

3.0 Table of Contents

Page No.

3.1 In-Text Tables

Page No.

3.2 In-Text Figures

List of Acronyms, Abbreviations and Definitions of Terms

AE	Adverse event
AFAIKL2	Recombinant camelid single domain antibody
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BP	Blood pressure
CEACAM6	Carcinoembryonic antigen-related cell adhesion molecule 6
CL	Systemic clearance
C_{max}	Maximum observed plasma concentration after dosing
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
i.v.	Intravenous
ICH	International Conference on Harmonization
INR	International normalized ratio
IRB	Institutional Review Board
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities

MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
PD	Progressive disease
PD	Pharmacodynamic
PK	Pharmacokinetic
PFS	Progression-Free Survival
PR	Partial response
PT	Prothrombin time
QT	A measure of the time between the start of the Q wave and the end of the T wave
QTc	The QT interval corrected for heart rate
RAP	Reporting and Analysis Plan
RECIST	Response Evaluation Criteria in Solid Tumour
RP2D	Recommended phase 2 dose
RR	Respiratory rate
SAE	Serious adverse event
SD	Stable disease
t½	Terminal elimination half-life
T_{max}	Time of maximum observed plasma drug concentration after dosing
TNM	Tumor, Node, Metastasis tumor staging classification
ULN	Upper limit of normal
V_{ss}	Volume of distribution at steady state
V_z	Volume of distribution
WBC	White blood cell

4.0 Ethical Conduct of the Study

The study protocol, amendments, and informed consent form were reviewed and approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC) at each participating site.

The study was conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH/GCP), the protocol, all applicable regulatory requirements, and the guiding principles of the Declaration of Helsinki.

Written informed consent to participate in the study was obtained from each patient before study enrollment and the performance of any study-specific procedures.

5.0 Investigators and Study Administration

5.1 Investigators

Site No.	Investigator / Institution
002	Sarina Piha-Paul, MD UT MD Anderson Cancer Center Department of Investigational Cancer Therapeutics 1515 Holcombe Boulevard, Unit 455 Houston, TX 77030
003	Afshin Dowlati, MD Case Western University University Hospitals Case Medical Center 11100 Euclid Avenue, LKS 1200 Cleveland, OH 44106
001*	Chandra Belani, MD Penn State Hershey Cancer Institute 500 University Drive, MC CH72 Hershey, PA 17033 *Site 001 enrolled and treated 1 patient in 2015, then was closed on 18Aug2017 while the study was ongoing.

5.2 Study Administration

The study was sponsored by Helix BioPharma Corp., 9120 Leslie Street, Suite 205, Richmond Hill, ON L4B 3J9, Canada.

The study was monitored by Theradex Oncology, a Contract Research Organization (CRO), located at 4365 US-1, Suite 101, Princeton, NJ 08540 USA. Data management, statistical analysis and clinical report writing services were also provided by Theradex Oncology.

Compliance with GCP was assured in the clinical trial in a number of ways including, but not limited to: site initiation visits, routine monitoring visits at the sites, and the site close-out visits conducted by Theradex Oncology; periodic teleconferences were conducted during the course of the study between Theradex Oncology, the Sponsor and the study sites regarding safety data and study status.

The Theradex Oncology study medical monitor was responsible for safety monitoring of the study which included a review of all serious adverse events (SAEs) as they were reported by the study sites. The study medical monitor was in contact with site monitors and site coordinators to evaluate adverse events and was available to discuss issues concerning safety with site staff.

Prior to site initiation, the Theradex Oncology site monitor reviewed the case report form (CRF) and other pertinent study materials with the Investigator's research staff to assure protocol compliance and the valid recording of study data. At routine monitoring visits the Theradex Oncology site monitor examined and verified CRFs using source documents in the individual subject's medical records, and assured that the study was conducted according to the approved protocol and in agreement with pertinent regulatory requirements. The review of medical records was done in a manner to assure that patient confidentiality was maintained.

6.0 Introduction

Helix BioPharma Corp. developed an immunoconjugate cancer therapeutic to exploit the acidic tumor extracellular environment produced by human solid tumors. The molecule, L-DOS47, is a protein conjugate consisting of jack bean urease conjugated to a llama monoclonal antibody (AFAIKL2) that is targeted to the carcinoembryonic antigen-related cell adhesion molecule 6 (CEACAM6) antigenic tumor marker. The urease and the AFAIKL2 antibody are chemically conjugated by a hetero-bifunctional cross linker yielding a final product with an antibody-to-enzyme ratio of 8-10:1. CEACAM6 is a glycosylphosphatidylinositol (GPI)-anchored cell adhesion molecule that is overexpressed in many cancers that is associated with adhesion and invasion. The AFAIKL2 antibody

serves as a targeting agent to deliver the enzyme to the affected sites while the urease enzyme converts urea, an abundant metabolite, into ammonia and generates a local pH increase. The combined effect of ammonia toxicity and pH increase is cytotoxic to cancer cells in culture and in xenograft models.

When targeted to lung tumors by the AFAIKL2 mAb at an appropriate i.v. dose, L-DOS47 can potentially kill the tumor cells through alkalinization of the local milieu and production of ammonia. However, as with many cancer treatments, at higher doses L-DOS47 has the potential to induce undesirable toxic effects. The primary goals of this Phase I study were to determine the safety and tolerability of L-DOS47, and to establish maximum tolerated dose (MTD) and recommended Phase II dose of L-DOS47 in combination with standard doublet chemotherapy of pemetrexed/carboplatin in patients with Stage IV (TNM M1a and M1b) recurrent or metastatic non-squamous non-small cell lung cancer (NSCLC).

Prior to this study, a first-in-human Phase I/II, open label, non-randomized, dose escalation study of L-DOS47 monotherapy in patients with non-squamous non-small cell lung cancer (NSCLC) had been initiated in Poland and was ongoing. The primary objective of the Phase I portion of that trial was to define the MTD of multiple doses of L-DOS47 administered i.v. to patients with non-squamous NSCLC. The primary objective of the Phase II portion was to make a preliminary assessment of the efficacy of L-DOS47 in patients with non-squamous NSCLC. The secondary objectives of both phases of that study were to evaluate the pharmacokinetics of L-DOS47, the immunogenicity, and the safety and tolerability of L-DOS47 in patients.

7.0 Study Objectives

Primary Objectives:

- Safety and tolerability of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Determination of dose limiting toxicity of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Determination of maximum tolerated dose (MTD) and recommended Phase II dose of L-DOS47 in combination treatment with pemetrexed/carboplatin

Secondary Objectives:

- Objective response rate of the combination treatment according to RECIST 1.1
- Evaluation of clinical benefit, defined as the percentage of patients who have achieved complete response, partial response, and stable disease following combination treatment with L-DOS47 + pemetrexed/carboplatin. For patients to be evaluable for

stable disease, the duration of stable disease must be at least 42 days from the first dose of study treatment.

Exploratory Objectives:

- Evaluation of the pharmacokinetics of L-DOS47 in combination treatment with pemetrexed/carboplatin
- Evaluation of the immunogenicity of L-DOS47

8.0 Investigational Plan

8.1 Overall Study Design and Plan

This was a Phase I, open label, multicenter, dose-escalation study to evaluate the safety and tolerability of ascending doses of L-DOS47 in combination with standard doublet chemotherapy of pemetrexed/carboplatin in patients with Stage IV (TNM M1a and M1b) non-squamous non-small cell lung cancer. The study initially utilized a standard "3 + 3" design of dose escalation. Patients were recruited into cohorts of L-DOS47 escalating doses, with a minimum of 3 and a maximum of 6 patients per cohort. As of Amendment 3, the study implemented an accelerated "1 + 2" design up to 6 µg/kg and the standard "3 + 3" design for the final two dosing cohorts. The starting dose of L-DOS47 was 0.59 µg/kg administered by intravenous infusion over 30 minutes. The standard of care doses of pemetrexed [500 mg/m^2 administered over 10 minutes] and carboplatin [AUC_6 mg/mL administered over 30 minutes], respectively, administered in combination with L-DOS47, remained constant across cohorts. As of Amendment 2, the L-DOS47 infusion could be increased from 30 minutes to 60 minutes in the event of a mild infusion reaction.

All patients at a given dose level had to complete Cycle 1 before escalation in subsequent patients could proceed. The decision for escalation to the next dose level was made after safety data were reviewed by a Safety Review Committee, which consisted of the Investigators, the Medical Monitor, and the Sponsor. Dose escalation was based on dose limiting toxicities (DLTs) occurring during the first cycle of treatment.

The sequence of administration of the combination therapy on Day 1 of each treatment cycle was:

1) pemetrexed intravenous infusion over 10 minutes;
2) approximately 30 minutes after the end of the pemetrexed infusion, carboplatin intravenously infused over 30 minutes;
3) approximately 30 minutes after the end of the carboplatin infusion, L-DOS47 intravenously infused over 30 minutes.

A treatment cycle was 21 days with patients receiving L-DOS47 on Days 1, 8, and 15 and pemetrexed/carboplatin on Day 1 of each treatment cycle.

Patients were to receive 4 cycles of combination treatment with L-DOS47 + pemetrexed/ carboplatin. Patients who did not progress following the 4 cycles of combination treatment and who did not experience unacceptable toxicity had the opportunity to continue to receive additional cycles of L-DOS47 treatment for as long as there was clinical benefit and it was well-tolerated, in the opinion of the Investigator, until disease progression. Patients who were unable to complete 4 cycles of L-DOS47 + pemetrexed/carboplatin combination treatment due to pemetrexed/carboplatin toxicity had the opportunity to continue receiving L-DOS47 treatment following discontinuation of pemetrexed/carboplatin, for as long as there was clinical benefit and it was well-tolerated, in the opinion of the Investigator, until disease progression.

Patient safety was monitored throughout the study and for a minimum of 30 days after last dose of study drug. Long-term follow-up for disease progression was conducted by radiologic assessments every 6 weeks (±7 days) until disease progression, the patient initiated non-study cancer treatment, the patient withdrew consent or became lost-to-follow-up. Survival data was captured by telephone call every 30 days (±7 days) and patients were followed until death. Severity of adverse events and laboratory abnormalities were reported according to NCI CTCAE version 4.0. Response to treatment was assessed after every 2 cycles using RECIST version 1.1.

8.1.1 Dose Escalation Phase

The following table shows the planned dose levels for L-DOS47 treatment:

Cohort	L-DOS47 Dose in µg/kg
-1*	0.46
1	0.59
2	0.78
3	1.5
4	3.0
5	6.0
6	9.0
7	12.0

*If the starting dose level resulted in DLT, patients were to be treated at the -1 dose level.

Enrollment in each dose cohort proceeded in the standard "3+3" schema where 3 patients were initially enrolled per cohort. As of Amendment 3, the study implemented an accelerated "1 + 2" design up to 6 µg/kg and the standard "3 + 3" design for the final two dosing cohorts. The decision to escalate to the next dose level was based on the observation of DLT during Cycle 1. If 0 of 3 patients had DLT, escalation could proceed to the next cohort. If, however, DLT was observed in 1 of the 3 patients, an additional 3 patients were to be enrolled at that dose. In a cohort of 6, if one patient had DLT, then dose escalation could proceed; if 2 or more patients had DLT, then that dose would be declared the maximally administered dose and dose escalation would cease. Three additional patients were to be entered at the next lowest dose level if only 3 patients had been treated previously at that dose. The MTD/RD was defined as the highest dose level at which ≤ 1 of 6 patients experienced a DLT during the first treatment cycle.

MTD Confirmation Cohort:

Once the MTD was defined, a confirmation cohort of approximately 10 patients was planned for enrollment at the MTD to determine the recommended Phase II dose for the combination treatment.

8.1.2 Dose Limiting Toxicity

DLT was defined as the occurrence of any of the following events (according to NCI CTCAE version 4.0) that occurred within 21 days after commencing study drug treatment and was considered to be possibly, probably, or definitely related to study drug treatment by the Investigator:

- Hematologic adverse events ≥ grade 4
- Non-hematologic adverse events ≥ grade 3
- One instance each of two unique grade 2 adverse events (accelerated dose cohorts only)

For the purpose of cohort evaluation, if a patient did not receive all of his/her scheduled L-DOS47 doses in Cycle 1 due to toxicity, this was considered a DLT. Patients experiencing a DLT during the first treatment cycle were to be withdrawn from the study.

8.1.3 Maximum Tolerated Dose

The maximum tolerated dose (MTD)/recommended dose (RD) was defined as the highest dose level at which ≤ 1 of 6 patients experienced a dose limiting toxicity during the first treatment cycle.

If the MTD/RD was not confirmed following the evaluation of the final dosing cohort defined in the protocol, consideration was to be given to test further cohorts. The same dosing schema was to be used in determining these cohorts.

Once the MTD was defined, a confirmation cohort of approximately 10 patients was to be enrolled at the MTD to determine the recommended Phase II doses for the combination treatment.

8.1.4 Dose Modifications

8.1.4.1 Dose reductions/modifications for L-DOS47

If a patient experienced an AE meeting the definition of DLT (see Section 9.1.2), then the patient was to be withdrawn from the study and not receive further doses of L-DOS47. Any AE occurring after the defined DLT criteria window was not considered a DLT.

If a patient's dose of L-DOS47 was to be reduced, it was to be given at the subsequent lower dose level of L-DOS47. Only 1 dose level reduction was allowed. To meet the criteria for retreatment, all toxicities considered by the Investigator to be related to therapy with L-DOS47 (except alopecia or anemia) must have resolved to ≤ Grade 2, or to a level considered acceptable by the Investigator, or to the patient's baseline values.

If the patient did not meet the retreatment criteria, the dose will to be held and the patient reassessed weekly (or sooner if deemed clinically appropriate) for possibility of retreatment. If treatment was delayed for more than 14 days, the patient was to be withdrawn from the study, unless discussed and agreed with the Medical Monitor.

Dose modification for subsequent cycles was required when any of the following dose delay conditions were met:

Dose delay	Occurrence	Action for L-DOS47
Up to 7 days	1st	None
Up to 7 days	2nd	Dose Reduction
Up to 7 days	3rd	Withdrawn[1]
8 to 14 days	1st	Dose Reduction
8 to 14 days	2nd	Withdrawn[1]

[1] The withdrawal of patients from the study was discussed with the Medical Monitor. A decision to not withdraw a patient had to be agreed upon by the Sponsor and Medical Monitor, clinically supported and documented.

Dose modification for subsequent cycles was required when any of the following L-DOS47 toxicity criteria conditions were met:

Toxicity	Grade	Occurrence	Relationship	Action for L-DOS47
Hematological				
Neutropenia				
	3 or 4	Any	Possible, probable, definite	None
	3 or 4	Any, prior delay of dosing	Possible, probable, definite	Dose Reduction
	3 or 4	2nd, prior dose reduction	Possible, probable, definite	Withdrawn[1]
Thrombocytopenia[2]				
	3 or 4	Any	Possible, probable, definite	None
	3 or 4	Any, prior delay of dosing	Possible, probable, definite	Dose Reduction
	3 or 4	2nd, prior dose reduction	Possible, probable, definite	Withdrawn[1]
Bleeding				
	1 or 2	1st	Possible, probable, definite	Dose Reduction
	1 or 2	Any, prior dose reduction	Possible, probable, definite	Withdrawn[1]
	3 or 4	1st	Possible, probable, definite	Withdrawn[1]
Non-Hematological				
	3	1st	Possible, probable, definite	Dose Reduction
	3	2nd, prior dose reduction	Possible, probable, definite	Withdrawn[1]
	4	1st	Possible, probable, definite	Withdrawn[1]

[1] The withdrawal of patients from the study was discussed with the Medical Monitor. A decision to not withdraw a patient had to be agreed upon by the Sponsor and Medical Monitor, clinically supported and documented.
[2] Without bleeding or platelet transfusion.

8.1.4.2 Dose reductions/modifications for pemetrexed and carboplatin

Doses were to be reduced for hematological and other adverse events. Dose adjustments were to be made according to the system showing the greatest degree of toxicity, graded using the Common Terminology Criteria for Adverse Events version 4.0 (CTCAE). Any patient who required a dose reduction was to continue to receive a reduced dose for the remainder of the study. Any patient with 2 prior dose reductions who experienced a toxicity that would cause a third dose reduction was to discontinue pemetrexed and carboplatin therapy.

Hematologic Toxicity:
Dose adjustments at the start of a subsequent cycle of therapy were based on platelet and neutrophils nadir (lowest value) counts from the preceding cycle of therapy. ANC had to be ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L prior to the start of any cycle. Treatment was to be delayed to allow sufficient time for recovery. Upon recovery, if treatment resumed, it was according to the guidelines below:

Dose adjustments for pemetrexed and carboplatin based on nadir hematologic values from preceding cycle:

Platelets (× 10^9/L) Nadir		ANC (× 10^9/L) Nadir	Percent of Previous Dose
> 50	and	≥ 0.5	100%
> 50	and	< 0.5	75%
< 50	and	any	75%
< 50 + bleeding	and	any	50%
any	and	< 1.0 + fever of ≥ 38.5°C	75%
Recurrence of Grade 3 or 4 thrombocytopenia after 2 dose reductions		Recurrence of Grade 3 or 4 neutropenia after 2 dose reductions	Pemetrexed and carboplatin discontinued

ANC = absolute neutrophil count

Non-hematologic toxicity:
In the event of diarrhea requiring hospitalization (or of at least Grade 3), treatment was to be delayed until diarrhea resolved before proceeding. Treatment with pemetrexed was to be resumed at 75% of the previous dose level. The carboplatin remained the same.

For other non-hematologic effects ≥ Grade 3, with the exception of alopecia and mucositis, treatment had to be delayed until resolution to less than or equal to the patient's baseline CTCAE grade before proceeding. Treatment was to resume at 75% of the previous dose level if deemed appropriate by the treating physician. For Grade 3 or 4 transaminase elevations, the drug dose level was not to be reduced.

Dose modifications for pemetrexed and carboplatin for mucositis:

	Dose for Next Cycle	
CTCAE Grade	**Pemetrexed**	**Carboplatin (AUC)**
Grade 0-2	100% of previous dose	100% of previous dose
Grade 3-4	50% of previous dose	100% of previous dose
Recurrence of Grade 3 or 4 after treatment at 2 dose reductions	pemetrexed discontinued	carboplatin discontinued

CTCAE = Common Terminology Criteria for Adverse Events

Dose modifications for pemetrexed and carboplatin in case of neurosensory toxicity:

	Dose for Next Cycle	
CTCAE Grade	**Pemetrexed**	**Carboplatin (AUC)**
Grade 0-1	100% of previous dose	100% of previous dose
Grade 2	100% of previous dose	50% of previous dose
Grade 3-4 (or recurrence of Grade 2 after treatment at dose reduction for Carboplatin)	pemetrexed discontinued	carboplatin discontinued

AUC = area under the curve; CTCAE = Common Terminology Criteria for Adverse Events

8.2 Discussion of Study Design

This was a Phase I, open label, multicenter, dose-escalation study of L-DOS47 in combination with standard doublet chemotherapy of pemetrexed/carboplatin administered to patients with Stage IV (TNM M1a and M1b) non-squamous NSCLC. Safety and tolerability were evaluated in cohorts of 1 to 6 patients enrolled in escalating dose levels of L-DOS47 until determination of the MTD. Pharmacokinetic parameters for L-DOS47 were evaluated from plasma samples collected from patients. The starting dose of L-DOS47 was 0.59 µg/kg administered by intravenous infusion over 30 minutes (after Amendment 2, over 60 minutes in the event of a mild infusion reaction). The doses of pemetrexed (500 mg/m^2 administered over 10 minutes) and carboplatin (AUC_6 mg/mL administered over 30 minutes) were the standard of care, administered in combination with L-DOS47, and remained constant across cohorts.

8.3 Selection of Study Population

8.3.1 Inclusion Criteria

Patients had to fulfill all of the following criteria to be eligible for the study:

1. Male or female patient ≥ 18 years of age;
2. Histologically or cytologically confirmed non-squamous NSCLC, classified as:
   - Chemotherapy-naive Stage IV (TNM M1a or M1b) non-squamous NSCLC for whom pemetrexed/carboplatin would be appropriate therapy
   - Stage IV (TNM M1a or M1b) non-squamous NSCLC recurrent following prior surgery, radiation and/or adjuvant chemotherapy, for whom pemetrexed/carboplatin would be appropriate therapy
   - Staging of non-squamous NSCLC had to be assessed according to TNM, 7th edition and based on computed tomography (CT) scan;
3. EGFR-mutation positive patients had to have progressed on or had intolerance to an EGFR small molecule tyrosine kinase inhibitor. The washout period for patients treated with an EGFR tyrosine kinase inhibitor was 7 days;

4. Patients whose tumors harbored an anaplastic lymphoma kinase (ALK) translocation had to have progressed on or had intolerance to an ALK inhibitor. The washout period for patients treated with an ALK inhibitor was 7 days;
5. No prior adjuvant chemotherapy within 6 months of the first treatment day if there was recurrent disease;
6. At least 1 site of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1;
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and minimum life expectancy of ≥ 3 months;
8. Adequate bone marrow function defined as: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, hemoglobin ≥ 9 g/dL, and platelet count ≥ 100 x 10^9/L;
9. Adequate renal function defined as creatinine ≤ 1.5 x institutional upper limit of normal (ULN);
10. Adequate liver function defined as: total bilirubin ≤ 1.5 x institutional ULN and not increasing more than 25% within the last 4 weeks, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x institutional ULN, or < 5 x ULN if liver abnormalities were due to underlying malignancy;
11. Male or female patients of child-producing potential had to agree to use an effective method of contraception during the study and for 90 days after the last day of treatment;
12. Females of childbearing potential had to have a negative serum pregnancy test;
13. Females had to not be breastfeeding;
14. Ability to understand study procedures and provision of signed and dated written informed consent prior to any study specific procedures;
15. Patients with treated and stable brain metastases as documented by repeat MRI showing stabilization one month after definitive response. Patients had to be off steroids and not taking antiepileptics for brain metastases.

8.3.2 Exclusion Criteria

Patients would not be entered in the study for any of the following reasons:

1. Histologic evidence of predominantly squamous cell NSCLC;
2. Patients with brain metastasis unless asymptomatic, not requiring steroids or antiseizure medications, and treated and stable for at least 4 weeks prior to start of study treatment;
3. Peripheral neuropathy > CTCAE grade 1;
4. Possibility of a curative local treatment (surgery and/or radiotherapy);
5. Previous chemotherapy except adjuvant treatment with progression of disease documented ≥ 6 months after end of adjuvant treatment (prior to Amendment 2, ≥ 12 months);

6. Received treatment in another clinical study within the 30 days prior to commencing study treatment or having side effects of a prior study drug that were not recovered to grade ≤ 1 or baseline, except for alopecia;
7. Concurrent chronic systemic immunotherapy, chemotherapy or hormone therapy;
8. Chronic treatment with systemic steroids (other than inhalers or topical steroids) or other medications to suppress the immune system; acute steroid use was permissible;
9. Significant cardiac disease including heart failure that met New York Heart Association (NYHA) class III and IV definitions, history of myocardial infarction within six months of study entry, uncontrolled dysrhythmias or poorly controlled angina;
10. Sustained QTc (the QT interval corrected for heart rate) with Fridericia's correction > 470 ms at screening or a history of additional risk factors for Torsades de Pointes (e.g., heart failure, hypokalemia, family history of long QT syndrome);
11. Known positive human immunodeficiency virus (HIV), known hepatitis B surface antigen positivity, or hepatitis C antibody positivity;
12. Previous malignancy within the last 5 years (except history of basal cell carcinoma of skin or pre-invasive carcinoma of the cervix with adequate treatment);
13. Serious uncontrolled medical condition, other Life threatening illness, significant organ dysfunction, or clinically significant laboratory abnormality, which in the opinion of the Investigator, would either compromise the patient's safety or interfere with evaluation of the safety of the study treatment;
14. History of severe psychiatric illness;
15. Dementia or significantly altered mental status that would prohibit the understanding or rendering of informed consent or compliance with the requirements of the protocol;
16. Life expectancy of < 3 months;
17. Known hypersensitivity reaction to any of the components of the study treatment;
18. Pregnancy (absence to be confirmed by ß-hCG test) or breastfeeding;
19. History of hepatic encephalopathy;
20. Presence of interstitial pneumonitis.

8.3.3 Removal of Patients from Treatment or Assessment

Protocol therapy was to be discontinued at any time if any of the following situations occurred:

1. Progressive disease.
2. The development of toxicity which, in the Investigator's judgment, precluded further therapy.
3. Patient refusal.
4. Lost to follow-up/noncompliance.
5. Intercurrent illness.

6. At the discretion of the Investigator.
7. Pregnancy.
8. Study termination.

Note: When a patient was removed from the study, the Investigator was to document the reason in the medical record and complete the appropriate case report form (CRF) page describing the reason for discontinuation. In addition, every effort was to be made to complete the appropriate study assessments.

8.3.4 Protocol Deviations

Protocol deviations were not collected in the CRFs and therefore are not part of the clinical database. Instances of noncompliance and resulting protocol deviations were collected in Monitor Express, the Theradex Oncology proprietary Clinical Trial Management System.

8.4 Treatments

8.4.1 Treatment Administered

Patients received L-DOS47 on Days 1, 8, and 15 and pemetrexed/carboplatin on Day 1 of each 21-day treatment cycle. The sequence of administration on Day 1 of each cycle was:

1) pemetrexed was prepared per the prescribing information sheet and administered by intravenous infusion at a dose of 500 mg/m^2 over 10 minutes (see Section 9.4.7.1 for pemetrexed pre-medications);
2) approximately 30 minutes after the end of the pemetrexed infusion, carboplatin, prepared per the drug package insert, was intravenously infused over 30 minutes at a dose of AUC_6 mg/mL;
3) approximately 30 minutes after the end of the carboplatin infusion, L-DOS47 was intravenously infused over 30 minutes*.

*As of Amendment 2, the L-DOS47 infusion time could be increased to 60 minutes in the event of a mild infusion reaction.

8.4.2 Identity of Investigational Product(s)

L-DOS47 drug product was provided by Helix BioPharma Corp. as a lyophilized cake in 3 mL stoppered and crimped Type I glass vials intended for reconstitution for i.v. infusion in normal saline (0.9% NaCl) solution with 0.02% polysorbate 80. L-DOS47 was stored at 2-8°C. The lot numbers used in the study were OBP-801-001 and OBP-801-003.

8.4.3 Method of Assigning Patients to Treatment Groups

Patients were assigned to treatment groups in the order that they were enrolled in the study.

8.4.4 Selection of Doses in the Study

Results of pivotal GLP repeat-dose toxicology studies in rats and monkeys showed premature deaths occurring at higher doses of i.v. L-DOS47 that were not predicted by any premonitory signs at lower doses. Therefore, careful monitoring of plasma C_{max} levels in patients was planned in the clinic. Prior to the current study, a first-in-human Phase I/II, open label, non-randomized, dose escalation study of L-DOS47 monotherapy in patients with non-squamous NSCLC was being conducted in Poland. In that study, patients had been treated at L-DOS47 doses ranging from 0.12 µg/kg to 13.55 µg/kg. The adverse events reported in that study were expected for the population under study; the safety profile was consistent with that of animals treated with L-DOS47. For the present study, considering preclinical toxicology studies, a very conservative starting dose was chosen which was relatively consistent when calculated by the three standard approaches to starting dose. A maximum safety factor of 10 and a human equivalent dose (HED) scaling from animal to human dose (body surface area) were also utilized. The L-DOS47 starting dose chosen for this trial was 0.59 µg/kg, with planned escalation following a modified Fibonacci schema.

8.4.5 Selection and Timing of Dose for Each Patient

L-DOS47 was administered by intravenous infusion on Days 1, 8, and 15 of each 21-day combination treatment cycle in Cycles 1 through 4. Patients who had not progressed following the 4 cycles of combination treatment and had not experienced unacceptable toxicity had the opportunity to receive additional cycles of L-DOS47 treatment for as long as there was clinical benefit and it was well-tolerated, in the opinion of the Investigator, until disease progression. Patients who were unable to complete 4 cycles of L-DOS47 + pemetrexed/carboplatin combination treatment due to pemetrexed/carboplatin toxicity had the opportunity to continue to receive additional cycles of L-DOS47 treatment following discontinuation of pemetrexed/ carboplatin, for as long as there was clinical benefit and it was well-tolerated, in the opinion of the Investigator, until disease progression.

Simultaneous dosing of patients within a dosing cohort was prohibited. Patient dosing was to be separated by at least 24 hours which allowed for the assessment of possible infusion reactions and/or allergic reactions and enabled communication between study centers.

The L-DOS47 dose of each cycle was calculated based on the patient's weight on Day 1 of that cycle. The dose was not adjusted for body weight on Day 8 or 15 of the treatment cycles. Full weight-based doses were to be used to treat obese patients.

If a patient exhibited signs and symptoms of anaphylaxis, he or she should was to be managed per local institutional guidelines. For mild infusion reactions (transient flushing, rash or low grade fever < 38ºC or < 100.4ºF), anti-histamine, corticosteroids, and other medical intervention could be used as needed. If symptoms resolved within 30 minutes, the infusion could be resumed at a minimum 50% reduction in rate. If symptoms recurred or worsened despite antihistamine and corticosteroids, the patient was to be removed from the study. If a patient exhibited signs and symptoms of moderate to severe (anaphylaxis) infusion reactions such as bronchospasm with or without urticaria, edema/angioedema, hypotension, then the L-DOS47 infusion was to be stopped immediately and the patient managed per local institutional guidelines.

Patients who experienced mild infusion reactions manageable with anti-histamine and corticosteroids could be pre-medicated for subsequent doses.

Patients were to remain in the out-patient observation area for 2 hours after completion of the L-DOS47 infusion for observation prior to discharge.

8.4.6 Blinding

This was an open-label safety and tolerability study. The treatments were not blinded.

8.4.7 Prior and Concomitant Treatment

Chronic use of systemic steroids was prohibited. Acute use of systemic steroids was permitted. Use of steroid inhalers and topical steroids was permitted.

Any medication the patient took other than the study treatment was considered a concomitant medication. All concomitant medications were to be recorded on the eCRF. At the Screening Visit, patients were asked what medications they had taken during the last 30 days. At each subsequent study visit, patients were asked what concomitant medications they were currently taking.

Other than the study treatments planned in this protocol, patients were not to receive the following medications during the study: hormonal agents, other investigational drugs, systemic corticosteroids, and immunotherapy.

Radiotherapy could be given concomitantly for the control of bone pain; irradiated lesions were not evaluable for response. Any medication which was considered necessary for the

patient's welfare and which would not interfere with administration of the study treatments, could be given at the discretion of the Investigator.

8.4.7.1 Pemetrexed pre-medication

- Vitamin Supplementation: patients were instructed to initiate folic acid 400 µg to 1000 µg orally once daily beginning 7 days before the first dose of pemetrexed and continue during the full course of therapy and for 21 days after the last dose of pemetrexed. Vitamin B12 1 mg was administered intramuscularly 1 week prior to the first dose of pemetrexed and every 3 cycles thereafter. Subsequent vitamin B12 injections could be given the same day as treatment with pemetrexed.
- Corticosteroids: Dexamethasone 4 mg orally was administered twice daily the day before, the day of, and the day after pemetrexed administration.

8.4.8 Treatment Compliance

L-DOS47 (and pemetrexed/carboplatin) was administered intravenously by clinical trial personnel in a clinic setting, thus ensuring that patients received the appropriate dose of study drug on schedule as per protocol. Any instances of noncompliance and resulting protocol deviations were recorded in Monitor Express.

8.4.9 Dose Delay and Modification

Study dose administration could be delayed and/or modified as described in Section 9.1.4.

8.4.10 Duration of Therapy

Patients were to receive 4 cycles of combination treatment with L-DOS47 + pemetrexed/ carboplatin. After 4 cycles, patients could continue to receive additional cycles of L-DOS47 alone until disease progression as long as there was clinical benefit and it was well-tolerated. Patients who were unable to complete 4 cycles of combination treatment due to pemetrexed/ carboplatin toxicity could receive additional cycles of L-DOS47 alone until disease progression as long as there was clinical benefit and it was well-tolerated.

8.5 Efficacy and Safety Variables

8.5.1 Efficacy and Safety Measurements

The schedule of study evaluations is presented in Section 9.5.1.1. Assessments prior to Day 1 of each cycle were used to determine whether a patient could start the cycle. Radiologic examination and tumor measurements were made after every 2 cycles (i.e., 6 weeks). Concomitant medications, physical examination, laboratory parameters, vital signs, ECOG performance status, and ECG were assessed at baseline, during the treatment period, and at off-study. Adverse events were monitored throughout the

treatment period and at off-study. Long-term follow-up was conducted until disease progression and survival data was captured until death (Section 9.5.1.3).

8.5.1.1 Schedule of Study Evaluations

	Pre-treatment Screening	During Treatment L-DOS47 + Pemetrexed/Carboplatin[2] Cycles 1 through 4 Cycle Days (D)				End-of-Treatment Visit[3]		Additional Treatment Cycles[3]	Follow-up Visits	
Procedures	**Days -28 to 0**	**D1**	**D8**	**D15**	**D21**	**Cycle 4 Day 21 7 (± 5) days post last dose**	**Early Termination (immediately)**	**L-DOS47 only[19]**	**30 Days post last dose**	**Thereafter, every 30 days* (± 7 days) or every 6 weeks** (± 7 days)**
Informed Consent[1]	X									
Inclusion/exclusion criteria	X	X								
Demographics	X									
Weight	X	X predose						X D1 predose		
Medical history	X									
Physical examination	X	X predose	X predose			X	X	X D1, 8, 15 predose		
Performance status (ECOG)	X	X				X	X	X D1		
Radiologic examination[6] and tumor assessment	X	X				X (if > 6 wks post last scan)	X (if > 6 wks post last scan)	X D1 every other cycle	X	X
Historic biopsy sample (if available)	X									
Tumor antigen assessment (CEACAM6)[7]		X predose Cycle 2	X predose Cycle 4			X (only if not done on	X (only if not done on			

	Pre-treatment Screening	During Treatment L-DOS47 + Pemetrexed/Carboplatin[2] Cycles 1 through 4 Cycle Days (D)				End-of-Treatment Visit[3]		Additional Treatment Cycles[3]	Follow-up Visits	
Procedures	**Days -28 to 0**	**D1**	**D8**	**D15**	**D21**	**Cycle 4 Day 21 7 (± 5) days post last dose**	**Early Termination (immediately)**	**L-DOS47 only[19]**	**30 Days post last dose**	**Thereafter, every 30 days* (± 7 days) or every 6 weeks** (± 7 days)**
		only	only			C4D8)	C4D8)			
Vital Signs (temp/HR/BP/RR/pulse oximetry)[8,20]	X	X pre- & post-dose	X pre- & post-dose	X		X	X	X D1, 8, 15		
Electrocardiogram[9, 20]	X	X pre- & post-dose	X pre- & post-dose			X	X	X D1 and 8 Predose & postdose (optional [10])		
Clinical lab tests[4] Hematology, Chemistry, Coagulation	X	X predose	X predose			X	X	X D1, 8, 15 predose		
Urinalysis[5]	X	X predose	X predose			X	X	X D 1, 8, 15 predose		
Pregnancy test[11]	X	X predose				X	X	X D1 predose		
L-DOS47 administration[12]		X	X	X				X D1, 8, 15		
Pemetrexed/Carboplatin administration[13]		X								

	Pre-treatment Screening	During Treatment L-DOS47 + Pemetrexed/Carboplatin[2] Cycles 1 through 4 Cycle Days (D)				End-of-Treatment Visit[3]		Additional Treatment Cycles[3]	Follow-up Visits	
Procedures	**Days -28 to 0**	**D1**	**D8**	**D15**	**D21**	**Cycle 4 Day 21 7 (± 5) days post last dose**	**Early Termination (immediately)**	**L-DOS47 only[19]**	**30 Days post last dose**	**Thereafter, every 30 days* (± 7 days) or every 6 weeks** (± 7 days)**
Plasma PK sampling[14,20]		X	X							
Serum collection for anti-L-DOS47 antibody testing[15]		X predose	X predose C1 only			X	X	X Day 1 predose	X	
Concomitant medications	X	X[16] predose	X[16] predose			X	X	X D1, 8, 15 predose	X	
Adverse Events		X[17]	X[17]	X[17]	X[17]	X	X	X D1, 8, 15 predose and postdose	X	
Disease progression and Survival[18]										X

ECOG: Eastern Cooperative Oncology Group; Temp: Temperature; HR; Heart rate; BP: Blood pressure; RR: Respiratory rate; PK: Pharmacokinetic; ECG: Electrocardiogram; CT: Computed tomography; MRI: Magnetic resonance imaging

1 Informed consent was obtained before any experimental procedure or test was performed.
2 Patients were administered up to 4 cycles of L-DOS47 during the study treatment period. Treatment cycles would be repeated for patients who tolerated the previous treatment cycle of L-DOS47 and showed no clinical signs of progression of disease.
3 The End-of-Treatment Visit was performed one time for all patients who discontinued the study at or before the end of Cycle 4. For patients who continued to receive additional cycles of L-DOS47 (i.e., Cycle 5 and beyond), this visit was performed twice: (i) after the completion of 4 cycles, and (ii) at the time of discontinuation from the study. Note: All patients who withdrawn from the study were to complete the End-of-Treatment Visit immediately at the time of withdrawal.

4 The corresponding procedures were performed on the day specified for each L-DOS47 cycle:
Hematology: CBC with differential and platelet count;
Serum chemistry: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), urea, calcium, bicarbonate, chloride, creatinine (by Cockcroft-Gault formula), globulin (serum globulin: total protein minus serum albumin), glucose, phosphate, potassium, sodium, magnesium, total bilirubin, total protein.
Coagulation: prothrombin time/international normalized ratio (PT/INR), activated partial thromboplastin time (aPTT).

5 Urinalysis: bilirubin, glucose, ketones, occult blood, protein.

6 Radiologic examinations were performed during screening, unless results from appropriate scans performed within 28 days prior to the first dose of study drug were available and every other treatment cycle (i.e., every 6 weeks) until disease progression; an MRI could be conducted only in exceptional cases. Radiologic examination was to be repeated at the End of Treatment Visit if > 6 weeks had passed since the last evaluation.

7 Tumor antigen (CEACAM6) assessment: blood samples were drawn (predose [0 hours]) on Day 1 (predose [0 hours]) of Cycle 2 and on Day 8 of Cycle 4 or the End of Treatment Visit (whichever occurred first).

8 Vital signs (temperature, heart rate, blood pressure, respiratory rate and oxygen saturation [pulse oximetry]) were assessed prior to pemetrexed/carboplatin administration on Day 1 of the cycle; on treatment days in which L-DOS47 was administered (Days 1, 8, and 15), vital signs were also serially recorded relative to start of L-DOS47 infusion as follows: Cycle 1, Days 1 and 8: predose and 10 and 20 minutes (during infusion), and 30 minutes (prior to end of infusion) and 1, 2, and 4 hours postdose; Cycle 2, Days 1 and 8: predose and 15 minutes (during infusion), and 30 minutes (prior to end of infusion). Cycle 2, Day 1 at 1 and 2 hours postdose; Cycle 2, Day 8 at 1, 2, and 4 hours postdose; Cycles 3 and 4, Days 1 and 8: predose and 30 minutes (prior to end of infusion). All cycles, Day 15: 15 minutes (during infusion), and 30 minutes (prior to end of infusion).

9 Serial 12-lead ECG measurements were recorded on Days 1 and 8 of each cycle at predose and at 1 and 1.5 hours postdose.

10 For additional cycles, all ECG recordings were optional.

11 In women of childbearing potential, serum ß-HCG tests were conducted at Screening and at the End-of-Treatment/Early Termination Visit. Urine ß-HCG tests were conducted on Day 1 of each treatment cycle.

12 L-DOS47 was administered on Days 1, 8, and 15 of each treatment cycle. Treatment with L-DOS47 could continue beyond four cycles for as long as the patient was receiving sustained clinical benefit and it was well tolerated, in the opinion of the Investigator, until disease progression.

13 Pemetrexed/carboplatin were administered according to standard prescribing information on the first day of treatment Cycles 1 through 4, prior to L-DOS47 administration.

14 Serial blood samples (plasma) for L-DOS47 PK were collected from all patients as follows: Cycle 1, Days 1 and 8: predose and serially postdose (time relative to the start of infusion) at 15 (during infusion), 30 (prior to end of infusion)*, 45 minutes* and 1*, 1.5, 2, 3, 4, 24, and 48 hours postdose; Cycles 2 and 4, Day 8: predose and serially postdose (time relative to the start of infusion) at 15 (during infusion), 30 (prior to end of infusion)*, 45 minutes* and 1*, 1.5, 2, 3, 4, and 24 hours postdose; Cycle 2, Day 1; Cycle 3, Days 1 and 8; Cycle 4, Day 1: predose and 30 minutes* postdose (time relative to the start of infusion, to be collected just prior to end of infusion).* If the L-DOS47 infusion time was increased from 30 minutes to 60 minutes in the event of a mild infusion reaction, there was no change in the PK sampling timepoints, which were all relative to the start of L-DOS47 infusion. PK samples collected at 30 minutes and 45 minutes were considered during infusion samples and PK sample collected at 60 minutes (1 hour) was a prior to end of infusion sample. All other timepoints remained the same.

15 Serum samples were collected (2 mL/ in SST tubes) for anti-L-DOS47 antibody testing on Cycle 1 (Day 1 [predose; baseline] and Day 8 [predose]), Cycles 2 through 4 (Day 1 [predose]), all additional cycles (i.e., Cycle 5 and beyond, Day 1 [predose], at the End-of-Treatment Visit or Early Termination Visit, and 30 days after the last dose.

16 Concomitant medications were recorded predose on Days 1 and 8 of each cycle.

17 Adverse events (AE) were recorded predose and postdose on Days 1, 8, and 15 of each cycle, and the Cycle 4 End-of-Treatment Visit. On non-visit days, AE was monitored by telephone contact. Adverse event monitoring on Day 21 occurred only if the patient was coming off study and the next cycle was not being initiated.

18 Patients were followed to collect data pertaining to progression and survival. *Survival data was captured by telephone call every 30 days (± 7 days) until death. **Follow-up for progression was conducted by radiologic assessments (CT scans of chest, abdomen and pelvis, or as appropriate per the Investigator) every 6 weeks (± 7 days) until disease progression, patient initiated non-study cancer treatment, patient withdrew consent, or patient was lost-to-follow-up.

19 Cycle 5, Day 1 assessments did not need to be repeated if the end of Cycle 4 evaluations were performed within 7 days prior to Day 1 of Cycle 5.

20 ECG/Vital signs/PK time window table presented below defines an acceptable lapse in assessment/sample collection.

ECG/Vital signs/PK time window [a]

	ECG	Vital signs	PK
During infusion	± 5 min	± 3 min	±2 min
Post infusion	± 5 min	± 5 min	± 5 min [b,c]

a. All timepoints were relative to the start of L-DOS47 infusion.
b. If the L-DOS47 infusion time was increased from 30 minutes to 60 minutes in the event of a mild infusion reaction, there was no change in the PK sampling timepoints. The PK sample collected at 60 minutes (1 hour) was the end of infusion sample. All other timepoints remained the same.
c. For PK samples collected at 24 and 48 hours timepoints, the window will be ± 30 min.

8.5.1.2 Off-Study Assessments

For the initial 4 cycles, The End-of-Treatment Visit was conducted Day 21 of Cycle 4 (patients who complete all 4 treatment cycles) or was the Early Termination visit (for patients withdrawn from the study), whichever occurred first. All patients were required to complete the End-of-Treatment Visit. Patients who completed the initial 4 cycles and continued treatment, completed the End-of-Treatment Visit on Day 21 of Cycle 4 and their next visit was Cycle 5, Day 1. Patients continuing beyond Cycle 4 completed the End-of-Treatment Visit again at the time of withdrawal from the study. All patients who were withdrawn from the study completed the End-of-Treatment Visit immediately at the time of withdrawal.

The following assessments were performed and measurements recorded:

- Physical examination
- ECOG performance status
- Radiologic examination (if > 6 weeks had passed since the last evaluation)
- Tumor antigen assessment: performed only if not done on Day 8 of Cycle 4
- Vital signs (temperature, heart rate, blood pressure, respiratory rate, oxygen requirement [pulse oximetry])
- 12-lead ECG
- Hematology, blood chemistry and coagulation
- Urinalysis
- Serum collection for anti-L-DOS47 antibody testing
- Serum pregnancy test for women of childbearing potential
- Concomitant medications
- Adverse event monitoring

8.5.1.3 Long-Term Follow-Up

Follow-up assessments were conducted after the End-of-Treatment Visit. Long-term follow-up for disease progression was conducted by radiologic assessments every 6 weeks (± 7 days) until disease progression, patient initiated non-study cancer treatment, patient withdrew consent or became lost-to-follow-up. Survival data was captured by telephone call every 30 days (± 7 days) and patients were followed until death.

8.5.2 Appropriateness of Measurements

Safety and efficacy assessments were standard, as indicated by the use of CTCAE Version 4.0 and RECIST 1.1, respectively.

8.5.3 Efficacy and Safety Variables

8.5.3.1 Safety Assessments

- AEs, vital signs, and laboratory parameters were assessed.
- All AEs and laboratory abnormalities were assessed according to CTCAE version 4.0.
- DLTs, SAEs and AEs leading to treatment discontinuation were determined.

Adverse Events (AEs): An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The AE reporting period commenced after the initial dosing of pemetrexed premedication. If an AE occurred before the first dose of study drug it was considered a non-treatment emergent AE. At each evaluation patients were interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event was based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms.

All AEs (except grade 1 and 2 laboratory abnormalities that did not require an intervention), regardless of causal relationship, were to be recorded in the case report form and source documentation. The Investigator determined the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 and their causal relationship. Those AEs not covered by these criteria were graded as outlined in the protocol.

AEs were followed until resolution or stabilization while the patient remained on-study. Once the patient was removed from study, events thought to be related to the study medication were followed until resolution or stabilization, unless, in the Investigator's opinion the event was unlikely to resolve due to the patient's underlying disease, or until the patient started a new treatment regimen or the patient was lost to follow-up.

Serious Adverse Events (SAEs): A SAE was defined as any untoward medical occurrence that at any dose:

- Resulted in death.
- Was Life threatening (i.e., the patient was at risk of death at the time of the event. It did not refer to an event that hypothetically might have caused death if it was more severe).

- Required in-patient hospitalization or prolongation of existing hospitalization excluding that for pain management, disease staging/re-staging procedures, or catheter placement unless associated with other serious events.
- Resulted in persistent or significant disability/incapacity.
- Was a congenital anomaly/birth defect.
- Other medically important condition.

Important medical events that might not result in death, Life threatening, or required hospitalization could be considered SAEs when, based on appropriate medical judgment, they might jeopardize the patient and required medical or surgical intervention to prevent 1 of the outcomes listed above.

8.5.3.2 Efficacy Assessments

Although response was not the primary endpoint of this study, patients with measurable disease were assessed by standard criteria. For the purposes of this study, patients were to be evaluated every 6 weeks. In addition to a baseline scan, confirmatory scans were also to be obtained 4 weeks following initial documentation of an objective response. Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in RECIST 1.1. Note: Lesions are either measurable or non-measurable using the criteria provided below.

8.5.3.2.1 Definitions Based on RECIST version 1.1

Response and progression were evaluated using the international criteria (version 1.1) proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee.

Lesions were either measurable or non-measurable using the following criteria:

Measurable Disease
Measurable lesions were defined as those that could be accurately measured in at least one dimension [longest diameter (LD) in the plane of measurement to be recorded] with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which could not be accurately measured with calipers were to be recorded as non-measurable)
- mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node had to be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

Non-measurable Disease
All other lesions (or sites of disease), including small lesion (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) were considered non-measurable disease.

All measurements were recorded in metric notation, using a ruler or calipers. All baseline evaluations were performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

8.5.3.2.2 Evaluation of Target and Non-Target Lesions

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

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).
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): Unequivocal progression of existing non-target lesions (The appearance of one or more new lesions is also considered progression). To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation.

8.5.3.2.2.1 Evaluation of Best Overall Response

Overall response determination as outlined in RECIST (version 1.1) took into account the assessments of both target and non-target lesions. Best overall response was the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best overall response assignment depended on findings of both target and non-target disease and the appearance of new lesions. Furthermore, depending on the nature of the study, it might also require confirmatory measurement.

A summary of the overall response status calculation at each time point for patients who had measurable disease at baseline is presented below.

Time Point Response: Patients with Target (+/- non-target) Disease:

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable			

Complete or partial responses might be claimed only if the criteria for each were confirmed by a repeated assessment at least 4 weeks later. In this circumstance, the best overall response could be interpreted as described below.

Best Overall Response when Confirmation of CR and PR Required:

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = inevaluable

* If CR was truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in the fact patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

8.5.4 Drug Concentration Measurements and Other Assessments

8.5.4.1 Pharmacokinetic Assessments

Plasma sampling for pharmacokinetic (PK) measurements of L-DOS47 concentrations were conducted during Cycles 1 through 4 as follows:

- Cycle 1, Days 1 and 8: predose, during the infusion, and serially postdose per protocol-defined timepoints up to 48 hours.
- Cycles 2 and 4, Day 8: predose, during the infusion, and serially postdose per protocol-defined timepoints up to 24 hours.
- Cycle 2, Day 1; Cycle 3, Days 1 and 8; Cycle 4, Day 1: predose and postdose (collected just prior to end of infusion).

8.5.4.2 Tumor Antigen Assessment

Blood samples for tumor antigen (CEACAM6) assessment were drawn Cycles 2 and 4 (or at the off treatment visit).

8.5.4.3 Immunogenicity

Immunogenicity of L-DOS47 was evaluated from serum samples collected each cycle, at the end of treatment or the early termination visit, and at the follow-up visit (30 days after the last dose).

8.6 Data Quality Assurance

Compliance with GCP was assured in the clinical trial in a number of ways including, but not limited to the site initiation visit, routine monitoring visits at the site, and the site close-out visit conducted by Theradex Oncology; periodic teleconferences conducted during the course of the study between Theradex Oncology, the Sponsor and the study site regarding safety data and study status.

The Theradex Oncology study medical monitor was responsible for safety monitoring of the study, which included a review of all serious adverse events (SAEs) as they were reported by the study site. The study medical monitor was in contact with site monitors and site coordinators to evaluate adverse events and was available to discuss issues concerning safety with site staff.

Prior to site initiation, the Theradex Oncology site monitor reviewed the case report form (CRF) and other pertinent study materials with the Investigator's research staff to assure protocol compliance and the valid recording of study data. At routine monitoring visits the Theradex Oncology site monitor examined and verified CRFs using source documents in the individual subject's medical records, and assured that the study was conducted according to the approved protocol and in agreement with pertinent regulatory requirements. The review of medical records was done in a manner to assure that patient confidentiality was maintained.

CRFs were monitored and collected, data entered, data edit checks performed, data discrepancies resolved, and the database locked according to Theradex Oncology SOPs.

After database lock, the data was retrieved from the Oracle® relational database and processed using SAS®. All statistical analyses were performed using SAS® statistical software (Version 9.4). Tables and listings were generated by validated SAS® programs.

8.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

All data summaries are descriptive and provided separately for each dose cohort. Data summaries include frequency counts and percent for categorical measures and the mean, median, standard deviation, minimum and maximum for continuous variables.

8.7.1 Determination of Sample Size

It is anticipated that up to 37 patients will be enrolled in this study (estimation based on 3 patients per cohort for 5 dose escalations, 6 patients per cohort for 2 dose escalation cohorts and 10 patients in the MTD expansion cohort).

8.7.2 Analysis of Data

Evaluation of the data for the study will consist primarily of data listings and summary displays. Demographic and other baseline characteristic information are summarized. Adverse events are tabulated by body system, preferred term, severity, and relation to treatment. Similar presentations are provided for serious adverse events, adverse events leading to discontinuation from study, and adverse events leading to death. The listing of laboratory parameters will indicate the normal range for each parameter. Each value is classified as falling above, below, or within the normal range.

RECIST 1.1[1] is used for tumor response evaluation. Tumor-related endpoints including best overall response, objective response rate, duration of response (CR or PR), clinical benefit (CR+PR+SD) will be summarized for patients with baseline measurable disease. Tumor response for patients with baseline non-measurable disease will be provided in a listing.

8.7.3 Study Endpoints

The primary endpoints are the number of patients with DLTs, toxicity, MTD and the recommended Phase II dose (RD) of L-DOS47 in combination with pemetrexed/ carboplatin.

The secondary endpoints are best overall response, objective response rate (CR or PR), clinical benefit rate (CR+PR+SD) and duration of response following combined treatment.

The exploratory endpoints are PK parameters for L-DOS47 in combination with pemetrexed/ carboplatin, antibody concentration and other immunogenicity data of L-DOS47.

8.7.4 Statistical Analysis Populations

Intent-to-Treat Population: Includes all patients enrolled in the study whether or not they met the eligibility criteria or received study drug. This population will be summarized for demographics and other baseline characteristics, and serve as the secondary analysis population for efficacy.

Safety Evaluable Population: Includes all patients who received any amount of L-DOS47 or pemetrexed premedication. This population will be summarized for all safety parameters.

Efficacy-Evaluable Population: Includes all patients who met the eligibility criteria with baseline measurable disease, completed 2 cycles of study treatment, and had at least one post-baseline tumor assessment. For patients with fewer than 2 cycles of study treatment, there must be clear evidence of clinical progression to be considered evaluable for efficacy. The efficacy-evaluable population will be the primary analysis population for efficacy.

8.7.5 Statistical Methods

8.7.5.1 Safety and Tolerability Analyses

All patients who received any amount of L-DOS47, or pemetrexed premedication will be evaluated for safety. Safety data includes adverse events, vital signs, laboratory parameters, and cardiographic values, etc. Descriptive statistics (e.g., mean, SD, median, minimum, and maximum values, and number and percent of patients within specified categories) will be used to summarize the safety parameters. Safety data will be summarized for each cohort.

8.7.5.1.1 Adverse Events

Treatment-Emergent Adverse Events (TEAEs) will be defined as all AEs that occurred from the date of first dose to 30 days after the last dose of study drug. TEAEs will be summarized and tabulated by MedDRA Version 17.1 system organ class and preferred term, by maximum CTCAE (Version 4.0) grade as well as by relationship to treatment (unrelated, unlikely, possible, probable, and definite). Drug-related TEAEs will include those considered to have a possible, probable or definite relationship to study drug. Patients with multiple TEAEs will only be counted once within a summary category: system organ class, preferred term, maximum grade (using the most severe grade), or relationship to treatment. Patients with events in more than one category will be counted once within each category. TEAEs classified as serious (SAEs), TEAEs leading to study

discontinuation, and TEAEs with the outcome of death will be summarized and patient narratives will be provided regarding these events. Dose limiting toxicities will be listed.

8.7.5.1.2 Laboratory Data

Hematology, blood chemistry, and coagulation data will be converted to common reporting units and graded according to CTCAE (Version 4.0) prior to summarization.

Laboratory data of hematology, blood chemistry, coagulation and urinalysis were collected at Baseline (last pre-treatment value from Day -28 to Day 1); for L-DOS47+Pemetrexed/ Carboplatin at Day 1, 8 of Cycle 1 to 4 and End of Treatment (last non-missing value recorded off-study but within 30 days after last dose), or immediately after early termination; for L-DOS47 only at Day 1, 8, 15 of additional Cycle x. For summary purposes, the Last Value will be defined as the last non-missing value after receiving study medication up to 30 days post last dose.

The absolute change from baseline will be summarized at each of the laboratory time points, using descriptive statistics (mean, median, SD, minimum, maximum) for hematology, blood chemistry and coagulation as specified below.

The changes from baseline to maximum CTCAE grade during the treatment period will be summarized using shift tables for every gradable hematology, blood chemistry and coagulation test. Maximum CTCAE Grade will be defined as the highest CTCAE version 4.0 Grade reported for a patient after first dose and up to 30 days post last dose.

A listing of patients with abnormal laboratory values defined as Grade 3 or 4 during the treatment period will be provided.

Laboratory tests include:
Hematology: hemoglobin, hematocrit, WBC, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands, combined other cells, sum of the differentials.

Blood Chemistry: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), urea, calcium, bicarbonate, chloride, creatinine (by Cockcroft-Gault formula), globulin (serum globulin: total protein minus serum albumin), glucose, phosphorus, potassium, sodium, magnesium, total bilirubin, total protein.

Coagulation: INR, PT, aPTT.

Urinalysis: glucose, total protein, ketones, bilirubin, occult blood.

8.7.5.2 Study Treatment Exposure and Compliance

The study drug L-DOS47 and the other two combined study treatment pemetrexed, carboplatin will be presented respectively. The number of cycles of study drug will be summarized using descriptive statistics (N, mean, median, standard deviation, and minimum, maximum). Study drug exposure will be summarized for Cycle 1 and for all treatment cycles combined. Duration of Exposure will be defined as the duration between the first and last dose of study drug (last date of study drug administration - first date of study drug administration + 1). Total Dose will be defined as the sum of all study drug administered. Total Intended Dose will be defined as the sum of the intended doses during the Duration of Exposure. Total intended dose is based on no modifications to dose or schedule. Total Prescribed Dose will be defined as the sum of all study drug prescribed during the Duration of Exposure. Total prescribed dose is based on any modifications to dose or schedule. The Percent Intended Dose will be defined as the total dose divided by the total intended dose multiplied by 100% for each patient. The percent compliance will be defined as the cumulative dose of study drug actually administered divided by the total prescribed dose multiplied by 100% for each patient. The frequency and percentage of patient receiving <100%, 100%, and >100% of their intended and prescribed dose will be summarized.

The number of patients with dose reduction, delay, interruption, and the reasons will each be summarized using frequency counts and percentages. The number of dose reduction, delay, interruption and their duration will also be summarized using descriptive statistics.

8.7.5.3 Concomitant Measures

Concomitant measures will be coded using the World Health Organization Drug Dictionary (WHO-DD version June 2014), tabulated by drug class and term, and summarized by frequency counts and percentages. Patients will be counted only once in each summary category (e.g., drug class or term). All medications that were ongoing at study start (Day 1) or started on Day 1 or thereafter up to and including 30 days after the last dose are concomitant.

8.7.5.4 ECOG Performance Status

ECOG status was collected at Baseline (last pre-treatment value from Day -28 to Day 1); for L-DOS47+Pemetrexed/Carboplatin at Day 1 of Cycle 1 to 4, and End of Treatment (last non-missing value recorded off-study but within 30 days after last dose), or immediately after early termination; for L-DOS47 only at Day 1 of additional Cycle x. The change from baseline score to maximum score over the treatment period will be summarized using a shift table.

8.7.5.5 Vital Signs

Vital signs were collected at Baseline (last pre-treatment value from Day -28 to Day 1); for L-DOS47+Pemetrexed/Carboplatin at Day 1, 8, 15 of Cycle 1 to 4, and End of Treatment (last non-missing value recorded off-study but within 30 days after last dose), or immediately after early termination; for L-DOS47 only at Day 1, 8, 15 of additional Cycle x. Vital signs including (temperature, pulse rate, blood pressure, respiratory rate, pulse oximetry will be summarized using descriptive statistics and provided in a listing for all time points. Height, weight and BSA will be summarized at baseline only.

8.7.5.6 Physical Exams

Physical exams were performed at Baseline (last pre-treatment value from Day -28 to Day 1), for L-DOS47+Pemetrexed/Carboplatin at Day 1, 8 of Cycle 1 to 4, and End of Treatment (last non-missing value recorded off-study but within 30 days after last dose), or immediately after early termination; for L-DOS47 only at Day 1, 8, 15 of additional Cycle x. Physical exam dates and indications of significant findings will be provided in a listing.

8.7.5.7 Cardiac Evaluations

ECG data was collected at Baseline (last pre-treatment value from Day -28 to Day 1); for L-DOS47+Pemetrexed/Carboplatin at Day 1, 8 of Cycle 1 to 4; and End of Treatment (last non-missing value recorded off-study but within 30 days after last dose), or immediately after early termination; for L-DOS47 only at Day 1, 8 of additional Cycle x.

ECG parameters include heart rate (HR), PR, QT, QTc and QRS. For each parameter, the values and change from baseline will be summarized using descriptive statistics (n, mean, median, standard deviation, minimum and maximum) at each scheduled assessment. In addition, the maximum change from baseline over the course of the study will also be summarized using descriptive statistics (n, mean, median, standard deviation, minimum and maximum). Prior to analysis, the triplicate values will be averaged for each patient.

For QT and QTc, the interval categories: ≤ 450 msec, > 450 msec, > 480 msec, and > 500 msec, will be summarized using descriptive statistics (frequency and percentage) at each scheduled assessment. The change from baseline categories: ≤ 30 msec increase, > 30 msec increase, and > 60 msec increase will also be summarized using descriptive statistics (frequency and percentage) at each scheduled assessment. In addition, the maximum interval and maximum increase from baseline over the course of the study will also be summarized using descriptive statistics (frequency and percentage). Prior to analysis, the triplicate values will be averaged for each patient.

8.7.5.8 Pharmacokinetics

Plasma samples for L-DOS47 PK were collected at allowable time windows (e.g., ± 5 min) from Cycle 1 through 4 at Day 1 and 8. PK parameters include maximum concentration (C_{max}), time of C_{max} (T_{max}), applicable area under the curve (AUC) parameters, terminal half-life (t½), systemic clearance (CL), volumes of distribution (V_z), volume of distribution at steady state (V_{ss}) and urinary excretion parameters.

The determination of PK parameters and summaries of descriptive statistics for plasma concentration time-point data and PK parameters are outside the scope of this RAP. The results of the evaluation will be compiled in a separate report.

8.7.5.9 Efficacy Analysis

Tumor assessments were to be performed at screening, unless results from appropriate scans performed within 28 days prior to the first dose of study drug are available and every other treatment cycle (i.e., every 6 weeks) until disease progression. Measurable lesions are defined as those that can be accurately measured in at least one dimension [longest diameter (LD)] with a minimum size of 10 mm by CT scan, 10 mm caliper measurement by clinical exam, or 20 mm by chest x-ray.

Best overall response will be assessed using RECIST version 1.1[1]. Frequency counts and percentages will be presented for the tumor response categories defined by RECIST 1.1. The objective overall antitumor response rate (CR or PR) will be defined as the proportion of patients with confirmed responses. The overall response rate and its 95% confidence interval will be calculated. For duration of response, life table estimates will be calculated using Kaplan-Meier methodology and the 95% confidence interval will be calculated for the median time. For duration of response, a patient alive with no disease progression will be censored at the date of the last evaluable tumor assessment.

8.7.5.9.1 Best Overall Response and Objective Response Rate

Best Overall Response:
Best Overall Response is defined as the best response assessment of target, non-target lesion and the appearance of new lesions from the start of study treatment until disease progression/recurrence, including unscheduled assessments. Valid response assessments ranked from best to worst are as follows: CR, PR, SD, and PD. CR and PR must be confirmed at least 4 weeks later. Symptomatic deterioration will not be considered PD when determining Best Overall Response. Best Overall Response for a patient without any evaluable assessments will be reported as Not Evaluable (NE).

The minimum duration of treatment for a valid assessment of Stable Disease is 42 days. Response data reported as Stable Disease (SD) that occurs before Study Day 42 will be

excluded from the determination of Best Overall Response. No minimum duration of treatment is required for assessments of complete response (CR) or partial response (PR).

A confirmatory scan for CR and PR is required and must be at least 4 weeks following initial documentation of the CR or PR; if this is not satisfied, that response will be considered unconfirmed. All unconfirmed assessments of CR and PR will be considered Stable Disease (SD) for the determination of Best Overall Response. A confirmed complete response is a CR which is followed by another CR without any intervening assessment of PD. A confirmed partial response is a PR preceded or followed by a CR or another PR, allowing for one interim assessment of SD.

Scheduled assessments having no data (i.e., incomplete assessment, not assessed, or missing) will be ignored and the best overall response will be based on the known assessments. However, if the first 2 (or more) scheduled assessments are not evaluable and followed by PD or death, Best Overall Response will be NE.

The percentage of patients in each of the best overall response categories (CR, PR, SD, PD, NE) will be calculated. Patients will be counted once in each of the response categories based on their best response assessment.

Best Overall Response and response date are captured on the Off-Study eCRF.

Objective Response Rate:
The objective response rate (ORR) is based on best overall response and is defined as the percentage of patients with a best overall response of CR or PR.

The two-sided 95% Clopper-Pearson confidence interval will be calculated for the objective response rate using the following SAS® code:

LowerCL = 1-betainv(1-alpha/2,N-x+1,x)
UpperCL = betainv(1-alpha/2,x+1,N-x)

where: N=sample size, X=number of responders, alpha=0.05 for a 95% confidence interval.[2]

Clinical Benefit Rate:
Clinical benefit will be calculated as the percentage of patients achieving complete response, partial response and stable disease, 95% CI is provided by the same method as above.

Summaries for Best Overall Response, ORR and clinical benefit will be presented for the Efficacy Evaluable, and Intent-to-Treat populations.

8.7.5.9.2 Duration of Response (CR or PR)

Duration of response is calculated from date of first response (first occurrence of CR or PR) to the first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause, whichever occurs first. For a patient without evidence of disease recurrence or objective disease progression or death, duration of response will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed PR or CR are included in the analysis.

If two or more consecutive tumor assessments have no data (incomplete assessment, not assessed, or missing) followed by a PD, the duration of response will be calculated at the time of the last prior assessment with valid data, and not at the time of PD. If a single assessment has no data, this assessment will be ignored and any prior and subsequent assessments will be used to determine the duration of response.

Life Table estimates are calculated using the Kaplan-Meier methodology. The 95% confidence interval for the median progression-free time will be presented and is calculated using the method by Brookmeyer and Crowley[3]. The 95% confidence intervals will be presented for point estimates of the survival distribution [1 months (30 days), 2 months (60 days), 3 months (90 days), 6 months (180 days), and 9 months (270 days) if applicable] using the method described by Kalbfleisch and Prentice[4]. The Kaplan-Meier curve for the duration of response will also be presented. These summaries will be presented for the Efficacy Evaluable populations.

The derived data used in the summarization of the duration of response will also be provided. These listings will include the patient number, treatment information, response, date of response (CR or PR), date of progression or censoring, and the duration of response in days.

8.7.6 Programming Considerations

All tables, data listings, figures (TLFs), and statistical analyses are generated using SAS® Version 9.4.

8.7.6.1 TLF Outputs

Unless otherwise noted, the estimated mean and median for a set of values are printed out to one more significant digit than the original values, and standard deviations are printed out to 2 more significant digits than the original values. The minimum and maximum report the same significant digits as the original values. For example, for age:

N	XX
Mean	XX.X

Standard Deviation	X.XX
Median	XX.X
Minimum	XX
Maximum	XX

Percentage values are printed with one digit to the right of the decimal point in parentheses 1 space after the count (e.g., 7 (12.8%), 13 (5.4%)).

For patient listings and variables with numeric fields, trailing zeroes to the right of the decimal point are not displayed.

Missing data in patient listings is represented as "NA" or "ND", with the footnote "NA = not applicable" or "ND = not done". Missing descriptive statistics due to non-estimability are reported as "-".

8.7.6.2 Data Conventions and Rules

This section provides rules for calculations and definitions for naming conventions that are common to all applicable tables.

The baseline value of a variable is defined as the last value obtained on or before the administration date and time of the first study drug dose.

For any variable where percent change from baseline is evaluated at Visit X: Percent Change from Baseline value = [(Visit X value - Baseline value)/Baseline value] x100

For any variable where absolute change from Baseline is evaluated at Visit X: Absolute Change from Baseline value = Visit X value - Baseline value

Concomitant medications missing both start and stop dates, or having a start date prior to the last dose of study drug and missing the stop date, or having a stop date after the start of study drug and missing the start date, are counted as concomitant.

Relative Study Day: The first day of treatment is Day 1. A minus (-) sign indicates days prior to the start of treatment (e.g., Day -3 represents 3 days before start of therapy; there is no Day 0). The relative study day for a specific visit (day of study relative to start of treatment) is calculated as: Visit Date - Date of First Dose +1 (for post-treatment visits) and Visit Date - Date of First Dose (for pre-treatment visits).

Relative Cycle Day: Cycle X Day 1 is the first day of dosing within the cycle. The relative cycle day for a specific visit (relative to first dosing day within the cycle) is calculated as: Visit Date - Date of First Dose Within Cycle + 1.

8.8 Changes in the Conduct of the Study or Planned Analyses

Conduct of the Study

The protocol and amendments are presented in Appendix 16.1. The original protocol was dated March 5, 2014. Version 1.1 of the protocol, dated April 22, 2014, was the first version used to enroll and treat patients. The protocol was subsequently updated three times.

In Amendment 1, dated June 2, 2015:

- The protocol mandated washout period was minimized to 7 days for patients treated with an EGFR tyrosine kinase inhibitor and/or for patients treated with an ALK inhibitor.
- Patients had to have no prior adjuvant chemotherapy within 6 months (shortened from 12 months) of the first treatment day if there was recurrent disease.
- Patients with treated and stable brain metastases could enroll if they were off steroids and not taking antiepileptics for brain metastases; patients with brain metastases that were active, symptomatic, or required treatment with steroids or antiepileptics were excluded.
- The instructions for L-DOS47 preparation were updated to include the guidance that full weight-based doses would be used to treat obese patients.
- The option to delayed treatment with pemetrexed and carboplatin for up to 42 days to allow recovery from drug-related pemetrexed and/or carboplatin toxicity was removed.
- The start of the adverse event/serious adverse event reporting period was defined as commencing after the initial dosing of pemetrexed premedication.
- Minor clarifications were made to timing and conduct of study evaluations.

In Amendment 2, dated September 28, 2016:

- The allowed interval for progression of disease documented after end of adjuvant treatment prior to enrollment was shortened from "≥ 12 months" to "≥ 6 months".
- The L-DOS47 infusion time could be increased from 30 minutes to 60 minutes in the event of mild infusion reaction; it was specified that the L-DOS47 infusion bag had to be used within 3 hours of preparation.
- The dose escalation scheme was modified: planned dose levels changed from "0.46, 0.59, 0.78, 1.04, 1.38, and 1.84 μg/kg" to "0.46, 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, and 12.0 μg/kg"; planned dose reductions were modified accordingly.
- Clarification was added to the PK sampling times in the event the L-DOS47 infusion time was increased from 30 minutes to 60 minutes in the event of a mild infusion reaction.

- Allowable time windows (e.g., ± 5 min) were added to ECGs, vital signs monitoring, and collection of PK samples; selected timepoints for ECGs, vital signs monitoring and PK sample collections were removed.
- Cycle 5, Day 1 assessments did not need to be repeated if the end of Cycle 4 evaluations were performed within 7 days prior to Day 1 of Cycle 5.
- Due to the addition of cohorts 6 and 7 to the dose escalation scheme, the anticipated total number of patients to be enrolled in the study increased from 40 to 52 patients.

In Amendment 3, dated August 10, 2017:

- An accelerated "1+2" dose design, up to the L-DOS47 dose level of 6µg/kg, was implemented and to be followed by the standard "3+3" design for the final two L-DOS47 dosing cohorts of 9 and 12 µg/kg.
- The anticipated total number of patients to be enrolled in the study decreased from 52 to 37 patients.
- In the accelerated dose escalation phase of the study, the definition of dose limiting toxicity (DLT) was updated to also include "One instance each of two unique grade 2 adverse events" that occurred within 21 days after commencing study drug treatment and considered to be possibly, probably, or definitely related to L-DOS47 by the Investigator.
- Chandra Belani, MD (Penn State Hershey) was removed from the list of Investigators and the Sponsor's address and phone number were updated.

Planned Analysis

There were no changes to the planned analysis.

9.0 Study Patients

A total of nnn patients were enrolled as shown in Table 1. The first patient was enrolled on xx Month year and treated beginning on xx Month year. The final patient was removed from the study on xx Month year. The study populations are summarized in Table 1.

Table 1: Study Populations
All Enrolled
(N=n)
LDOS001 Phase I Study

Study Populations	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
All Enrolled [1]	nnn (100.0%)	nnn (100.0%)	nnn (100.0%)
Met All Eligibility Criteria	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Did Not Meet Eligibility Criteria	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Inclusion	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Exclusion	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Waiver Granted	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Safety Evaluable [2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Efficacy Evaluable [3]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Patients who consented to participate in the study. Number of All Enrolled patients used as denominator to calculate percentages.
[2] Patients treated with any amount of L-DOS47 or Pemetrexed premedication.
[3] Patients who met the eligibility criteria with baseline measurable disease, completed 2 cycles of study therapy, and had at least one post- baseline tumor assessment, or, patients with less than 2 cycles of study therapy must have clear evidence of clinical progression to be considered evaluable for efficacy.
Note: waivers no longer granted after eCRF update post-March 2018 Helix audit.

Cross-References: Appendix Listings 16.2.1.1, 16.2.1.2.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.

9.1 Disposition of Patients

Of the nnn patients treated in the study, [insert description of reasons patient went off study here]. Patient disposition is summarized in Table 2.

Table 2: Patient Disposition
All Enrolled
(N=n)
LDOS001 Phase I Study

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
Patient Disposition	Dose 1	Repeat	Overall
Number of Treated Patients	nnn	nnn	nnn
Patients Off-Study [1]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Reasons for Off-Study [2]			
Off-Study Reason	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Off-Study Reason	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Off-Study Reason	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Off-Study Reason	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Off-Study Reason	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Off-Study Reason	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Off-Study Reason	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Treated Patients used as denominator to calculate percentages.
[2] Patients Off-Study used as denominator to calculate percentages.

Cross-References: Appendix Listing 16.2.1.2.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Only present Off-Study reason categories that are used in the database from the "Off-Study" CRF.
Sort "Reasons for Off-Study" in descending order of "Overall" frequency.

9.2 Protocol Deviations

Instances of noncompliance and resulting protocol deviations were collected in Monitor Express. Protocol deviations are [insert the deviations if data is available, otherwise there were no important deviations noted during the study].

10.0 Efficacy and Pharmacokinetic Evaluations

10.1 Data Sets Analyzed

The patient populations analyzed in this report are as follows:

Intent-to-Treat Population (N=nnn): All patients registered in the study whether or not they met the eligibility criteria or received study treatment. This population will be summarized for demographics and other baseline characteristics, and serve as the secondary analysis population for efficacy.

Safety Evaluable Population (N=nnn): All patients who received any amount of L-DOS47, or Pemetrexed premedication. This population will be summarized for all safety parameters.

Efficacy Evaluable Population (**N=nnn**): All patients who met the eligibility criteria with baseline measurable disease, completed 2 cycles of study therapy, and had at least one post-baseline tumor assessment. For patients with fewer than 2 cycles of study treatment, there must be clear evidence of clinical progression to be considered evaluable for efficacy. The efficacy-evaluable population will be the primary analysis population for efficacy.
[Insert description of patient exclusions here, if applicable.]

10.2 Patient Demographic and Other Baseline Characteristics

10.2.1 Demographics and Baseline Characteristics

Demographic characteristics are summarized in Table 3. Of the nnn patients treated in the study, nnn patients (xx.x%) were male and nnn female (xx.x%). The median age was xx.x years (range: xx to xx). xx patients (xx.x%) were [insert Ethnic Origin discussion here]. At baseline, nnn patients (xx.x%) had ECOG performance status of 0, nnn patients (xx.x%) had ECOG status of 1.

Table 3: Demographic Characteristics
Intent-to-Treat
(N=n)
LDOS001 Phase I Study

Demographic Characteristics	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Number of Patients [1]	nnn	nnn	nnn
Age (years)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
18 to 64	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
65 +	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Unknown	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Gender			
Female	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Male	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
BSA (m^2)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Race			
Asian	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
White	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Black or African American	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Native Hawaiian or Pacific Islander	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
American Indian or Alaska Native	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Not Reported	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Other	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Ethnicity			
Hispanic or Latino	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Not Hispanic or Latino	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
ECOG Performance Status			
0	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
1	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.

Cross-References: Appendix Listings 16.2.4.1 and 16.2.9.3.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.

The exact age was calculated in years without decimal places as follows:

Age (years) = (Year of On-Study – Year of Birth) – Correction

Where: Correction = 1, if Birth Month > On-Study Month or Birth Month = On-Study Month and Birth Day > On-Study Day
Else: Correction = 0
Sort Age categories as shown in table.
Sort Gender categories in descending order of "Overall" frequency.
Sort Race categories in descending order of "Overall" frequency.
Sort Ethnicity categories in descending order of "Overall" frequency.
Sort ECOG Performance Status categories as shown in table.

10.2.2 Baseline Disease Characteristics

Baseline disease characteristics are summarized in Table 4. Histopathology was [insert histopathology discussion here]. The median duration of disease for all patients, calculated from the Date of Initial Diagnosis to the Date of Inform Consent Form, was xxxx.x (Months) (range: xxxx to xxxx Months).

Table 4: Baseline Disease Characteristics
Intent-to-Treat
(N=n)
LDOS001 Phase I Study

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
Disease Characteristics	Dose 1	Repeat	Overall
Number of Patients	nnn	nnn	nnn
Histopathology [1]			
Histopathology Reported	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Histopathology Reported	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Duration of Disease (Months)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx

[1] Number of Patients used as denominator to calculate percentages.

Cross-References: Appendix Listing 16.2.4.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Duration is calculated in Months: (Date of Informed Content - Date of Initial Diagnosis)/(365.25/12).
Sort categories in descending order of "Overall" frequency.

10.2.3 Prior Cancer Therapy

Prior cancer therapies are summarized in Table 5; patients may have been treated with more than one category of prior therapy. [Insert prior therapy discussion here for each category.]

Table 5: Prior Cancer Therapy
Intent-to-Treat
(N=n)
LDOS001 Phase I Study

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
Prior Therapy [1]	Dose 1	Repeat	Overall
Number of Patients [2]	nnn	nnn	nnn
Number of Patients With:			
Prior Chemotherapy	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Prior Immunotherapy	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Prior Hormonal Therapy	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Other Prior Therapy	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Prior Cancer Radiation	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Prior Cancer Surgeries	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Patients may be counted in more than one prior therapy category.
[2] Number of Patients used as denominator to calculate percentages.

Cross-References: Appendix Listings 16.2.4.2, 16.2.4.3, 16.2.4.4.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Prior Therapies include Chemotherapy, Hormonal Therapy, Immunotherapy, Other therapy, Prior Radiation Therapy and Prior Cancer Surgeries.
Patient counts presented.
Patient may be in more than one prior therapy category.

10.2.4 Concomitant Measures

All medications that were ongoing at study start (Day 1) or taken on Day 1 or thereafter up to 30 days post last dose are summarized in Attachment Table 14.1.2. Table 6 presents all medications that were ongoing at study start (Day 1) or taken on Day 1 or thereafter up to 30 days post last dose in at least XX% of safety patients (> nnn patients). [Insert concomitant measures discussion here.]

Table 6: Summary of Concomitant Measures Received by at Least XX% of Patients
Safety Evaluable
(N=n)
LDOS001 Phase I Study

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
WHO-DD ATC Class Category Level II [1][2]	Dose 1	Repeat	Overall
Number of Patients [3]	nnn	nnn	nnn
Number of Patients Taking Concomitant Measures	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Patients may be counted in more than one therapeutic class; patients are only counted once within a therapeutic class.
[2] Summarizes medications that were ongoing at study start (Day 1) or started on Day 1 or thereafter up to 30 days post last dose.
[3] Number of Patients used as denominator to calculate percentages.

Cross-References: Attachment Table 14.1.2 and Appendix Listing 16.2.10.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Present all "Therapeutic Class" categories found in the database.
Only present concomitant measures that occur in XX% or more of patients.
Sort "Therapeutic Class" column in descending order based on column frequency count.

10.3 Measurements of Treatment Compliance

Patients received L-DOS47 intravenously for 30 to 60 minutes on Days 1, 8 and 15 of each cycle for the first 4 cycles or until the evidence of disease progression, intolerable adverse events, or withdrawal of patient consent. Pemetrexed and carboplatin were infused on Day 1 of the first 4 cycles.

The drug administration data are presented in Appendix 16.2.5.1 and are summarized in Table 10 through Table 12 in Section 12.1.

10.4 Efficacy Results and Tabulation of Individual Patient Data

Patients were assessed for tumor response and evidence of disease progression after every 6 weeks. Tumor response was evaluated using RECIST version 1.1. Of the nnn Intent-to-Treat patients in the study, nnn were evaluable for response. The efficacy

evaluable population served as the primary analysis population; the intent-to-treat served as the secondary analysis population.

10.4.1 Best Overall Response

Of the nnn patients in the efficacy evaluable population, nnn patients (xx.x%) had CR, nnn patients (xx.x%) had PR, nnn patients (xx.x%) had SD as their best response to therapy, nnn patients (xx.x%) had PD and nnn patients (xx.x%) were NE. The Objective Response Rate is xx.x% (95% CI: xx.x%, xx.x%). The Clinical Benefit Rate is xx.x% (95% CI: xx.x%, xx.x%). Best Overall Response, Objective Response and Clinical Benefit are summarized in Table 7.

Table 7: Best Overall Response Summary
Efficacy Evaluable
(N=n)
LDOS001 Phase I Study

Best Overall Response	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Number of Patients [1]	nnn	nnn	nnn
Complete Response (CR)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Partial Response (PR)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Stable Disease (SD)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Progressive Disease (PD)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Not Evaluable	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Objective Response Rate (CR+PR) [2][4]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Lower 95% Confidence Limit	xx.x%	xx.x%	xx.x%
Upper 95% Confidence Limit	xx.x%	xx.x%	xx.x%
Clinical Benefit (CR+PR+SD) [3][4]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Lower 95% Confidence Limit	xx.x%	xx.x%	xx.x%
Upper 95% Confidence Limit	xx.x%	xx.x%	xx.x%

[1] Number of Patients used as denominator to calculate percentages.
[2] Objective Response Rate is based on patients with either a Complete Response (CR) or Partial Response (PR).
[3] Clinical Benefit is based on patients with either a CR or PR or SD (stable disease).
[4] Clopper-Pearson method used for the calculation of the 95% confidence interval.

Cross-References: Appendix Listings 16.2.6.1 - 16.2.6.3.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Assumptions: Assessments of SD before Study Day 42 were treated as missing. Confirmatory scans for CR and PR must have been at least 4 weeks (28 days) following initial documentation of a valid objective response or that response was considered unconfirmed. If scheduled assessments had no data (incomplete assessment, not assessed, or missing), the best overall response was based upon the known assessments.
The two-sided 95% Clopper-Pearson confidence interval was calculated for the response rates using the following SAS® code:

```
LowerCL = 1-betainv(1-alpha/2,N-x+1,x)
UpperCL = betainv(1-alpha/2,x+1,N-x)
```

where: N=sample size, X=number of responders, alpha=0.05 for a 95% confidence interval [2].

Of the nnn patients in the Intent-to-Treat population, nnn patients (xx.x%) had CR, nnn patients (xx.x%) had PR, nnn patients (xx.x%) had SD as their best response to therapy, nnn patients (xx.x%) had PD and nnn patients (xx.x%) were NE. The Objective Response Rate is xx.x% (95% CI: xx.x%, xx.x%). The Clinical Benefit Rate is xx.x% (95% CI: xx.x%, xx.x%). Best Overall Response, Objective Response and Clinical Benefit are summarized in Table 8. Figure 1 is a Waterfall Plot to show best change in lesion size from baseline overtime.

Table 8: Best Overall Response Summary
Intent-to-Treat
(N=n)
LDOS001 Phase I Study

Best Overall Response	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Number of Patients [1]	nnn	nnn	nnn
Complete Response (CR)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Partial Response (PR)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Stable Disease (SD)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Progressive Disease (PD)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Not Evaluable	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Objective Response Rate (CR+PR) [2][4]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Lower 95% Confidence Limit	xx.x%	xx.x%	xx.x%
Upper 95% Confidence Limit	xx.x%	xx.x%	xx.x%
Clinical Benefit (CR+PR+SD) [3][4]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Lower 95% Confidence Limit	xx.x%	xx.x%	xx.x%
Upper 95% Confidence Limit	xx.x%	xx.x%	xx.x%

[1] Number of Patients used as denominator to calculate percentages.
[2] Objective Response Rate is based on patients with either a Complete Response (CR) or Partial Response (PR).
[3] Clinical Benefit is based on patients with either a CR or PR or SD (stable disease).
[4] Clopper-Pearson method used for the calculation of the 95% confidence interval.

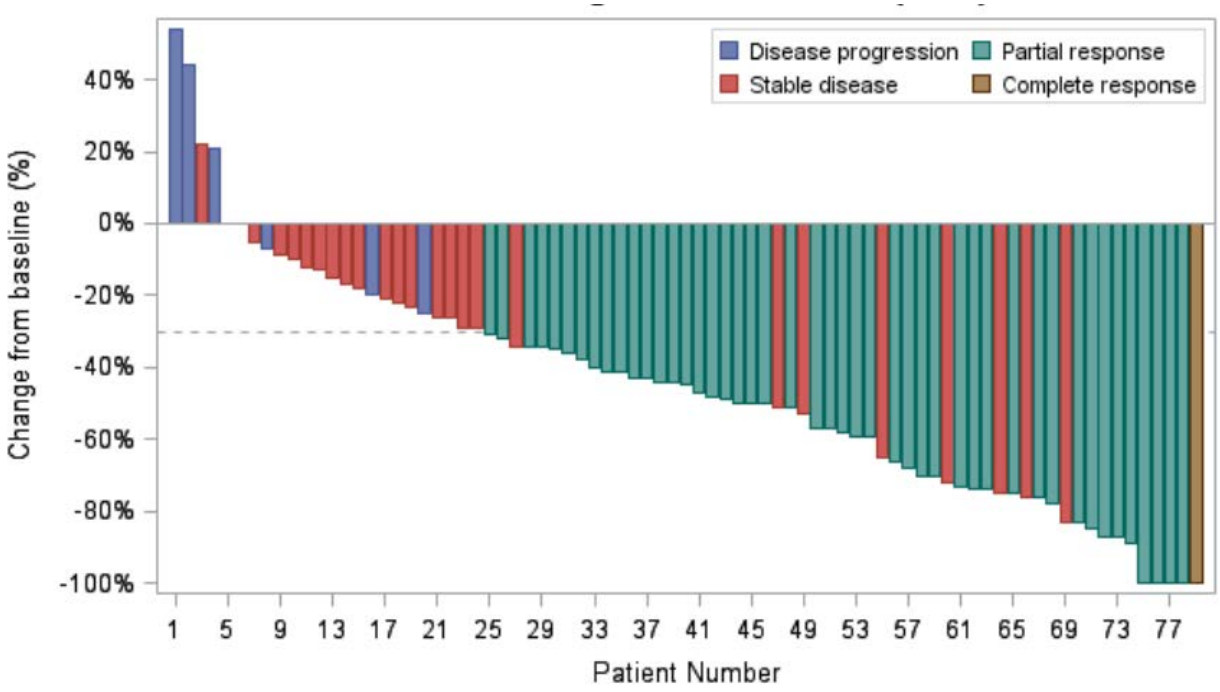
Cross-References: Appendix Listings 16.2.6.1 - 16.2.6.3.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Assumptions: Assessments of SD before Study Day 42 were treated as missing. Confirmatory scans for CR and PR must have been at least 4 weeks (28 days) following initial documentation of a valid objective response or that response was considered unconfirmed. If scheduled assessments had no data (incomplete assessment, not assessed, or missing), the best overall response was based upon the known assessments.
The two-sided 95% Clopper-Pearson confidence interval was calculated for the response rates using the following SAS® code:

LowerCL = 1-betainv(1-alpha/2,N-x+1,x)
UpperCL = betainv(1-alpha/2,x+1,N-x)

where: N=sample size, X=number of responders, alpha=0.05 for a 95% confidence interval [2].

Figure 1: Best Change in Lesion Size from Baseline Overtime (Waterfall Plot)
Efficacy Evaluable
(N=n)
LDOS001 Phase I Study



PROGRAMMER'S NOTE: Use Efficacy Evaluable population. Present patient ID on X-axis; percentage of best change in lesion from baseline for target lesions on Y-axis.
Cross-References: Appendix Listing 16.2.6.1- 16.2.6.3

10.4.2 Duration of Response

Duration of response is calculated from date of first response (first occurrence of CR or PR) to the first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patient without evidence of objective disease progression or death, duration of response will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed PR or CR are included in the analysis. Duration of response is summarized in Table 9 for the efficacy evaluable population. Of the [nnn] patients who had a CR or PR, the median duration of response was xxx days (95% CI: xxx days, xxx days). The progression-free rate at 1 month (30 days) was xx.x%, at 2 months (60 days) was xx.x%, xx.x%, at 3 months (90 days), xx.x% at 6 months (180 days), and xx.x% at 9 months (270 days), if applicable.

Duration of clinical benefit is calculated from date of first occurrence CR or PR or SD to the first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause, is also summarized in Table 10. Only patients with a SD or confirmed CR or PR are included in the analysis. Of the [nnn] patients who

had clinical benefit, the median duration of clinical benefit was xxx days (95% CI: xxx days, xxx days).

Table 9: Life Table Summary of Duration of Response
Efficacy Evaluable
(N=n)
LDOS001 Phase I Study

Duration of Response	Overall
Number of Patients	nnn
Number of Events	xx (xx.x%)
Number Censored	xx (xx.x%)
Duration of Response[1][2]	
75% Duration	xxx days
Median	xxx days
Lower 95% Confidence Limit	xx.x%
Upper 95% Confidence Limit	xx.x%
25% Duration	xxx days
Progression-Free Rate	
1 Month (30 days)	xx.x%
2 Month (60 days)	xx.x%
3 Months (90 days)	xx.x%
6 Months (180 days)	xx.x%
9 Months (270 days)	xx.x%

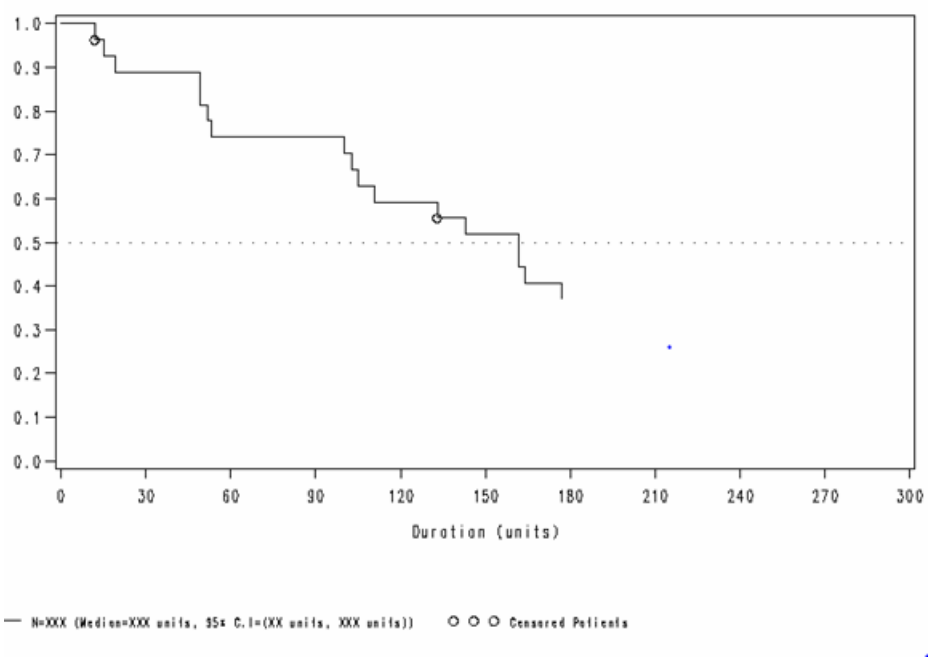
[1] Duration of Response is calculated from date of first response (first occurrence of CR or PR) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patient without evidence of objective disease progression or death, duration of response will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed PR or CR are included in the analysis.
[2] Life Table estimates are calculated using Kaplan-Meier methodology. Confidence interval for the median duration time is calculated using the method by Brookmeyer and Crowley.

Cross-References: Attachments Table 14.2.1.1, Figure 2, and Appendix Listing 16.2.6.1-16.2.6.3

PROGRAMMER'S NOTES:
Only include if CR or PR responses are found in the database.
Life Table estimates are calculated using Kaplan-Meier methodology. Confidence interval for the median survival time is calculated using the method by Brookmeyer and Crowley.

The Kaplan-Meier curve for the duration of response for the efficacy evaluable population is presented in Figure 2. The point where the Kaplan-Meier curve crosses the horizontal reference line represents the median duration of response.

Figure 2: Duration of Response
Efficacy Evaluable
(N=n)
LDOS001 Phase I Study



Duration of Response is calculated from date of first response (first occurrence of CR or PR) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patient without evidence of objective disease progression or death, duration of response will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed PR or CR are included in the analysis.

Cross-References: Attachments Tables 9, Table 14.2.1.1, and Appendix Listing 16.2.6.1-16.2.6.3.

PROGRAMMER'S NOTES:
Only include if CR or PR responses are found in the database.
Kaplan-Meier curve generated using SAS. Draw horizontal reference line representing 50% level (median).
Present Progression Free Survival Probability on y-axis.

Table 10: Life Table Summary of Duration of Clinical Benefit
Efficacy Evaluable
(N=n)
LDOS001 Phase I Study

Duration of Response	Overall
Number of Patients	nnn
Number of Events	xx (xx.x%)
Number Censored	xx (xx.x%)
Duration of Clinical Benefit [1][2]	
75% Duration	xxx days
Median	xxx days
Lower 95% Confidence Limit	xx.x%
Upper 95% Confidence Limit	xx.x%
25% Duration	xxx days
Progression-Free Rate	
1 Month (30 days)	xx.x%
2 Month (60 days)	xx.x%
3 Months (90 days)	xx.x%
6 Months (180 days)	xx.x%
9 Months (270 days)	xx.x%

[1] Duration of Clinical Benefit is calculated from date of first (CR or PR or SD) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patient without evidence of objective disease progression or death, duration of clinical benefit will be censored at the date of the last evaluable tumor assessment. Only patients with a SD or confirmed CR or PR are included in the analysis.

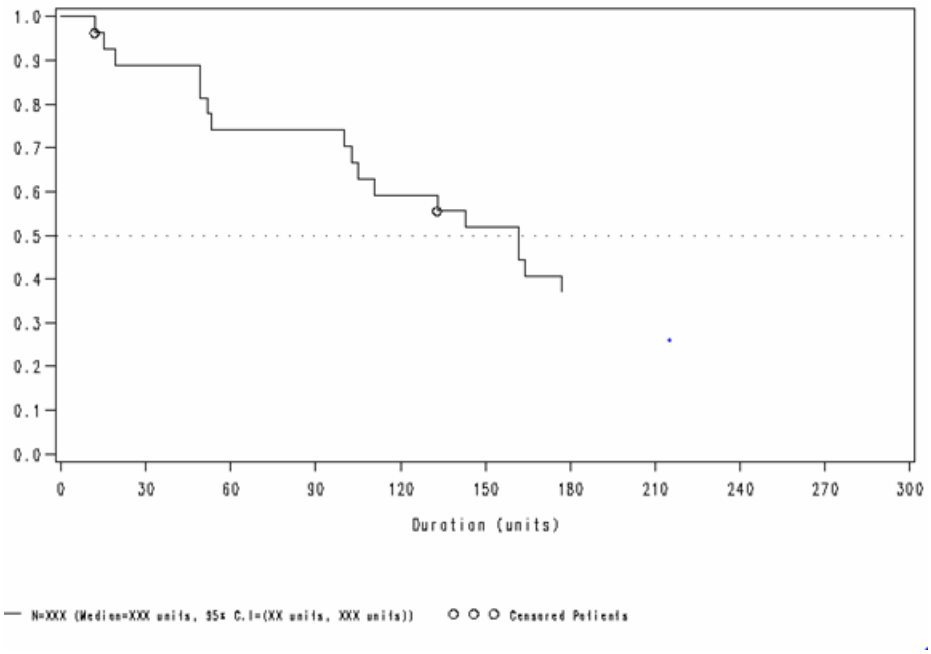
[2] Life Table estimates are calculated using Kaplan-Meier methodology. Confidence interval for the median duration time is calculated using the method by Brookmeyer and Crowley.

Cross-References: Attachments Table 14.2.1.1, Figure 3, and Appendix Listing 16.2.6.1-16.2.6.3

PROGRAMMER'S NOTES:
Only include if CR or PR responses are found in the database.
Life Table estimates are calculated using Kaplan-Meier methodology. Confidence interval for the median survival time is calculated using the method by Brookmeyer and Crowley.

The Kaplan-Meier curve for the duration of clinical benefit for the efficacy evaluable population is presented in Figure 3. The point where the Kaplan-Meier curve crosses the horizontal reference line represents the median duration of clinical benefit.

Figure 3: Duration of Clinical Benefit
Efficacy Evaluable
(N=n)
LDOS001 Phase I Study



Duration of Clinical Benefit is calculated from date of first (CR or PR or SD) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patient without evidence of objective disease progression or death, duration of clinical benefit will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed SD or CR or PR are included in the analysis.

Cross-References: Attachments Tables 10, Table 14.2.1.1, and Appendix Listing 16.2.6.1-16.2.6.3.

PROGRAMMER'S NOTES:
Only include if CR or PR responses are found in the database.
Kaplan-Meier curve generated using SAS. Draw horizontal reference line representing 50% level (median).
Present Progression Free Survival Probability on y-axis.

10.4.3 Analysis of Efficacy

There were no statistical comparisons planned among the dose cohorts. All data summaries were descriptive. Statistical methods are presented in Appendix 16.1.9.

10.4.4 Statistical/Analytical Issues

There are no specific hypothesis related to the analysis. The 95% Clopper-Pearson confidence intervals were calculated for objective response rates.[2]

10.4.5 Tabulation of Individual Response Data

Patient listing of target and non-target lesion evaluations are provided in Appendix Listing 16.2.6.1. The individual patient response at each tumor assessment is provided in Appendix Listing 16.2.6.2.

10.4.6 Drug Dose, Drug Concentration and Relationships to Response

[Insert discussion on drug concentration and dose-response, if data is available.]

10.4.7 Drug-Drug and Drug-Disease Interactions

[Insert relationship between response and concomitant therapy and between response and past and/or concurrent illness, if data is available.]

10.4.8 By-Patient Displays

Not applicable.

10.4.9 Efficacy Conclusions

A total of nnn patients were evaluated for efficacy in the efficacy-evaluable population. The Objective Response Rate was xx.x% (95% CI: xx.x%, xx.x%). The clinical benefit rate was xx.x% (95% CI: xx.x%, xx.x%). [Insert additional efficacy summary described here.]

10.5 Pharmacokinetic Results

[Insert PK summary here, or "The PK results will be presented in a separate report."]

11.0 Safety Evaluation

Protocol specified time windows in Protocol Table 10 Schedule of study evaluation were used for applicable safety table assessments.

11.1 Extent of Exposure, Compliance and Dose

A total of nnn patients (xx.x%) received study therapy and were therefore evaluable for safety.

Patients received L-DOS47 intravenously on Days 1, 8 and 15 of each cycle for the first 4 cycles or until the evidence of disease progression, intolerable adverse events, or withdrawal of patient consent. Drug administration and compliance during Cycle 1, and for all treatment cycles are summarized in the following sections. The other study treatment Pemetrexed and Carboplatin will also be summarized separately.

11.1.1 Cycle 1

Study drug L-DOS47 administration, intended dose and compliance are summarized in Table 11 for Cycle 1 only. The median duration of exposure was xxx.x days (range: xxx to xxx days). Percent Compliance was calculated by dividing the cumulative dose of study drug actually administered during Cycle 1 by the prescribed cumulative dose during Cycle 1. Median compliance was xxx.xx% (range: xxx.x% to xxx.x%) with nnn patients receiving 100% of their prescribed dose, nnn patients receiving < 100% and nnn patients receiving > 100%. Percent Intended Dose was calculated as the cumulative dose of study drug actually administered during Cycle 1 divided by the intended cumulative dose during Cycle 1. Median intended dose was xxx.xx% (range: xxx.x% to xxx.x%) with nnn patients receiving 100% of their intended dose, nnn patients receiving < 100% and nnn patients receiving > 100%.
[Insert dose relationship discussion here].

Table 11: Summary of L-DOS47 Administration and Compliance During Cycle 1
Safety Evaluable
(N=n)
LDOS001 Phase I Study

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
L-DOS47 Administration	Dose 1	Repeat	Overall
Number of Patients	nnn	nnn	nnn
Duration of Exposure (days) [1]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Total Dose (mg) [2]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Total Intended Dose (mg) [3]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Total Prescribed Dose (mg) [4]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Percent Intended Dose (%) [5]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Percent Compliance (%) [6]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx

Table 11: Summary of L-DOS47 Administration and Compliance During Cycle 1
Safety Evaluable
(N=n)
LDOS001 Phase I Study

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
L-DOS47 Administration	Dose 1	Repeat	Overall
Maximum	xx	xx	xx
Percent Intended Dose Category [7]			
>100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
<100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Percent Compliance Category [7]			
>100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
<100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Duration of Exposure was defined as the duration between the first and last dose of L-DOS47 for Cycle 1.
[2] Total Dose was defined as the sum of all L-DOS47 administered.
[3] Total Intended Dose was defined as the sum of the intended doses, ie, total intended dose based on no modifications to dose or schedule.
[4] Total Prescribed Dose was defined as the sum of the prescribed doses, ie, total prescribed dose based on any modifications to dose or schedule.
[5] The Percent Intended Dose was defined as the cumulative dose of study drug actually administered divided by the total intended dose multiplied by 100% for each patient.
[6] The Percent Compliance was defined as the cumulative dose of study drug actually administered divided by the prescribed dose multiplied by 100% for each patient.
[7] Number of Patients used as denominator to calculate percentages.

Cross-References: Appendix Listing 16.2.5.1.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Summarize for Cycle 1 only.
Compliance categories may need to be modified based on the data.

11.1.2 All Treatment Cycles

Study drug L-DOS47 administration, intended dose and compliance are summarized in Table 12 for all treatment cycles combined. The median number of treatment cycles received was xxx.x cycles (range: xxx to xxx cycles) and the median duration of exposure was xxx.x days (range: xxx to xxx days). Percent Compliance was calculated by dividing the cumulative dose of study drug actually administered by the prescribed cumulative dose. Median compliance was xxx.xx% (range: xxx.x% to xxx.x%) with nnn patients receiving 100% of their prescribed dose, patients receiving < 100% and nnn patients receiving > 100%. Percent Intended Dose was calculated as the cumulative dose of study drug actually administered for all cycles only divided by the intended cumulative dose for all cycles. Median intended dose was xxx.xx% (range: xxx.x% to xxx.x%) with nnn patients

receiving 100% of their intended dose, nnn patients receiving < 100% and nnn patients receiving > 100%. [Insert dose relationship discussion here.]

Table 12: Summary of L-DOS47 Administration and Compliance for All Treatment Cycles
Safety Evaluable
(N=n)
LDOS001 Phase I Study

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
L-DOS47 Administration	Dose 1	Repeat	Overall
Number of Patients	nnn	nnn	nnn
Number of Cycles			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Duration of Exposure (days) [1]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Total Dose (mg) [2]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Total Intended Dose (mg) [3]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Total Prescribed Dose (mg) [4]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx

Table 12: Summary of L-DOS47 Administration and Compliance for All Treatment Cycles
Safety Evaluable
(N=n)
LDOS001 Phase I Study

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
L-DOS47 Administration	Dose 1	Repeat	Overall
Percent Intended Dose (%) [5]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Percent Compliance (%) [6]			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Percent Intended Dose Category [7]			
>100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
<100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Percent Compliance Category [7]			
>100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
<100%	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Duration of Exposure was defined as the duration between the first and last dose of study drug for all cycles.
[2] Total Dose was defined as the sum of all study drug administered.
[3] Total Intended Dose was defined as the sum of the intended doses, ie, total intended dose based on no modifications to dose or schedule.
[4] Total Prescribed Dose was defined as the sum of the prescribed doses, ie, total prescribed dose based on any modifications to dose or schedule.
[5] The Percent Intended Dose was defined as the cumulative dose of study drug actually administered divided by the total intended dose multiplied by 100% for each patient.
[6] The Percent Compliance was defined as the cumulative dose of study drug actually administered divided by the prescribed dose multiplied by 100% for each patient.
[7] Number of Patients used as denominator to calculate percentages.

Cross-References: Appendix Listing 16.2.5.1.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Summarize for all treatment cycles.
Compliance categories may need to be modified based on the data.

The number of patients with dose reductions, dose delay, dose interruptions, and dose discontinuations are summarized in Table 13. [Add text]

Table 13: Summary of Patients with L-DOS47 Dose Reductions/Delay/Interruptions/Discontinuations
Safety Evaluable
(N=n)
LDOS001 Phase I Study

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
L-DOS47 Administration	Dose 1	Repeat	Overall
Number of Patients[1]	nnn	nnn	nnn
Patients with No Dose Reduction	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Reduction Due to AE	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Reduction Due to Non-compliance	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Reduction Due to Other Reasons	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with No Dose Delay	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Delay Due to AE	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Delay Due to Non-compliance	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Delay Due to Other Reasons	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with No Dose Interruption	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Interruption Due to AE	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Interruption Due to Non-compliance	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Interruption Due to Other Reasons	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Any Dose Interruption (at least one)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
One Interruption	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Two Interruptions	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Etc for 3,4…			
Patients with Dose Reduction and Interruption	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to AE	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to Non-compliance	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to Other Reasons	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Delay and Reduction	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to AE	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to Non-compliance	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to Other Reasons	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Delay and Interruption	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to AE	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to Non-compliance	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to Other Reasons	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Delay, Reduction and Interruption	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to AE	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Due to Non-compliance	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

Due to Other Reasons	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Patients with Dose Discontinuation Due to AE [1]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.

Cross-References: Appendix Listing 16.2.5.1.1, 16.2.7.2.1 - 16.2.7.2.8

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.

11.2 Adverse Events

All reported adverse events were converted to preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA Version 17.1) translation dictionary . Adverse events were categorized by system organ class and preferred term. Treatment-Emergent Adverse Events (TEAEs) were defined as all AEs that occurred after the first dose of study medication up to 30 days post last dose. AEs were graded according to NCI CTCAE (Version 4.0). Patients with multiple TEAEs were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category.

11.2.1 Brief Summary of Adverse Events

Table 14 presents the overall summary of the TEAEs that were reported during the study. Sections 12.2.2 through 12.2.2.4 present the summary of TEAEs by system organ classes, preferred terms, the events reported most frequently, the events considered to be related to study therapy, the most severe events, and the events considered to be both related to study therapy and severe. Dose limiting toxicities (DLTs) are presented in Section 12.2.2.5 and the determination of MTD and the recommended Phase II dose are discussed in the discussion of safety results and conclusions.

Of the nnn patients treated in the study, nnn (xx.x%) experienced at least one TEAE. [Insert discussion of any exceptions or patients without TEAEs here.]

Table 14: Overall Summary of Treatment-Emergent Adverse Events
Safety Evaluable
(N=n)
LDOS001 Phase I Study

Treatment-Emergent Adverse Events	LDOS47DoseCohort(µg/kg)+Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients:			
With Any Treatment-Emergent Adverse Events (TEAEs)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Drug-Related TEAEs[2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Severity Grade 3, 4 or 5	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Severity Grade 3, 4 or 5 Drug-Related TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Any Serious TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Any Serious, Drug-Related TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Who Discontinued Drug Due to TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Who Discontinued Drug Due to Drug-Related TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Who Died Due to TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Who Died Due to Drug-Related TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Considered to have a Possible, Probable or Definite relationship to study drug.

Cross-References: Appendix Listing 16.2.7.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Excludes events with incomplete information for grade or drug relationship. Add footnote if required: See Listing 16.2.7.3 for excluded events.

11.2.2 Display of Adverse Events

All TEAEs are summarized by system organ class in Table 15 for all patients. TEAEs were reported for ≥ XX% of patients in the following system organ classes, in descending order: [List most common TEAEs here.] TEAEs in other system organ classes were reported for < XX% of patients.

Table 15: Summary of Treatment-Emergent Adverse Events by System Organ Class
Safety Evaluable
(N=n)
LDOS001 Phase I Study

MedDRA System Organ Class	All TEAEs	Related [3] Any Grade [4]	Any Relationship ≥Grade 3 [4]	Related [3] ≥Grade 3 [4]
Number of Patients [1]	nnn	nnn	nnn	nnn
Number of Patients with Any TEAEs [2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Blood and lymphatic system disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Cardiac disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Ear and labyrinth disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Eye disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Gastrointestinal disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
General disorders and administration site conditions	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Infections and infestations	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Investigations	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Metabolism and nutrition disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Musculoskeletal and connective tissue disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Nervous system disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Psychiatric disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Renal and urinary disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Reproductive system and breast disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Respiratory, thoracic and mediastinal disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Skin and subcutaneous tissue disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Vascular disorders	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs that occurred after the first dose of study medication up to 30 days post last dose.
[3] Considered to have a Possible, Probable or Definite relationship to study drug.
[4] Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening, 5=fatal.

Cross-References: Attachments Table 14.3.1.2, 14.3.1.3, 14.3.1.4, 14.3.1.5, 14.3.1.6 and Appendix Listing 16.2.7.1.

PROGRAMMER'S NOTES:
Sort System Organ Class in descending order using "All Adverse Events" frequency column.
Excludes events with incomplete information for grade or drug relationship. Add footnote if required: See Listing 16.2.7.3 for excluded events.

11.2.2.1 Frequently Reported Adverse Events

Table 16 presents the TEAEs reported for ≥ "XX"% of patients overall, regardless of severity or drug relationship. The most frequently reported TEAEs, regardless of severity or drug relationship, were MedDRA Preferred Term (nnn patients, xx.x%), [insert additional details here]. All TEAEs are summarized by system organ class and frequency in Attachment Table 14.3.1.2.

Table 16: Summary of Treatment-Emergent Adverse Events Occurring in at Least "XX"% of Patients by System Organ Class and Preferred Term
Safety Evaluable
(N=n)
LDOS001 Phase I Study

MedDRA System Organ Class	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
MedDRA Preferred Term	Dose 1	Repeat	Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any TEAEs [2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs that occurred after the first dose of study medication up to 30 days post last dose.

Cross-References: Attachment Table 14.3.1.2 and Appendix Listing 16.2.7.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Only present adverse events that occur "XX"% or more Overall.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.
Excludes events with incomplete information for grade or drug relationship. Add footnote if required: See Listing 16.2.7.3 for excluded events

11.2.2.2 Drug-Related Adverse Events

Table 17 presents the TEAEs reported for ≥ "XX"% of patients overall that were considered to be drug-related (considered to have a Possible, Probable or Definite relationship to study therapy), regardless of severity. The most frequently reported drug-related TEAEs were MedDRA Preferred Term (nnn patients, xx.x%), [insert additional details here]. All drug-related TEAEs are summarized by system organ class and frequency in Attachment Table 14.3.1.3.

Table 17: Summary of Drug-Related, Treatment-Emergent Adverse Events Occurring in at Least "XX"% of Patients by System Organ Class and Preferred Term
Safety Evaluable
(N=n)
LDOS001 Phase I Study

MedDRA System Organ Class MedDRA Preferred Term	L-DOS47 Dose Cohort (µg/kg)+ Pemetrexed/Carboplatin Dose 1	 Repeat	 Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any Drug-Related, TEAEs [2][3]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs that occurred after the first dose of study medication up to 30 days post last dose.
[3] Considered to have a Possible, Probable or Definite relationship to study drug.

Cross-References: Attachment Table 14.3.1.3 and Appendix Listing 16.2.7.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Only present drug-related adverse events that occur in "XX"% or more Overall.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.
Excludes events with incomplete information for grade or drug relationship. Add footnote if required: See Listing 16.2.7.3

for excluded events.

11.2.2.3 Severe Adverse Events

Table 18 presents the TEAEs reported for ≥ "XX"% of patients overall that were considered to be severe (≥ Grade 3 in severity), regardless of drug relationship. The most frequently reported severe TEAEs were MedDRA Preferred Term (nnn patients, xx.x%), [insert additional details here]. All severe TEAEs are summarized by system organ class and frequency in Attachment Table 14.3.1.5.

Table 18: Summary of Grade 3 or Greater, Treatment-Emergent Adverse Events Occurring in at Least "XX"% of Patients by System Organ Class and Preferred Term
Safety Evaluable
(N=n)
LDOS001 Phase I Study

MedDRA System Organ Class MedDRA Preferred Term	L-DOS47 Dose Cohort (µg/kg)+Pemetrexed/Carboplatin Dose 1	 Repeat	 Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any Grade 3 or Greater, TEAEs [2][3]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term		nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term or maximum grade to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs that occurred after the first dose of study medication up to 30 days post last dose.
[3] Grade: 3=Severe, 4=Life threatening, 5=Fatal.

Cross-References: Attachment Table 14.3.1.5 and Appendix Listing 16.2.7.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Only present grade 3 or greater adverse events that occur in "XX"% or more Overall.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.
Excludes events with incomplete information for grade or drug relationship. Add footnote if required: See Listing 16.2.7.3 for excluded events.

11.2.2.4 Severe and Drug-Related Adverse Events

Table 19 presents a summary of all severe and drug-related TEAEs reported. TEAEs that were both considered to be drug-related and ≥ Grade 3 in severity were reported by nnn patients (xx.x%). The reported severe and drug-related TEAEs were MedDRA Preferred Term (nnn patients, xx.x%), [insert additional details here]. All severe and drug-related TEAEs are summarized by system organ class and frequency in Attachment Table 14.3.1.6.

Table 19: Summary of Grade 3 or Greater, Drug-Related, Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Evaluable
(N=n)
LDOS001 Phase I Study

MedDRA System Organ Class	L-DOS47 Dose Cohort(µg/kg)+Pemetrexed/Carboplatin		
MedDRA Preferred Term	Dose 1	Repeat	Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any Grade 3 or Greater, Drug-Related, TEAEs [2][3][4]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs that occurred after the first dose of study medication up to 30 days post last dose.
[3] Grade: 3=Severe, 4=Life threatening, 5= fatal.
[4] Considered to have a Possible, Probable or Definite relationship to study drug.

Cross-References: Attachment Table 14.3.1.6 and Appendix Listing 16.2.7.1.

PROGRAMMER'S NOTES:

L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Only present grade 3 or greater drug-related adverse events.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.
Excludes events with incomplete information for grade or drug relationship. Add footnote if required: See Listing 16.2.7.3 for excluded events.

11.2.2.5 Dose-Limiting Toxicities

Dose limiting toxicities (DLTs) were not reported for nnn patients (xx.x%) but were reported for nnn patients (xx.x%). The patients with DLTs are summarized below and in Table 20; patient narratives are presented in Section 11.3.2.

[Insert DLT discussions by patient here.]

Table 20: Patient Listing of Dose Limiting Toxicities
Safety Evaluable
(N=n)
LDOS001 Phase I Study

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	MedDRA Preferred Term	Grade [1]	Onset /Day [2]	Duration (Days) [3]	Relation To Therapy	Outcome [4]
ccc-ppp XX/Male	xxx	MedDRA Preferred Term	x	xx/ xx	x	Relationship	x
		MedDRA Preferred Term	x	xx/ xx	xx	Relationship	x
ccc-ppp XX/Female	xxx	MedDRA Preferred Term	x	xx/ xx	x	Relationship	x
		MedDRA Preferred Term	x	xx/ xx	xx	Relationship	x
		MedDRA Preferred Term	x	xx/ xx	xx	Relationship	x

[1] Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening, 5= Fatal.
[2] On-Study day relative to first dose.
[3] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
[4] Outcome: 1=Recovered/Resolved, 2=Recovering/Resolving, 3=Not Recovered/Not Resolved, 4=Recovered/Resolved with sequelae, 5=Fatal, 6=Unknown.

Cross-References: Attachment Table 14.3.2.1 and Appendix Listing 16.2.7.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
DLT defined by flag in Adverse Event dataset.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.

11.2.3 Analysis of Adverse Events

Safety results were tabulated and summarized by dose cohort for all patients who received L-DOS47.

Of the xx patients who received L-DOS47 (N=xx), xx reported adverse events. xx patients (xx.x%) reported a drug-related event, xx patients (xx.x%) reported a grade 3 or greater event, and xx patients (xx.x%) reported an event that was both drug-related and grade 3 or greater in severity.

Frequently reported TEAEs were as follows: xxxxxx (xx.x%), xxxxxx (xx.x%), xxxxxx (xx.x%), xxxxxx (xx.x%) and xxxxxx (xx.x%). The most frequently reported L-DOS47-related events were in the xxxxxx system organ class [additional analysis as appropriate].

Frequently reported drug-related TEAEs that were grade 3 or greater in severity were [insert additional details here].

11.2.4 Listing of Adverse Events by Patient

The adverse events listings by patient are provided in Appendix Listing 16.2.7.1.

11.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

11.3.1 Listing of Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

11.3.1.1 Deaths

On-study deaths or deaths within the 30 day follow-up period post last dose were reported for nnn patients ([insert patient numbers here]), nnn patients [insert additional details here]. Table 21 presents the summary of the TEAEs leading to death; patient narratives are presented in Section 12.3.2.

Table 21: Patient Listing of Treatment-Emergent Adverse Events Leading to Death
Safety Evaluable
(N=n)
LDOS001 Phase I Study

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	MedDRA Preferred Term	Grade [1]	Onset /Day[2]	Duration (Days)[3]	Relation To Therapy	Outcome [4]
ccc-ppp XX/Male	xxx	MedDRA Preferred Term	x	xx/xx	xx	Relationship	x

[1] Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening, 5= Fatal.
[2] On-Study day relative to first dose.
[3] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
[4] Outcome: 1=Recovered/Resolved, 2=Recovering/Resolving, 3=Not Recovered/Not Resolved, 4=Recovered/Resolved with sequelae, 5=Fatal, 6=Unknown .

Cross-References: Attachment Table 14.3.2.6 and Table 14.3.2.7 and Appendix Listing 16.2.7.1 and Listing 16.2.7.4

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.

Table 22 presents the summary of patients who died during the study or within the 30-day follow-up period post last dose; patient narratives are presented in Section 12.3.2.

Table 22: Patient Listing of Deaths On-Study or Within the 30 Day Follow-up Period
Safety Evaluable
(N=n)
LDOS001 Phase I Study

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	Last Dose Date	Date Off Study	Date of Death	Days [1]	Primary Cause of Death
ccc-ppp XX/Male	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	x/x	Reported Cause of Death

[1] Off-Study to Death calculated in days.

Cross-References: Attachment Table 14.3.2.8 and Appendix Listing 16.2.7.4.

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.

11.3.1.2 Other Serious Adverse Events

Treatment-emergent serious adverse events (SAE) were reported for nnn of the nnn patients treated in the study. Of these, nnn patients ([insert patient numbers here]) had SAEs that were considered to be related to study therapy which included [insert details here]. SAEs are presented by patient in Table 23 and also in the patient narratives in Section 12.3.2.

Table 23: Patient Listing of Serious Adverse Events
Safety Evaluable
(N=n)
LDOS001 Phase I Study

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	MedDRA Preferred Term	Grade [1]	Onset /Day[2]	Duration (Days)[3]	Relation To Therapy	Outcome [4]
ccc-ppp XX/Male	xxx	MedDRA Preferred Term	x	xx/xx	x	Relationship	x
		MedDRA Preferred Term	x	xx/xx	xx	Relationship	x
ccc-ppp XX/Female	xxx	MedDRA Preferred Term	x	xx/xx	x	Relationship	x
		MedDRA Preferred Term	x	xx/xx	xx	Relationship	x
		MedDRA Preferred Term	x	xx/xx	xx	Relationship	x
ccc-ppp XX/Male	xxx	MedDRA Preferred Term	x	xx/xx	xx	Relationship	x
		MedDRA Preferred Term	x	xx/xx	xx	Relationship	x

A serious adverse event is defined as any untoward medical occurrence at any dose that results in death, life threatening, hospitalization, significant disability or congenital anomaly or birth defect.
[1] Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening, 5=Fatal.
[2] On-Study day relative to first dose.
[3] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
[4] Outcome: 1=Recovered/Resolved, 2=Recovering/Resolving, 3=Not Recovered/Not Resolved, 4=Recovered/Resolved with sequelae, 5=Fatal, 6=Unknown.

Cross-References: Attachment Table 14.3.2.2 and Table 14.3.2.3 and Appendix Listing 16.2.7.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.

11.3.1.3 Other Significant Adverse Events

The nnn patients ([insert patient numbers here]) who discontinued study medication due to TEAEs are summarized in Table 24; patient narratives are presented in Section 11.3.2. The drug-related TEAEs resulting in treatment discontinuation are [insert description and patient numbers here].

Table 24: Patient Listing of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation
Safety Evaluable
(N=n)
LDOS001 Phase I Study

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	MedDRA Preferred Term	Grade [1]	Onset /Day[2]	Duration (Days)[3]	Relation To Therapy	Outcome [4]
ccc-ppp XX/Male	xxx	MedDRA Preferred Term	x	xx/xx	x	Relationship	x
		MedDRA Preferred Term	xx	xx/xx	xx	Relationship	x
ccc-ppp XX/Female	xxx	MedDRA Preferred Term	x	xx/xx	x	Relationship	x
		MedDRA Preferred Term	xx	xx/xx	xx	Relationship	x
		MedDRA Preferred Term	xx	xx/xx	xx	Relationship	x
ccc-ppp XX/Male	xxx	MedDRA Preferred Term	xx	xx/xx	xx	Relationship	x
		MedDRA Preferred Term	xx	xx/xx	xx	Relationship	x

[1] Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening, 5=Fatal.
[2] On-Study day relative to first dose.
[3] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
[4] Outcome: 1=Recovered/Resolved, 2=Recovering/Resolving, 3=Not Recovered/Not Resolved, 4=Recovered/Resolved with sequelae, 5=Fatal, 6=Unknown.

Cross-References: Cross-References: Attachment Table 14.3.2.4 and Table 14.3.2.5 and Appendix Listing 16.2.7.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.

11.3.2 Patient Narratives

Patient narratives are presented for patients who had an SAE, were removed from the study due to toxicity, had DLT, or died within 30 days of receiving study drugs.

Patient ccc-ppp (SAEs: [Insert Grade and event description here])
This xx-year-old [insert narrative discussion here].

11.4 Clinical Laboratory Evaluations

Table 25 presents a summary of patients with Grade 3 and 4 laboratory values during the treatment period including the 30 day follow-up period post last dose.

Table 25: Patient Listing of Grade 3 and 4 Laboratory Values During Treatment Period
Safety Evaluable
(N=n)
LDOS001 Phase I Study

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	Abnormal Laboratory Test	Baseline Grade [1]	Post Grade [1]	Onset/Day [2]	Result	Unit
ccc-ppp XX/Male	xxx	Laboratory Test Name	x	x	x/xx	‹xx	xxx
	xxx	Laboratory Test Name	x	x	x/xx	‹xx	xxx
ccc-ppp XX/Female	xxx	Laboratory Test Name	x	x	x/xx	‹xx	xxx
	xxx	Laboratory Test Name	x	x	x/xx	‹xx	xxx
	xxx	Laboratory Test Name	x	x	x/xx	‹xx	xxx
ccc-ppp XX/Male	xxx	Laboratory Test Name	x	x	x/xx	‹xx	xxx
	xxx	Laboratory Test Name	x	x	x/xx	‹xx	xxx

[1] Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening, 5=Fatal.
[2] On-Study day relative to first dose within cycle.

Cross-References: Attachment Tables 14.3.4.1-14.3.4.4 and Appendix Listings 16.2.7.1, 16.2.8.1-16.2.8.5

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.

Summaries of the shift from baseline to maximum severity grade for hematology and blood chemistry parameters are provided in Tables 14.3.4.1 and 14.3.4.2. Summaries of quantitative changes from baseline for hematology, blood chemistry and coagulation parameters are provided in Tables 14.3.4.3 and 14.3.4.4.

Individual patient laboratory data are provided in Appendix Listings 16.2.8.1-16.2.8.8 for hematology, blood chemistry, coagulation, urinalysis and other significant laboratory tests.

[Insert discussion of clinically significant laboratory findings].

11.5 Performance Status, Vital Signs, Physical Findings, ECG Findings and Other Observations Related to Safety

[Insert discussion of changes in performance status, physical examination findings and vital signs and ECG parameter findings.]

11.6 Safety Conclusions

[Insert Safety conclusions.]

12.0 Discussion and Overall Conclusions

[Insert discussion and conclusions.]

13.0 Tables, Figures and Graphs Referred to but not Included in the Text

List of Tables and Figures

14.0 Reference List

[1] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. (2009) New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 45: 228-247.

[2] Clopper CJ, Pearson ES. (1934) The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial. Biometrika; 26(4)404-413.

[3] Brookmeyer, R. and Crowley, J. (1982), A Confidence Interval for the Median Survival Time, Biometrics, 38, 29-41.

[4] Kalbfleisch, J.D. and Prentise, R.L. (1980) The Statistical Analysis of Failure Time Data. New York: John Wiley & Sons, Inc.

15.0 Appendices

RAP-Specific Sections Presenting Sample Tables and Listings

Tables for Section 14: Referred to But Not Presented In-Text

Table 14.1.1
Vital Signs at Baseline Including Height and Weight
Safety Evaluable
(N=n)

Vital Signs	L-DOS47 Dose Cohort(µg/kg)+ Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Systolic Blood Pressure (mmHg)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Diastolic Blood Pressure (mmHg)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Pulse Rate (beats/min)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx

Cross-Reference: Appendix Listings 16.2.9.2.

PROGRAMMER'S NOTES:

Table 14.1.1
Vital Signs at Baseline Including Height and Weight
Safety Evaluable
(N=n)

Vital Signs	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Temperature (unit)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Respiration (breaths/min)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Pulse Oximetry (%)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Height (cm)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x

Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Weight (kg)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
BSA (mA^2)			
N	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx

Cross-Reference: Appendix Listings 16.2.9.2.

PROGRAMMER'S NOTES:

```
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the
3 dose levels.
```

Table 14.1.2
Summary of Concomitant Measures
Safety Evaluable
(N=n)

WHO-DD ATC Class Category Level II WHO-DD Preferred Term [1][2]	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin Dose 1	Repeat	Overall
Number of Patients[3]	nnn	nnn	nnn
Number of Patients Receiving Concomitant Measures	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD ATC Class Category Level II	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
WHO-DD Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED			

[1] Patients may be counted in more than one therapeutic class; patients are only counted once within a therapeutic class.
[2] Summarizes medications that were ongoing at study start (Day 1) or started on Day 1 or thereafter up to 30 days post last dose.
[3] Number of Patients used as denominator to calculate percentages.

Cross-References: Appendix Listing 16.2.10.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Present all "Therapeutic Class" categories found in the database.
Sort "Therapeutic Class" column in descending order based on "Overall" column frequency count.

Table 14.2.1.1
Life Table Analysis of Duration of Response (CR or PR): Confidence Intervals for Point Estimates
Efficacy Evaluable
(N=n)

	Number at Risk	Cumulative Events [1]	Progression-Free Rate	95% Confidence Interval [2]	
				Lower	Upper
Baseline	nnn	nnn	100.0%	xx.x%	xx.x%
1 Month (30 days)	nnn	nnn	xx.x%	xx.x%	xx.x%
2 Month (60 days)	nnn	nnn	xx.x%	xx.x%	xx.x%
3 Months (90 days)	nnn	nnn	xx.x%	xx.x%	xx.x%
6 Months (180 days)	nnn	nnn	xx.x%	xx.x%	xx.x%
9 Months (270 days)	nnn	nnn	xx.x%	xx.x%	xx.x%

[1] Duration of Response is calculated from date of first response (first occurrence of CR or PR) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patient without evidence of objective disease progression or death, duration of response will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed PR or CR are included in the analysis.
[2] Life Table estimates are calculated using Kaplan-Meier methodology. Confidence interval for a point estimate on the survival distribution is calculated using the method by Kalbfleisch and Prentice.
Cross-References: Appendix Listing 16.2.6.3

PROGRAMMER'S NOTES:
Life Table estimates are calculated using Kaplan-Meier methodology. Confidence interval for a point estimate on the survival distribution was calculated using the method by Kalbfleisch and Prentice.

Table 14.2.1.2
Life Table Analysis of Duration of Response (CR or PR): Confidence Intervals for Point Estimates
Intent-to-Treat
(N=n)

	Number at Risk	Cumulative Events [1]	Progression-Free Rate	95% Confidence Interval [2]	
				Lower	Upper
Baseline	nnn	nnn	100.0%	xx.x%	xx.x%
1 Month (30 days)	nnn	nnn	xx.x%	xx.x%	xx.x%
2 Months (60 days)	nnn	nnn	xx.x%	xx.x%	xx.x%
3 Months (90 days)	nnn	nnn	xx.x%	xx.x%	xx.x%
6 Months (180 days)	nnn	nnn	xx.x%	xx.x%	xx.x%
9 Months (270 days)	nnn	nnn	xx.x%	xx.x%	xx.x%

[1] Duration of Response is calculated from date of first response (first occurrence of CR or PR) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patient without evidence of objective disease progression or death, duration of response will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed PR or CR are included in the analysis.
[2] Life Table estimates are calculated using Kaplan-Meier methodology. Confidence interval for a point estimate on the survival distribution is calculated using the method by Kalbfleisch and Prentice.
Cross-References: Appendix Listing 16.2.6.3

PROGRAMMER'S NOTES:
Life Table estimates are calculated using Kaplan-Meier methodology. Confidence interval for a point estimate on the survival distribution is calculated using the method by Kalbfleisch and Prentice.

Table 14.2.2
Patient Listing for Duration of Response (CR or PR)
Intent-to-Treat
(N=n)

Patient Age/Sex	L-DOS47 Dose Cohort (µg/kg)	Date of First Dose	Date of First CR	Date of First PR	Date of PD	Date of Censoring	Duration of Response [1]
ccc-ppp XX/Male	xxx	ddmmmyyyy	ddmmmyyyy		ddmmmyyyy		xxx
ccc-ppp XX/Female	xxx	ddmmmyyyy		ddmmmyyyy		ddmmmyyyy	xxx
ccc-ppp XX/Male	xxx	ddmmmyyyy		ddmmmyyyy	ddmmmyyyy		xxx
ccc-ppp XX/Female	xxx	ddmmmyyyy		ddmmmyyyy		ddmmmyyyy	xxx
ccc-ppp XX/Female	xxx	ddmmmyyyy	ddmmmyyyy			ddmmmyyyy	xxx
ccc-ppp XX/Male	xxx	ddmmmyyyy	ddmmmyyyy		ddmmmyyyy		xxx
ccc-ppp XX/Male	xxx	ddmmmyyyy	ddmmmyyyy			ddmmmyyyy	xxx

[1] Duration of Response is calculated from date of first response (first occurrence of CR or PR) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patient without evidence of objective disease progression or death, duration of response will be censored at the date of the last evaluable tumor assessment. Only patients with a confirmed PR or CR are included in the analysis.
Note: CR= complete response, PR= partial response, PD = progressive
Cross-Reference: Appendix Listing 16.2.6.3

PROGRAMMER'S NOTES:
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Data used in the SAS Life Table procedure.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Table 14.3.1.1
Summary of Treatment-Emergent Adverse Events During Cycle 1
Safety Evaluable
(N=n)

Treatment-Emergent Adverse Events[1]	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Number of Patients [2]	nnn	nnn	nnn
Number of Patients:			
With Any TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Drug-Related TEAEs [3]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Severity Grade 3, 4 or 5	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Severity Grade 3, 4 or 5 Drug-Related TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Any Serious TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
With Any Serious, Drug-Related TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Who Discontinued Drug Due to TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Who Discontinued Drug Due to Drug-Related TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Who Died Due to TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Who Died Due to Drug-Related TEAEs	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs occurring on or after the first study medication date up to 30 days post last dose.
[2] Number of Patients used as denominator to calculate percentages.
[3] Considered to have a Possible, Probable or Definite relationship to study drug.
Cross-References: Appendix Listing 16.2.7.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.

Table 14.3.1.2
Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Evaluable
(N=n)

MedDRA System Organ Class MedDRA Preferred Term	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin Dose 1	Repeat	Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any TEAEs [2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs occurring on or after the first study medication date up to 30 days post last dose.
Cross-References: Appendix Listing 16.2.7.1

PROGRAMMER’S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Sort System Organ Class and then Preferred term in descending order using “Overall” frequency column.

Table 14.3.1.3
Summary of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
Safety Evaluable
(N=n)

MedDRA System Organ Class MedDRA Preferred Term	L-DOS47 Dose Cohort (µg/kg)+Pemetrexed/Carboplatin Dose 1	 Repeat	 Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any Drug-Related TEAEs [2][3]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs occurring on or after the first study medication date up to 30 days post last dose.
[3] Considered to have a Possible, Probable or Definite relationship to study drug.
Cross-References: Appendix Listing 16.2.7.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.

Table 14.3.1.4
Summary of Treatment-Emergent Adverse Events by Highest Drug Relationship, System Organ Class and Preferred Term
Safety Evaluable
(N=n)

MedDRA System Organ Class MedDRA Preferred Term Highest Drug Relationship	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin Dose 1	 Repeat	 Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any TEAEs [2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Unrelated	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Unlikely	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Possible	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Probable	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Definite	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Not Related [3]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Related [4]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED			

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs occurring on or after the first study medication date up to 30 days post last dose.
[3] Considered to be Unrelated or have an Unlikely relationship to study drug.
[4] Considered to have a Possible, Probable or Definite relationship to study drug.
Cross-References: Appendix Listing 16.2.7.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.
Excludes events with incomplete information for grade or drug relationship. Add footnote if required: See Listing 16.2.7.3 for excluded events.

Table 14.3.1.5
Summary of Treatment-Emergent Adverse Events by Maximum Severity Grade, System Organ Class and Preferred Term
Safety Evaluable
(N=n)

MedDRA System Organ Class MedDRA Preferred Term Maximum Severity Grade	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin Dose 1	 Repeat	 Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any TEAEs [2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
< Grade 3	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 1	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 2	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 3	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 4	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 5	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
>= Grade 3	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs occurring on or after the first study medication date up to 30 days post last dose.
Cross-References: Appendix Listing 16.2.7.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.
Excludes events with incomplete information for grade or drug relationship. Add footnote if required: See Listing 16.2.7.3 for excluded events.

Table 14.3.1.6
Summary of Drug-Related, Treatment-Emergent Adverse Events by Maximum Severity Grade, System Organ Class and Preferred Term
Safety Evaluable
(N=n)

MedDRA System Organ Class MedDRA Preferred Term Maximum Severity Grade	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin Dose 1	 Repeat	 Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any Drug-Related TEAE [2][3]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
< Grade 3	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 1	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 2	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 3	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 4	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Grade 5	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
>= Grade 3	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs occurring on or after the first study medication date up to 30 days post last dose.
[3] Considered to have a Possible, Probable or Definite relationship to study drug.
Cross-References: Appendix Listing 16.2.7.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.
Excludes events with incomplete information for grade or drug relationship. Add footnote if required: See Listing 16.2.7.3 for excluded events.

Table 14.3.2.1
Patient Listing of Dose Limiting Toxicities
Safety Evaluable
(N=n)

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset Cycle/Day [1]	Duration of AE [2]	Treatment Duration [3]	Grade [4]	Serious [5]	Drug Relationship	Outcome [6]
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	x	x	x	x	Relationship	x
ccc-ppp XX/Female	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	x	x	x	x	Relationship	x
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	x	x	Relationship	x
ccc-ppp XX/Female	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	x	x	x	x	Relationship	x

[1] Onset day relative to first dose.
[2] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
[3] Treatment Duration calculated from first dose of study medication to treatment discontinuation.
[4] Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening, 5=Fatal.
[5] Serious: 1=Not serious, 2=Death, 3=Life threatening, 4=Hospitalization, 5=Significant Disability, 6=Congenital Anomaly/Birth Defect, 7=Other Medically Important Event.
[6] Outcome: 1=Recovered/Resolved, 2=Recovering/Resolving, 3=Not Recovered/Not Resolved, 4=Recovered/Resolved with sequelae, 5=Fatal, 6=Unknown.
Cross-References: Appendix Listings 16.2.7.1

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
DLT defined by flag in Adverse Event dataset; 'Dose Limiting Toxicity' tic box checked on AE CRF.

Table 14.3.2.2
Summary of Serious Adverse Events by System Organ Class and Preferred Term
Safety Evaluable
(N=n)

MedDRA System Organ Class MedDRA Preferred Term	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any Serious Adverse Events [2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] A serious adverse event is defined as any untoward medical occurrence at any dose that results in death, life threatening, hospitalization, significant disability or congenital anomaly or birth defect.
Cross-References: Appendix Listing 16.2.7.1

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Use Serious Code > 1. Serious: 1=Not Serious, 2=Results in Death, 3=Life threatening, 4=Hospitalization, 5=Significant Disability,6=Congenital Anomaly or Birth Defect, 7=Other Medically Important Event.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.
Medical writer may take away this table if it is too short.

Table 14.3.2.3
Patient Listing of Serious Adverse Events
Safety Evaluable
(N=n)

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset Cycle/Day[1]	Last Dose to AE Onset[2]	Duration of AE[3]	Outcome [4]	Action [5]	Drug Relationship
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	x/xx	xx	xx	x	x	Relationship
ccc-ppp XX/Female	xxx	ADVERSE EVENT (MedDRA Preferred Term)	x/xx	xx	xx	x	x	Relationship
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	x/xx	xx	xx	x	x	Relationship
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	x/xx	xx	xx	x	x	Relationship

A serious adverse event is defined as any untoward medical occurrence at any dose that results in death, life threatening, hospitalization, significant disability or congenital anomaly or birth defect.
[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Duration calculated in days from Onset Date to the Resolution Date.
[4] Outcome: 1=Recovered/Resolved, 2=Recovering/Resolving, 3=Not Recovered/Not Resolved, 4=Recovered/Resolved with sequelae, 5=Fatal, 6=Unknown.
[5] Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Cross-References: Appendix Listings 16.2.7.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Use Serious Code > 1. Serious: 1=Not serious, 2=Death, 3=Life threatening, 4=Hospitalization, 5=Significant Disability, 6=Congenital Anomaly/Birth Defect, 6=Other Medically Important Event.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Medical writer may take away this table if there is no SAE.

Table 14.3.2.4
Summary of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term
Safety Evaluable
(N=n)

MedDRA System Organ Class MedDRA Preferred Term	L-DOS47 Dose Cohort (μg/kg) + Pemetrexed/Carboplatin Dose 1	 Repeat	 Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any Treatment-Emergent Adverse Events Leading to Treatment Discontinuation [2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs occurring on or after the first study medication date up to 30 days after the last dose.
Cross-References: Appendix Listing 16.2.7.1, 16.2.7.2.8

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 μg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Use Action Code =9. Action Taken: Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.

Table 14.3.2.5
Patient Listing of Treatment-Emergent Adverse Events Leading to Treatment Discontinuation
Safety Evaluable
(N=n)

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset Cycle/Day[1]	Last Dose to Onset[2]	Treatment Duration[3]	Duration of AE[4]	Serious[5]	Drug Relationship
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	x	Relationship
ccc-ppp XX/Female	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	x	Relationship
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	x	Relationship
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	x	Relationship

[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Treatment Duration calculated from first dose of study medication to treatment discontinuation.
[4] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
[5] Serious: 1=Not serious, 2=Death, 3=Life threatening, 4=Hospitalization, 5=Significant Disability, 6=Congenital Anomaly or Birth Defect, 7=Other Medically Important Event.
Cross-References: Appendix Listings 16.2.7.1, 16.2.7.2.8

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Use Action Code = 9. Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.

Table 14.3.2.6
Summary of Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term
Safety Evaluable
(N=n)

MedDRA System Organ Class MedDRA Preferred Term	L-DOS47 Dose Cohort (μg/kg) + Pemetrexed/Carboplatin Dose 1	Repeat	Overall
Number of Patients [1]	nnn	nnn	nnn
Number of Patients with Any Treatment-Emergent Adverse Events Leading to Death[2]	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA Preferred Term	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
MedDRA System Organ Class	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
[2] Patients with multiple Treatment-Emergent Adverse Events (TEAEs) were only counted once within a summary category: system organ class, preferred term, maximum grade, or relationship to treatment. Patients with events in more than one category were counted once within each category. TEAEs were defined as all AEs occurring on or after the first study medication date up to 30 days post last dose.
Cross-References: Appendices Listings 16.2.7.1 and 16.2.7.4

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 μg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Sort System Organ Class and then Preferred term in descending order using "Overall" frequency column.
Medical writer may take away this table if it is too short.

Table 14.3.2.7
Patient Listing of Treatment-Emergent Adverse Events Leading to Death
Safety Evaluable
(N=n)

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset Cycle/Day[1]	Last Dose to Death[2]	Off-Study to Death[3]	Drug Relationship
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	Relationship
ccc-ppp XX/Female	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	Relationship
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	Relationship
ccc-ppp XX/Male	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	Relationship

[1] Onset day relative to first dose.
[2] Last Dose to Death calculated in days.
[3] Off-Study to Death calculated in days.
Cross-References: Appendices Listings 16.2.7.1 and 16.2.7.4

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Medical writer may take away this table if there is no death.

Table 14.3.2.8
Patient Listing of Deaths On-Study or Within the 30 Days Follow-up Period
Safety Evaluable
(N=n)

Patient Age/Sex	L-DOS47 Dose Level (µg/kg)	Cause of Death	Date of Death[1]	Date of Last Dose	Last Dose to Death[2]	Off-Study Date	Off-Study to Death[3]
ccc-ppp XX/Male	xxx	Reported Primary Cause of Death	ddmmmyyyy	ddmmmyyyy	xx	ddmmmyyyy	xx
ccc-ppp XX/Female	xxx	Reported Primary Cause of Death	ddmmmyyyy	ddmmmyyyy	xx	ddmmmyyyy	xx
ccc-ppp XX/Male	xxx	Reported Primary Cause of Death	ddmmmyyyy	ddmmmyyyy	xx	ddmmmyyyy	xx
ccc-ppp XX/Male	xxx	Reported Primary Cause of Death	ddmmmyyyy	ddmmmyyyy	xx	ddmmmyyyy	xx

[1] Includes deaths within 30 days after the Off-Study Date.
[2] Last Dose to Death calculated in days.
[3] Off-Study to Death calculated in days.
Cross-Reference: Appendix Listing 16.2.7.4.

PROGRAMMER'S NOTES:
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Medical writer may take away this listing if there is no death.

Table 14.3.4.1
Summary of Shift from Baseline to Maximum CTCAE Grade During Treatment Period for Hematology Tests
Safety Evaluable
(N=n)

Hematology Test	Baseline Severity Grade L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin					
Maximum CTCAE Grade [1][2]	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Overall
Lab Parameter1 (unit)						
Cohort 1						
Grade 0	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 1	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 2	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 3	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 4	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 5	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Overall	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Repeat						
Overall						
Grade 0	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 1	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 2	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 3	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 4	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 5	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Overall	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Lab Parameter2 (unit)						
Cohort 1						

[1] Number of patients with both a baseline evaluation and an on-study evaluation used as denominator to calculate percentages.
[2] Maximum CTCAE Grade was defined as the highest CTCAE Grade reported for a patient after first dose.
Cross-References: Appendices Listing 16.2.8.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Grand total used as denominator to calculate percentages within each dose level.
Hematology Parameters: hemoglobin, hematocrit, WBC, platelets, neutrophils, lymphocytes, Monocytes, Eosinophils, Basophils, etc.
Coagulation parameter: INR, PT, aPTT. Only gradable parameters are included in the table.

Table 14.3.4.2
Summary of Shift from Baseline to Maximum CTCAE Grade During Treatment Period for Blood Chemistry Tests
Safety Evaluable
(N=n)

Blood Chemistry Test	Baseline Severity Grade L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin					
Maximum CTCAE Grade [1][2]	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Overall
Lab Parameter1 (unit)						
Dose 1						
Grade 0	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 1	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 2	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 3	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 4	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 5	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Overall	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Repeat						
Overall						
Grade 0	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 1	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 2	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 3	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 4	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Grade 5	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Overall	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)	nnn(xx.x%)
Lab Parameter2 (unit)						
Cohort1						

[1] Number of patients with both a baseline evaluation and an on-study evaluation used as denominator to calculate percentages.
[2] Maximum CTCAE Grade was defined as the highest CTCAE Grade reported for a patient after first dose.
Cross-References: Appendices Listing 16.2.8.2.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Grand total used as denominator to calculate percentages within each dose level.
Chemistry Parameters: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), urea, calcium, bicarbonate, chloride, creatinine (by Cockcroft-Gault formula), globulin (serum globulin: total protein minus serum albumin), glucose, phosphate, potassium, sodium, magnesium, total bilirubin, total protein. Only gradable parameters are included in the table.

Table 14.3.4.3
Summary of Absolute Change from Baseline During Treatment Period for Hematology Tests
Safety Evaluable
(N=n)

Hematology Test	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin					
Timepoint	Dose 1		Repeat		Overall	
Statistics	Actual	Change	Actual	Change	Actual	Change
Lab Parameter1 (unit)						
Baseline						
N	nnn		nnn		nnn	
Mean	xx.x		xx.x		xx.x	
Standard Deviation	xx.xx		xx.xx		xx.xx	
Median	xx.x		xx.x		xx.x	
Minimum	xx		xx		xx	
Maximum	xx		xx		xx	
Timepoint						
N	nnn	nnn	nnn	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx
REPEAT TIMEPOINTS AS NEEDED						
Lab Parameter2 (unit)						
Baseline						

Cross-Reference: Appendices Listing 16.2.8.1.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Hematology Parameters: hemoglobin, hematocrit, WBC, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands, combined other cells, sum of the differentials and coagulation parameters: PT, aPTT, INR.
Laboratory data for hematology and coagulation were collected at the following scheduled times: Baseline (last pre-treatment value from Day -28 to Day 1); for L-DOS47+Pemetrexed/ Carboplatin at Day 1, 8 of Cycle 1 to 4 and End of Treatment (last non-missing value recorded off-study but within 30 days post last dose), or immediately after early termination; for L-DOS47 only at Day 1, 8, 15 of Cycle x.
Absolute Change = Visit Value - Baseline Value.
Use protocol specified time windows in protocol Table 10 Schedule of study evaluation.

Table 14.3.4.4
Summary of Absolute Change from Baseline During Treatment Period for Blood Chemistry Tests
Safety Evaluable
(N=n)

Blood Chemistry Test	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin					
Timepoint	Dose 1		Repeat		Overall	
Statistics	Actual	Change	Actual	Change	Actual	Change
Lab Parameter1 (unit)						
Baseline						
N	nnn		nnn		nnn	
Mean	xx.x		xx.x		xx.x	
Standard Deviation	xx.xx		xx.xx		xx.xx	
Median	xx.x		xx.x		xx.x	
Minimum	xx		xx		xx	
Maximum	xx		xx		xx	
Timepoint						
N	nnn	nnn	nnn	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx
REPEAT TIMEPOINTS AS NEEDED						
Lab Parameter2 (unit)						
Baseline						

Cross-Reference: Appendices Listing 16.2.8.2.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Chemistry Parameters: albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), urea, calcium, bicarbonate, chloride, creatinine (by Cockcroft-Gault formula), globulin (serum globulin: total protein minus serum albumin), glucose, phosphate, potassium, sodium, magnesium, total bilirubin, total protein.
Laboratory data for clinical chemistry was collected at Baseline (last pre-treatment value from Day -28 to Day 1); for L-DOS47+Pemetrexed/ Carboplatin at Day 1, 8 of Cycle 1 to 4 and End of Treatment (last non-missing value recorded off-study but within 30 days post last dose), or immediately after early termination; for L-DOS47 only at Day 1, 8, 15 of Cycle x.
Absolute Change = Visit Value - Baseline Value.
Use protocol specified time windows in protocol Table 10 Schedule of study evaluation.

Table 14.3.4.5
Summary of Change from Baseline for 'ECG Parameter (units)'
Safety Evaluable
(N=n)

Time Period / Statistics	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin					
	Dose 1		Repeat		Overall	
	Actual	Change	Actual	Change	Actual	Change
Baseline						
N	nnn		nnn		nnn	
Mean	xx.x		xx.x		xx.x	
Standard Deviation	xx.xx		xx.xx		xx.xx	
Median	xx.x		xx.x		xx.x	
Minimum	xx		xx		xx	
Maximum	xx		xx		xx	
Timepoint 1						
N	nnn	nnn	nnn	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx
REPEAT AS NEEDED						
Overall, Maximum Change						
N	nnn	nnn	nnn	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx

Cross-References: Appendix Listing 16.2.9.4.

PROGRAMMER'S NOTES:
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Five tables to be populated:
For Y=1, 'ECG Parameter (units)'= HR (beats/min);

For Y=2, 'ECG Parameter (units)'= PR (msec);
For Y=3, 'ECG Parameter (units)'= QT (msec);
For Y=4, 'ECG Parameter (units)'= QTc (msec);
For Y=5, 'ECG Parameter (units)'= QRS (msec);
ECG data was collected at Baseline (last pre-treatment value from Day -28 to Day 1); for L-DOS47+Pemetrexed/Carboplatin at Day 1, 8 of Cycle 1 to 4; and End of Treatment (last non-missing value recorded off-study but within 30 days post last dose), or immediately after early termination; for L-DOS47 only at Day 1, 8, 15 of Cycle x.
Absolute Change = Visit Value - Baseline Value.
Use protocol specified time windows in protocol Table 10 Schedule of study evaluation.

Table 14.3.4.6
Categorical Summary of 'QT/QTc Parameter' Interval
Safety Evaluable
(N=n)

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
'QT/QTc Parameter'[1]	Dose 1	Repeat	Overall
Number of Patients	nnn	nnn	nnn
Baseline			
Interval <=450 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval >450 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval >480 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval >500 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Timepoint 1			
Interval <=450 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval >450 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval >480 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval >500 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED			
Overall, Maximum Interval			
Interval <=450 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval >450 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval >480 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval >500 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
Cross-References: Appendix Listing 16.2.9.4.

PROGRAMMER'S NOTES: Two tables to be populated:
For Y=1, 'QT/QTc Parameter'= QT.
For Y=2, 'QT/QTc Parameter'= QTc.
QT, QTc data was collected at Baseline (last pre-treatment value from Day -28 to Day 1); for L-DOS47+Pemetrexed/Carboplatin at Day 1, 8 of Cycle 1 to 4; and End of Treatment (last non-missing value recorded off-study but within 30 days post last dose), or immediately after early termination; for L-DOS47 only at Day 1, 8, 15 of Cycle x.
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Use protocol specified time windows in protocol Table 10 Schedule of study evaluation.

Table 14.3.4.7
Categorical Summary of 'QT/QTc Parameter' Interval Change from Baseline
Safety Evaluable
(N=n)

Interval Change from Baseline 'QT/QTc Parameter'[1]	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Number of Patients	nnn	nnn	nnn
Timepoint 1			
Interval Increase <= 30 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval Increase > 30 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval Increase > 60 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
REPEAT AS NEEDED			
Overall, Maximum Increase			
Interval Increase <= 30 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval Increase > 30 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Interval Increase > 60 msec	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
Cross-References: Appendix Listing 16.2.9.4.

PROGRAMMER'S NOTES:
Two tables to be populated:
For Y=1, 'QT/QTc Parameter'= QT.
For Y=2, 'QT/QTc Parameter'= QTc.
QT, QTc data was collected at Baseline (last pre-treatment value from Day -28 to Day 1); for L-DOS47+Pemetrexed/Carboplatin at Day 1, 8 of Cycle 1 to 4; and End of Treatment (last non-missing value recorded off-study but within 30 days post last dose), or immediately after early termination; for L-DOS47 only at Day 1, 8, 15 of Cycle x.
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Use protocol specified time windows in protocol Table 10 Schedule of study evaluation.

Table 14.3.5.1
Summary of Shift from Baseline to Maximum ECOG Performance Status Score
Safety Evaluable
(N=n)

L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin Maximum Score [1][2]	Baseline Performance Status (ECOG) Score 0	Score 1	Overall
Dose 1			
Score 0	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 1	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 2	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 3	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 4	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 5	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Overall	nnn (xx.x%)	nnn (xx.x%)	nnn (100.0%)
Repeat			
Score 0	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 1	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 2	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 3	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 4	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 5	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Overall	nnn (xx.x%)	nnn (xx.x%)	nnn (100.0%)
Overall			
Score 0	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 1	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 2	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 3	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 4	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Score 5	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Overall	nnn (xx.x%)	nnn (xx.x%)	nnn (100.0%)

[1] Number of patients with both a baseline evaluation and an on-study evaluation used as denominator to calculate percentages.
[2] Maximum Score was the highest ECOG Performance Status for a patient after first dose.
Cross-References: Appendix Listing 16.2.9.3.

PROGRAMMER'S NOTES:
Grand total used as denominator to calculate percentages within each dose level.
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.

Table 14.3.6.1
Summary of Anti-L-DOS47 Antibodies
Safety Evaluable
(N=n)

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin		
	Dose 1	Repeat	Overall
Visit			
Number of Patients	nnn	nnn	nnn
Cycle 1 Day 1 (Baseline)			
Positive	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Negative	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Inconclusive	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Cycle 1 Day 8			
Positive	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Negative	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Inconclusive	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Cycle 2 Day 1			
Positive	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Negative	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)
Inconclusive	nnn (xx.x%)	nnn (xx.x%)	nnn (xx.x%)

[1] Number of Patients used as denominator to calculate percentages.
Cross-References: Appendix Listing 16.2.9.5

PROGRAMMER'S NOTES:
The immunogenicity of L-DOS47 will be evaluated from serum samples collected on Cycle 1, Day 1 (predose; baseline) and Day 8 (predose), Cycles 2 through 4 (Day 1, predose), all additional cycles (Cycle 5 and beyond, Day 1 (predose), at the end of treatment or early termination visit, and at the follow-up visit (30 days post last dose).
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Present this table only data is available.
Use protocol specified time windows in protocol Table 10 Schedule of study evaluation.

Table 14.3.6.2
Summary of Titer Values of Anti-L-DOS47 Antibodies
Safety Evaluable
(N=n)

	L-DOS47 Dose Cohort(µg/kg)+ Pemetrexed/Carboplatin		
Visit	Dose 1	Repeat	Overall
Number of Patients	nnn	nnn	nnn
Cycle 1 Day 1 (Baseline)			
N	nnn	nnn	nnn
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Cycle 1 Day 8			
N	nnn	nnn	nnn
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
Cycle 2 Day 1			
N	nnn	nnn	nnn
Median	xx.x	xx.x	xx.x
Minimum	xx	xx	xx
Maximum	xx	xx	xx
<Repeat for all available visits>			

Note: Only present anti-L-DOS47 antibodies that confirmed positive. Title values listed as '<5' are screened negative for binding antibodies.
Cross-Reference: Appendix Listings 16.2.9.5

PROGRAMMER'S NOTES:
The immunogenicity of L-DOS47 will be evaluated from serum samples collected on Cycle 1, Day 1 (predose; baseline) and Day 8 (predose), Cycles 2 through 4 (Day 1, predose), all additional cycles (i.e., Cycle 5 and beyond, Day 1 (predose), at the end of treatment or early termination visit, and at the follow-up visit (30 days post last dose).
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Present this table only data is available.
Use protocol specified time windows in protocol Table 10 Schedule of study evaluation.

Table 14.3.6.3
Change from Baseline of Tumour Antigen CEACAM6
Safety Evaluable
(N=n)

	L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin					
Timepoint	Dose 1		Repeat		Overall	
Statistics	Actual	Change	Actual	Change	Actual	Change
Cycle 2 Day 1 predose						
N	nnn		nnn		nnn	
Mean	xx.x		xx.x		xx.x	
Standard Deviation	xx.xx		xx.xx		xx.xx	
Median	xx.x		xx.x		xx.x	
Minimum	xx		xx		xx	
Maximum	xx		xx		xx	
Cycle 4 Day 8						
N	nnn	nnn	nnn	nnn	nnn	nnn
Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Standard Deviation	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx	xx.xx
Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
Minimum	xx	xx	xx	xx	xx	xx
Maximum	xx	xx	xx	xx	xx	xx

<Repeat for all available visits>

Cross-Reference: Appendices Listing 16.2.9.6

PROGRAMMER'S NOTES:
Tumor antigen (CEACAM6= carcinoembryonic antigen related cell adhesion molecule 6) assessment: blood samples will be drawn (predose [0 hours]) on Day 1 (predose [0 hours]) of Cycle 2 and on Day 8 of Cycle 4 or the End of Treatment Visit (whichever occurs first)
L-DOS47 Dose cohorts = 0.59, 0.78, 1.5/3.0/6.0, 9.0, 12.0 µg/kg. Combine 1.5/3.0/6.0 in one column as only 1 subject is in each of the 3 dose levels.
Present this table only if data is available.
Use protocol specified time windows in protocol Table 10 Schedule of study evaluation.

Listings for Section 16

Appendix 16.2.1.1
Inclusion/Exclusion Criteria
All Enrolled (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Eligible	Protocol Version Date	Category	Identifier	Waiver Number
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	No	ddmmmyyyy	Inclusion	xx	
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	No	ddmmmyyyy	Exclusion	xx	
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	No, Waiver	ddmmmyyyy	Inclusion	xx	xxxx
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			
ccc-ppp	xxx	Yes	ddmmmyyyy			

Note: waivers no longer granted after eCRF update post-March 2018 Helix audit.
Cross-References: Case Report Form INCLUSION/EXCLUSION CRITERIA (IE)

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.1.2
Patient Disposition
All Enrolled (N=n)

Patient	L-DOS47 Dose Level(µg/kg)	Date Off-Study	Day[1]	Reason	ITT	Safety Evaluable	Efficacy Evaluable
ccc-ppp	xxx	ddmmmyyyy	xxx	Progressive Disease	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	No
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Progressive Disease	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Other:Specify	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	No	No
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Other:Specify	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Reason	Yes	Yes	Yes
ccc-ppp	xxx	ddmmmyyyy	xxx	Other:Specify	Yes	Yes	Yes

[1] Day relative to first dose.
Cross-References: Case Report Form Off-Study Summary (OF).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.4.1
Demographic and Disease-Related Characteristics
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level(µg/kg)	Sex	Date of Birth	Age (years)	Race	Ethnicity	ICF/Registration Date
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Race	Ethnicity	ddmmmyyyy/ddmmmyyyy
ccc-ppp	xxx	Gender	ddmmmyyyy	xx	Other/Specify	Ethnicity	ddmmmyyyy/ddmmmyyyy

Cross-References: Case Report Form DEMOGRAPHICS (DM).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.4.1
Demographic and Disease-Related Characteristics
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Histopathology (Behavior Classification)[1]	Initial Diagnosis Date	Duration of Disease (months)
ccc-ppp	xxx	Histopathology Reported (Histopathology Classification)	ddmmmyyyy	xxx.x
ccc-ppp	xxx	Histopathology Reported (Histopathology Classification)	ddmmmyyyy	xxx.x
ccc-ppp	xxx	Histopathology Reported (Histopathology Classification)	ddmmmyyyy	xxx.x
ccc-ppp	xxx	Histopathology Reported (Histopathology Classification)	ddmmmyyyy	xxx.x
ccc-ppp	xxx	Histopathology Reported (Histopathology Classification)	ddmmmyyyy	xxx.x
ccc-ppp	xxx	Histopathology Reported (Histopathology Classification)	ddmmmyyyy	xxx.x
ccc-ppp	xxx	Histopathology Reported (Histopathology Classification)	ddmmmyyyy	xxx.x
ccc-ppp	xxx	Histopathology Reported (Histopathology Classification)	ddmmmyyyy	xxx.x
ccc-ppp	xxx	Histopathology Reported (Histopathology Classification)	ddmmmyyyy	xxx.x

[1] ICD-O version 3.
Cross-References: Case Report Form DEMOGRAPHICS (DM).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.4.2
Prior Cancer Therapy
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Regimen Number	Agent/Treatment	Prior Therapy Type	Start Date	Stop Date	Stop Day[1]	Best Response
ccc-ppp	xxx	x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
		x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
		x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
		x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx		NO PRIOR THERAPY					
ccc-ppp	xxx	x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
		x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
		x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
		x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	x	Prior Therapy Name	Type	ddmmmyyyy	ddmmmyyyy	-xx	Response

[1] Day relative to the first dose of study medication or ongoing.
Cross-References: Case Report Form PRIOR CANCER THERAPY (PT).

PROGRAMMER'S NOTES:
Prior Therapy Type includes: Chemotherapy, Hormonal Therapy, Immunotherapy, and Other.
Best Response includes: Complete Response, Partial Response, Stable Disease, Progressive Disease, Unknown, and Not Applicable.
When "No Prior Therapy" is indicated, enter "NO PRIOR THERAPY" in the 'Agent/Treatment' column.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Start Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.4.3
Prior Cancer Radiation
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Site	Start Date	Stop Date	Stop Day [1]	Best Response
ccc-ppp	xxx	NO PRIOR RADIATION				
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response
ccc-ppp	xxx	Reported Site	ddmmmyyyy	ddmmmyyyy	-xx	Response

[1] Day relative to the first dose of study medication or ongoing.
Cross-References: Case Report Form PRIOR CANCER RADIATION (PR).

PROGRAMMER'S NOTES:
When "No Prior Radiation" is indicated, enter "NO PRIOR RADIATION" in the 'Site' column.
Best Response includes: Complete Response, Partial Response, Stable Disease, Progressive Disease, Unknown, and Not Applicable
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Start Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.4.4
Prior Cancer Surgeries
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Procedure (including site)	Procedure Date	Day [1]	Findings (Pathology/Cytology)
ccc-ppp	xxx	Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
ccc-ppp	xxx	Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
ccc-ppp	xxx	Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
ccc-ppp	xxx	Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
ccc-ppp	xxx	Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
ccc-ppp	xxx	Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
ccc-ppp	xxx	Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings
		Procedure Reported and Site	ddmmmyyyy	xx	Description of Findings

[1] Day relative to the first dose of study medication or ongoing.
Cross-References: Case Report Form PRIOR CANCER SURGERIES (SG).

PROGRAMMER’S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort “Patient” in ascending order using “ppp”, and then “ccc” portion of patient number.
Sort “Procedure Date” in ascending order within “Patient”.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.4.5
Medical History/Baseline Symptoms
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Date Obtained	Day[1]	Condition (Preferred Term) (System Organ Class)[2]	Ongoing	Grade	Related to Study Disease	Therapy Given
ccc-ppp	xxx	ddmmmyyyy	-xx	Condition (MedDRA Preferred Term) (MedDRA System Organ Class)	No	Mild	No	xxx
				Condition (MedDRA Preferred Term) (MedDRA System Organ Class)	No	Moderate	No	xxx
ccc-ppp	xxx	ddmmmyyyy	-xx	Condition (MedDRA Preferred Term) (MedDRA System Organ Class)	Yes	Mild	No	xxx

[1] Day relative to the first dose of study medication or ongoing.
[2] MedDRA Version 17.1
Cross-References: Case Report Form MEDICAL HISTORY (MH).

PROGRAMMER'S NOTES:
Grade: 1=Mild, 2=Moderate, 3=Severe, Not Applicable, Unknown.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.4.6
Pregnancy Test
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Method	Sample Date	Cycle/Day [1]	Result	Reason Not Done
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	ddmmmyyyy	x/xx	Negative	
ccc-ppp	xxx	xxx	NOT PERFORMED			Post-Menopausal

[1] Day relative to the first dose of study medication.
Cross-References: Case Report Form PREGNANCY (TP).

PROGRAMMER'S NOTES:
If Pregnancy Test is not performed, enter "NOT PERFORMED" in the 'Sample Date' column.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.5.1.1
L-DOS47 Administration
Safety Evaluable (N=n)

Patient	Cycle	Start Date	Day [1]	Start Time /Stop Time	Dose Level (µg/kg)	Lot No.	Total Dose	Dose Modified	Dose Reduced:Reason	Dose Delayed:Reason	Dose Interrupted:Reason
ccc-ppp	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
ccc-ppp	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx

[1] On-Study day relative to first dose within cycle.
Cross-Reference: Case Report Form L-DOS47 EXPOSURE (EX).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Start Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.5.1.2
Carboplatin Administration
Safety Evaluable (N=n)

Patient	Cycle	Start Date	Day [1]	Start Time /Stop Time	Dose Level (AUC6 mg/mL)	Lot No.	Total Dose	Dose Modified	Dose Reduced:Reason	Dose Delayed:Reason	Dose Interrupted:Reason
ccc-ppp	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
ccc-ppp	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx

[1] On-Study day relative to first dose within cycle.
Cross-Reference: Case Report Form Carboplatin EXPOSURE (EX1).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Start Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.5.1.3
Pemetrexed Administration
Safety Evaluable (N=n)

Patient	Cycle	Start Date	Day [1]	Start Time /Stop Time	Dose Level (mg/m2)	Lot No.		Dose Modified	Dose Reduced:Reason	Dose Delayed:Reason	Dose Interrupted:Reason
ccc-ppp	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
ccc-ppp	x	Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx
		Ddmmmyyyy	xx	HH:MM/HH:MM	xxx	xx	xxx	xxx	xxx:xxx	xxx:xxx	xxx:xxx

[1] On-Study day relative to first dose within cycle.
Cross-Reference: Case Report Form Pemetrexed EXPOSURE (EX2).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Start Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.5.2
Pharmacokinetic Sampling: Blood
Safety Evaluable (N=n)

Patient	Dose Level (µg/kg)	Cycle	Day	Planned Time Point	Sample Date	Sample Time	Collection Status
ccc-ppp	xxx	1	1	Pre-dose	ddmmmyyyy	hh:mm	Collected
				End of L-DOS47 infusion	ddmmmyyyy	hh:mm	Collected
				15 min after SOI	ddmmmyyyy	hh:mm	Not collected
				30 min after SOI	ddmmmyyyy	hh:mm	Collected
				45 min Postdose			
				1 hr Postdose	ddmmmyyyy	hh:mm	Collected
				1.5 hrs Postdose			
				2 hrs Postdose	ddmmmyyyy	hh:mm	Collected
				3 hrs Postdose			
				4 hrs Postdose	ddmmmyyyy	hh:mm	Collected
				6 hrs Postdose	ddmmmyyyy	hh:mm	Collected
				24 hrs Postdose			
				48 hrs Postdose	ddmmmyyyy	hh:mm	Collected
		1	8	Pre-dose	ddmmmyyyy	hh:mm	Collected

Cross-References: Case Report Forms PHARMACOKINETICS (PK, PK1, PK2)

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Sample Date" in ascending order within "Patient".
Sort "Sample Time" in ascending order within "Sample Date".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.6.1
Extent of Disease: Target and Non-Target Lesions
Intent-to-Treat (N=n)

Patient	Dose Level (ug/kg)	Cycle	Date of Procedure	Day [1]	Lesion Type	Lesion Number	Organ	Primary Site	Procedure
ccc-ppp	xxx	Baseline	ddmmmyyyy	-xx	Target	x	Other: Specify		xxxx
					Target	x	Reported Organ		xxxx
					Target	x	Reported Organ		xxxx
									xxxx
					Non-Target	x	Reported Organ	xxxx	
					Non-Target	x	Reported Organ	xxxx	
		x	ddmmmyyyy	xx	Target	x	Reported Organ		
					Target	x	Reported Organ		
					Target	x	Reported Organ		
					Non-Target	x	Reported Organ	xxxx	
					Non-Target	x	Reported Organ	xxxx	
					Non-Target	x	Reported Organ	xxxx	
		End-Study	ddmmmyyyy	xx	Target	x	Reported Organ		
					Target	x	Reported Organ		
					Target	x	Reported Organ		
					Non-Target	x	Reported Organ	xxxx	
					Non-Target	x	Reported Organ	xxxx	
					Non-Target	x	Reported Organ	xxxx	

[1] Baseline day relative to the first dose; On-Study day relative to first dose within cycle; End-Study day relative to last dose.
Cross-References: Case Report Forms TARGET LESION ASSESSMENT (BT, XT), NON-TARGET LESION ASSESSMENT (BN, XN), NEW LESIONS (NL).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portions of patient number.
Sort "Date" in ascending order within "Patient".
Sort "Lesion Type" in descending order within "Date".
Sort "Lesion Number" in ascending order within "Lesion Type".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.6.1
Extent of Disease: Target and Non-Target Lesions
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle	Date of Performed	Day [1]	Lesion Type	Lesion Number	Anatomical Location	Previous RT to Lesion	Progression Since RT?
							Location		
ccc-ppp	xxx	Baseline	ddmmmyyyy	xx	Target	x	Location	No	
					Target	x	Location	No	
					Target	x		No	
							Location		
					Non-Target	x	Location	Yes	xx
					Non-Target	x		Yes	xx
							Location		
		x	ddmmmyyyy	xx	Target	x	Location	No	
					Target	x	Location	No	
					Target	x		No	
							Location		
					Non-Target	x	Location	Yes	xx
					Non-Target	x	Location	Yes	xx
					Non-Target	x		Yes	xx
							Location		
		End-Study	ddmmmyyyy	xx	Target	x	Location	No	
					Target	x	Location	No	
					Target	x		No	
							Location		
					Non-Target	x	Location	Yes	xx
					Non-Target	x	Location	Yes	xx
					Non-Target	x	Location	Yes	xx

[1] Baseline day relative to the first dose; On-Study day relative to first dose within cycle; End-Study day relative to last dose.
Cross-References: Case Report Forms TARGET LESION ASSESSMENT (BT, XT), NON-TARGET LESION ASSESSMENT (BN, XN), NEW LESIONS (NL).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portions of patient number.
Sort "Date" in ascending order within "Patient".
Sort "Lesion Type" in descending order within "Date".
Sort "Lesion Number" in ascending order within "Lesion Type".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.6.1
Extent of Disease: Target and Non-Target Lesions
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle	Date of Performed	Day [1]	Lesion Type	Lesion Number	RECIST Measurement (mm)	Total Sum(mm)	Lesion Assessable	Non-Target Lesion Evaluation
ccc-ppp	xxx	Baseline	ddmmmyyyy	-xx	Target	x	xx		Yes	
					Target	x	xx		Yes	
					Target	x	xx		Yes	
								xx		
					Non-Target	x				Present
					Non-Target	x				Absent
					New Lesion	x				
		x	ddmmmyyyy	xx	Target	x	xx		Yes	
					Target	x	xx		Yes	
					Target	x	xx		Yes	
								xx		
					Non-Target	x				
					Non-Target	x				Present
					Non-Target	x				
		End-Study	ddmmmyyyy	xx	Target	x	xx		Yes	
					Target	x	xx		Yes	
					Target	x	Not Assessable		Yes	
								xx		
					Non-Target	x				Present
					Non-Target	x				Present

[1] Baseline day relative to the first dose; On-Study day relative to first dose within cycle; End-Study day relative to last dose.
Cross-References: Case Report Forms TARGET LESION ASSESSMENT (BT, XT), NON-TARGET LESION ASSESSMENT (BN, XN), NEW LESIONS (NL).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portions of patient number.
Sort "Date" in ascending order within "Patient".
Sort "Lesion Type" in descending order within "Date".
Sort "Lesion Number" in ascending order within "Lesion Type".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.6.2
Cycle Response Assessment
Intent-to-Treat (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle	Date of Procedure	Day [1]	Target Lesion Response	Non-Target Lesion Response[2]	New Lesions	Symptomatic Deterioration	Deterioration Date	Overall Response For This Cycle
ccc-ppp	xxx	x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Complete Response	Complete Response	No	No		Complete Response
		End-Study	ddmmmyyyy	xx	Complete Response	Complete Response	No	No		Complete Response
ccc-ppp	xxx	x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	Yes	ddmmmyyyy	Stable Disease
		x	ddmmmyyyy	xx	Complete Response	Complete Response	No	No		Complete Response
		End-Study	ddmmmyyyy	xx	Complete Response	Complete Response	No	No		Complete Response
ccc-ppp	xxx	x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		End-Study	ddmmmyyyy	xx	Progression	Progression	No	No		Progression
ccc-ppp	xxx	x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Stable Disease	NON-CR/NON-PD	No	No		Stable Disease
		x	ddmmmyyyy	xx	Complete Response	Complete Response	No	No		Complete Response
		End-Study	ddmmmyyyy	xx	Complete Response	Complete Response	No	No		Complete Response

[1] On-Study day relative to first dose within cycle; End-Study day relative to last dose.
[2] NON-CR/NON-PD=Neither complete response nor disease progression
Cross-References: Case Report Form CYCLE RESPONSE ASSESSMENT (RS).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portions of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.6.3
Patient Listing for Duration of Clinical Benefit (CR or PR or SD)
Intent-to-Treat (N=n)

Patient /Age/Sex	L-DOS47 Dose Level(µg/kg)	Date of First Dose	Date of First CR[1]	Date of First PR[1]	Date of SD[1]	Date of Progression (PD)	Date of Censoring	Duration of Clinical Benefit (day) [2]
ccc-ppp xx/x	xx	ddmmmyyyy	ddmmmyyyy					xxx
ccc-ppp xx/x	xx	ddmmmyyyy		ddmmmyyyy			ddmmmyyyy	xxx
ccc-ppp xx/x	xx	ddmmmyyyy			ddmmmyyyy	ddmmmyyyy		xxx
ccc-ppp xx/x	xx	ddmmmyyyy		ddmmmyyyy			ddmmmyyyy	xxx
ccc-ppp xx/x	xx	ddmmmyyyy	ddmmmyyyy					xxx

[1] CR = complete response, PR = partial response, SD= stable disease
[2] Duration of Clinical Benefit is calculated from date of first (CR or PR or SD) to first date of recurrence or objectively documented PD (not including symptomatic deterioration) or death due to any cause. For a patient without evidence of objective disease progression or death, duration of clinical benefit will be censored at the date of the last evaluable tumor assessment. Only patients with a SD or confirmed CR or PR are included in the analysis.
Cross-Reference: Case Report Forms: RECIST Cycle Response Assessment (RS)

PROGRAMMER'S NOTES:
Data used in the SAS Life Table procedure.
Sort "Patient" in ascending order using "ppp", and then "ccc" portions of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.1
Adverse Events
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term) (MedDRA System Organ Class)[1]	DLT	Onset/ Day[2]	Onset Resolved Dates	Therapy Given	Maximum Grade	Serious [3]	Drug Related	Action [4]	Outcome [5]
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term) (MedDRA System Organ Class)	No	xx/xx	ddmmmyyyy ddmmmyyyy	No	Mild	x	Probable	x	x
		ADVERSE EVENT (MedDRA Preferred Term) (MedDRA System Organ Class)	Yes	xx/xx	ddmmmyyyy ongoing	No	Moderate	x	Probable	x	x
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term) (MedDRA System Organ Class)	No	xx/xx	ddmmmyyyy	Yes	Mild	x	Possible	x	x

[1] MedDRA Version 17.1.
[2] On-Study day relative to first dose.
[3] Serious: 1=Not Serious, 2=Results in Death, 3=Life threatening, 4=Hospitalization, 5=Significant Disability, 6=Congenital Anomaly or Birth Defect, 7=Other Medically Important Event.
[4] Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
[5] Outcome: 1=Recovered/Resolved, 2=Recovering/Resolving, 3=Not Recovered/Not Resolved, 4=Recovered/Resolved with sequelae, 5=Fatal, 6=Unknown.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Maximum Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening, 5=Fatal.
Drug Relationship: 1=Unrelated, 2=Unlikely, 3=Possible, 4=Probable, 5=Definite.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Onset Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.2.1
Treatment-Emergent Adverse Events Leading to Dose Reduction
Safety Evaluable
(N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset/Day [1]	Last Dose to Onset [2]	Treatment Duration [3]	Duration of AE [4]	Serious	Drug Relationship
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	Yes	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						

[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Treatment Duration calculated from first dose to treatment discontinuation.
[4] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Use Action Code =2. Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.2.2
Treatment-Emergent Adverse Events Leading to Dose Interruption
Safety Evaluable
(N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset/Day[1]	Last Dose to Onset [2]	Treatment Duration [3]	Duration of AE [4]	Serious	Drug Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	No	Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	Yes	Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	No	Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	No	Relationship

[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Treatment Duration calculated from first dose to treatment discontinuation.
[4] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Use Action Code =3. Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.2.3
Treatment-Emergent Adverse Events Leading to Dose Delay
Safety Evaluable
(N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset/Day [1]	Last Dose to Onset [2]	Treatment Duration [3]	Duration of AE [4]	Serious	Drug Relationship
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	Yes	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						

[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Treatment Duration calculated from first dose to treatment discontinuation.
[4] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Use Action Code =4. Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.2.4
Treatment-Emergent Adverse Events Leading to Dose Reduction and Interruption
Safety Evaluable
(N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset/Day [1]	Last Dose to Onset [2]	Treatment Duration [3]	Duration of AE [4]	Serious	Drug Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	No	Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	Yes	Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	No	Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	No	Relationship

[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Treatment Duration calculated from first dose to treatment discontinuation.
[4] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Use Action Code =5. Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.2.5
Treatment-Emergent Adverse Events Leading to Dose Delay and Reduction
Safety Evaluable
(N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset/Day [1]	Last Dose to Onset [2]	Treatment Duration [3]	Duration of AE [4]	Serious	Drug Relationship
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	Yes	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						

[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Treatment Duration calculated from first dose to treatment discontinuation.
[4] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Use Action Code =6. Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.2.6
Treatment-Emergent Adverse Events Leading to Dose Delay and Interruption
Safety Evaluable
(N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset/Day [1]	Last Dose to Onset [2]	Treatment Duration [3]	Duration of AE [4]	Serious	Drug Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	No	Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	Yes	Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	No	Relationship
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term)	xx/xx	xx	xx	xx	No	Relationship

[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Treatment Duration calculated from first dose to treatment discontinuation.
[4] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Use Action Code =7. Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.2.7
Treatment-Emergent Adverse Events Leading to Dose Delay, Reduction and Interruption
Safety Evaluable
(N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset/Day [1]	Last Dose to Onset [2]	Treatment Duration [3]	Duration of AE [4]	Serious	Drug Relationship
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	Yes	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						

[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Treatment Duration calculated from first dose to treatment discontinuation.
[4] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Use Action Code =8. Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.2.8
Treatment-Emergent Adverse Events Leading to Dose Discontinuation
Safety Evaluable
(N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term)	Onset/Day [1]	Last Dose to Onset [2]	Treatment Duration [3]	Duration of AE [4]	Serious	Drug Relationship
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	Yes	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						
ccc-ppp	xxx	ADVERSE EVENT	xx/xx	xx	xx	xx	No	Relationship
		(MedDRA Preferred Term)						

[1] Onset day relative to first dose.
[2] Last Dose to Onset calculated in days.
[3] Treatment Duration calculated from first dose to treatment discontinuation.
[4] Duration of Adverse Event calculated in days from the Onset Date to the Resolution Date.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Use Action Code =9. Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.3
Patients With Incomplete Adverse Event Information Excluded From Summary Tables
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Adverse Event (MedDRA Preferred Term) (MedDRA System Organ Class)[1]	DLT	Onset/Day [2]	Onset Resolved Dates	Therapy Given	Maximum Grade	Serious [3]	Drug Relationship	Action [4]	Outcome [5]
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term) (MedDRA System Organ Class)	No	xx/xx	ddmmmyyyy ddmmmyyyy	No	Mild	x		x	x
		ADVERSE EVENT (MedDRA Preferred Term) (MedDRA System Organ Class)	Yes	xx/xx	ddmmmyyyy ongoing	No	Moderate	x	Probable		
ccc-ppp	xxx	ADVERSE EVENT (MedDRA Preferred Term) (MedDRA System Organ Class)	No	xx/xx	ddmmmyyyy	Yes	Mild	x			x

[1] MedDRA Version 17.1.
[2] On-Study day relative to first dose.
[3] Serious: 1=Not Serious, 2=Results in Death, 3=Life threatening, 4=Hospitalization, 5=Significant Disability,6=Congenital Anomaly or Birth Defect, 7=Other Medically Important Event.
[4] Action Taken: 1 = None, 2 = Dose Reduced, 3 = Dose Interrupted, 4= Dose Delayed, 5 = Dose Reduced and Interrupted, 6 = Dose Delayed and Reduced, 7 = Dose Delayed and Interrupted, 8 = Dose Delayed, Reduced, Interrupted, 9 = Dose Discontinued.
[5] Outcome: 1=Recovered/Resolved, 2=Recovering/Resolving, 3=Not Recovered/Not Resolved, 4=Recovered/Resolved with sequelae, 5=Fatal, 6=Unknown.
Cross-References: Case Report Form ADVERSE EVENTS (AE).

PROGRAMMER'S NOTES:
Maximum Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Life threatening, 5=Fatal.
Drug Relationship: 1=Unrelated, 2=Unlikely, 3=Possible, 4=Probable, 5=Definite.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Onset Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.4
Death Summary
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Date of Death	Primary Cause of Death
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF
ccc-ppp	xxx	ddmmmyyyy	Cause of Death Reported on CRF

Cross-References: Case Report Form DEATH SUMMARY (DS).

PROGRAMMER'S NOTES:
Present for every death record in the database.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.7.4
Death Summary
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Date of Death	Date of First Dose	Date of Last Dose	Date of Off-Study	Treatment Duration [1]	First Dose to Death (days)	Last Dose to Death (days)	Off-Study to Death (days)
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx
ccc-ppp	xxx	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	ddmmmyyyy	xx	xx	xx	xx

[1] Treatment duration calculated from the first dose of study medication to treatment discontinuation.
Cross-References: Case Report Forms DEATH SUMMARY (DS), L-DOS47 EXPOSURE (EX), OFF-STUDY SUMMARY (OF).

PROGRAMMER'S NOTES:
Present for every death record in the database.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.8.1
Clinical Laboratory Tests - Hematolog
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle/Day	Sample Date	Sample Time	Day [1]	Lab Code	Laboratory Test 1[2] Results	Laboratory Test 1[2] Normal Range	Laboratory Test 1[2] Units	Laboratory Test 2[2] Results	Laboratory Test 2[2] Normal Range	Laboratory Test 2[2] Units
ccc-ppp	xxx	x/xx	ddmmmyyyy	hh:mm	-xx	xxxx	xx.x H G1	xx.x - xx.x	unit	xx.x H G1	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		EOT	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
ccc-ppp	xxx	x/xx	ddmmmyyyy	hh:mm	-xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x L G1	xx.x - xx.x	unit	xx.x L G1	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		EOT	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit

[1] Pre-Study day relative to the first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose.
[2] Reported Result: H = High (Above Normal Range), L = Low (Below Normal Range); Calculated CTCAE 4.0 Grade 1 to 4.
Cross-References: Case Report Form HEMATOLOGY (HM).

PROGRAMMER'S NOTES:
Repeat page as required.
Include following Hematology Tests: hemoglobin, hematocrit, WBC, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils, bands, combined other cells, sum of the differentials.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.8.2
Clinical Laboratory Tests - Blood Chemistry
Safety Evaluable (N=n)

		DoseLevel		Sample		Day	Lab	Laboratory Test 1[2]				Laboratory Test 2[2]			
Patient	Fasted	(ug/kg)	Cycle	Date	Time	[1]	Code	Results		Normal Range	Units	Results		Normal Range	Units
ccc-ppp	xxx	xxx	x	Ddmmmyyyy	hh:mm	-xx	xxxx	xx.x G1	H	xx.x - xx.x	Unit	xx.x G1	H	xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			EOT	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
ccc-ppp	xxx	xxx	x	Ddmmmyyyy	hh:mm	-xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x G1	L	xx.x - xx.x	Unit	xx.x G1	L	xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			x	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit
			EOT	Ddmmmyyyy	hh:mm	xx	xxxx	xx.x		xx.x - xx.x	Unit	xx.x		xx.x - xx.x	Unit

[1] Pre-Study day relative to the first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose.
[2] Reported Result: H = High (Above Normal Range), L = Low (Below Normal Range); Calculated CTCAE 4.0 Grade 1 to 4.
Cross-References: Case Report Form BLOOD CHEMISTRY (BC).

PROGRAMMER'S NOTES:
Repeat page as required.
Include following Blood Chemistry Tests: : albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), urea, calcium, bicarbonate, chloride, creatinine (by Cockcroft-Gault formula), globulin (serum globulin: total protein minus serum albumin), glucose, phosphate, potassium, sodium, magnesium, total bilirubin, total protein.
Data is presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.8.3
Clinical Laboratory Tests - Coagulation
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle/Day	Sample Date	Sample Time	Day [1]	Lab Code	Laboratory Test 1[2] Results	Normal Range	Units	Laboratory Test 2[2] Results	Normal Range	Units
ccc-ppp	xxx	x/xx	ddmmmyyyy	hh:mm	-xx	xxxx	xx.x H G1	xx.x - xx.x	unit	xx.x H G1	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		EOT	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
ccc-ppp	xxx	x/xx	ddmmmyyyy	hh:mm	-xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x L G1	xx.x - xx.x	unit	xx.x L G1	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		EOT	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit

[1] Pre-Study day relative to the first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose.
[2] Reported Result: H = High (Above Normal Range), L = Low (Below Normal Range); Calculated CTCAE 4.0 Grade 1 to 4.
Cross-References: Case Report Form COAGULATION (GA).

PROGRAMMER'S NOTES:
Repeat page as required.
Include following Coagulation Tests: INR, PT, aPTT.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.8.4
Clinical Laboratory Tests – Urinalysis
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle/Day	Sample Date	Time	Day [1]	Lab Code	Laboratory Test 1[2]			Laboratory Test 2[2]		
							Results	Normal Range	Units	Results	Normal Range	Units
ccc-ppp	xxx	x/xx	ddmmmyyyy	hh:mm	-xx	xxxx	xx.x H G1	xx.x - xx.x	unit	xx.x H G1	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		EOT	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
ccc-ppp	xxx	x/xx	ddmmmyyyy	hh:mm	-xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x L G1	xx.x - xx.x	unit	xx.x L G1	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		EOT	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit

[1] Pre-Study day relative to the first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose.
[2] Reported Result: H = High (Above Normal Range), L = Low (Below Normal Range); Calculated CTCAE 4.0 Grade 1 to 4.
Cross-References: Case Report Form URINALYSIS (US).

PROGRAMMER'S NOTES:
Repeat page as required.
Include following Urinalysis Tests: Occult blood, glucose, total protein, ketones, Bilirubin.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

DIRECTORY/FILE.SAS FINAL – ddmmmyy:hh:mm
LDOS001 Page 1 of x

Appendix 16.2.8.5
Other Clinically Significant Laboratory Results
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle/Day	Sample Date	Time	Day [1]	Lab Code	Laboratory Test 1[2] Results	Normal Range	Units	Laboratory Test 2[2] Results	Normal Range	Units
ccc-ppp	xxx	x/xx	ddmmmyyyy	hh:mm	-xx	xxxx	xx.x H G1	xx.x - xx.x	unit	xx.x H G1	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		EOT	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
ccc-ppp	xxx	x/xx	ddmmmyyyy	hh:mm	-xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x L G1	xx.x - xx.x	unit	xx.x L G1	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		x/xx	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit
		EOT	ddmmmyyyy	hh:mm	xx	xxxx	xx.x	xx.x - xx.x	unit	xx.x	xx.x - xx.x	unit

[1] Pre-Study day relative to the first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose.
[2] Reported Result: H = High (Above Normal Range), L = Low (Below Normal Range); Calculated CTCAE 4.0 Grade 1 to 4.
Cross-References: Case Report Form Other Clinically Significant Laboratory Results (UL).

PROGRAMMER'S NOTES:
Repeat page as required.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.9.1
Physical Examination
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level(µg/kg)	Cycle/Day	Examination Date	Day [1]	Significant Findings
ccc-ppp	xxx	Pre-Study	ddmmmyyyy	-xx	No
		x/xx	ddmmmyyyy	xx	No
		x/xx	ddmmmyyyy	xx	No
		x/xx	ddmmmyyyy	xx	No
		EOT	ddmmmyyyy	xx	No
ccc-ppp	xxx	Pre-Study	ddmmmyyyy	-xx	No
		x/xx	ddmmmyyyy	xx	No
		x/xx	ddmmmyyyy	xx	No
		x/xx	ddmmmyyyy	xx	No
		EOT	ddmmmyyyy	xx	Yes
ccc-ppp	xxx	Pre-Study	ddmmmyyyy	-xx	No
		x/xx	ddmmmyyyy	xx	No
		x/xx	ddmmmyyyy	xx	No
		x/xx	ddmmmyyyy	xx	No
		EOT	ddmmmyyyy	xx	No

[1] Pre-Study Day relative to first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose.
Cross-References: Case Report Form PHYSICAL EXAMINATION (PE).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.9.2
Vital Signs
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle/Day	Date Performed	Scheduled Timepoint	Time	Day [1]	Blood Pressure (mmHg) Systolic	Blood Pressure (mmHg) Diastolic	Temperature (unit)	Pulse (beats/min)	Respiration Rate (/min)	Pulse Oximetry (%)
ccc-ppp	xxx	x/xx	ddmmmyyyy	Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
			ddmmmyyyy	Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
			ddmmmyyyy	Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx
				Timepoint	hh:mm	xx	xxx	xx	xx.x	xxx	xx	xx

[1] Pre-Study day relative to first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose.
Cross-References: Case Report Forms SCREENING VITAL SIGNS and VITAL SIGNS (VS, VSx).

PROGRAMMER'S NOTES:
When "Not done" is indicated, enter "NOT DONE" in the 'Time' column.
Add records for "Other unscheduled timepoints" within a day if necessary.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date Performed" in ascending order within "Patient". Sort "Time" in ascending order within "Date".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.9.2
Vital Signs
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)*	Cycle	Date /Day Performed	Scheduled Timepoint	Time	Day [1]	Body Weight (kg)	Height (cm)[2]	BSA (mA2)
ccc-ppp	xxx	x/xx	ddmmmyyyy	Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
			ddmmmyyyy	Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
			ddmmmyyyy	Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x
				Timepoint	hh:mm	xx	xx.x	xxx	xx.x

[1] Pre-Study day relative to first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose
[2] Completed at screening only.
Cross-References: Case Report Forms SCREENING VITAL SIGNS and VITAL SIGNS (VS, VSx).

PROGRAMMER'S NOTES:
When "Not done" is indicated, enter "NOT DONE" in the 'Time' column.
Add records for "Other unscheduled timepoints" within a day if necessary.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date Performed" in ascending order within "Patient". Sort "Time" in ascending order within "Date".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.9.3
ECOG Performance Status
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle/Day	Date Performed	Day [1]	ECOG Performance Status
ccc-ppp	xxx	Pre-Study	ddmmmyyyy	-xx	0 Fully active, able to carry on all pre-disease activities without restriction.
		x/xx	ddmmmyyyy	xx	1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature, e.g., light house work, office work.
		x/xx	ddmmmyyyy	xx	2 Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
		x/xx	ddmmmyyyy	xx	3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
		x/xx	ddmmmyyyy	xx	4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
		End Study	ddmmmyyyy	xx	5 Dead.
ccc-ppp	xxx	Pre-Study	ddmmmyyyy	-xx	0 Fully active, able to carry on all pre-disease activities without restriction.
		x/xx	ddmmmyyyy	xx	1 Restricted in physically strenuous activity but ambulatory and able to carry work of a light or sedentary nature, e.g., light house work, office work.
		x/xx	ddmmmyyyy	xx	2 Ambulatory and capable of all self-care but unable to carry out work activities. Up and about more than 50% of waking hours.
		x/xx	ddmmmyyyy	xx	3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
		x/xx	ddmmmyyyy	xx	4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
		End Study	ddmmmyyyy	xx	5 Dead.

[1] Day relative to the first dose; End of treatment day relative to last dose.
Cross-References: Case Report Form PERFORMANCE STATUS (ES).

PROGRAMMER'S NOTES:
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date Performed" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.9.4
Electrocardiogram
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle/ Day	Date Performed	Planned Timepoint	Time	Day [1]	Heart Rate (beats/min)	PR (msec)	QT (msec)	QTc (msec)	QRS (msec)
ccc-ppp	xxx	Screening	ddmmmyyyy		hh:mm	-xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy		hh:mm	-xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy		hh:mm	-xx	xx	xx	xx.x	xxx	xxx
		x/xx	ddmmmyyyy	Pre-dose	hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy	Pre-Dose	hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy	Pre-Dose	hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy	1 hr post	hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy	1 hr post	hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy	1 hr post	hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy	1.5 hrs post	hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy	1.5 hrs post	hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy	1.5 hrs post	hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy		hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy		hh:mm	xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy		hh:mm	xx	xx	xx	xx.x	xxx	xxx
ccc-ppp	xxx	Screening	ddmmmyyyy		hh:mm	-xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy		hh:mm	-xx	xx	xx	xx.x	xxx	xxx
			ddmmmyyyy		hh:mm	-xx	xx	xx	xx.x	xxx	xxx

[1] Pre-Study day relative to first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose.
Cross-References: Case Report Forms ELECTROCARDIOGRAM (EG).

PROGRAMMER'S NOTES:
When "Not done" is indicated, enter "NOT DONE" in the 'Time' column.
Add records for "Other unscheduled timepoints" within a day if necessary.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date Performed" in ascending order within "Patient". Sort "Time" in ascending order within "Date".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.9.4
Electrocardiogram
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle/Day	Date Performed	Planned Timepoint	Time	Day [1]	Clinical Significance	If abnormal, details
ccc-ppp	xxx	Screening	ddmmmyyyy		hh:mm	-xx	Normal	Details
			ddmmmyyyy		hh:mm	-xx	Normal	Details
			ddmmmyyyy		hh:mm	-xx	Normal	Details
		x/xx	ddmmmyyyy	Pre-dose	hh:mm	xx	Normal	Details
			ddmmmyyyy	Pre-Dose	hh:mm	xx	Normal	Details
			ddmmmyyyy	Pre-Dose	hh:mm	xx	Normal	Details
			ddmmmyyyy	1 hr post	hh:mm	xx	Normal	Details
			ddmmmyyyy	1 hr post	hh:mm	xx	Normal	Details
			ddmmmyyyy	1 hr post	hh:mm	xx	Normal	Details
			ddmmmyyyy	1.5 hrs post	hh:mm	xx	Normal	Details
			ddmmmyyyy	1.5 hrs post	hh:mm	xx	Normal	Details
			ddmmmyyyy	1.5 hrs post	hh:mm	xx	Normal	Details
			ddmmmyyyy		hh:mm	xx	Normal	Details
			ddmmmyyyy		hh:mm	xx	Normal	Details
			ddmmmyyyy		hh:mm	xx	Normal	Details
ccc-ppp	xxx	Screening	ddmmmyyyy		hh:mm	-xx	Normal	Details
			ddmmmyyyy		hh:mm	-xx	Normal	Details
			ddmmmyyyy		hh:mm	-xx	Normal	Details

[1] Pre-Study day relative to first dose; On-Study day relative to first dose within cycle; End of treatment day relative to last dose.
Cross-References: Case Report Forms ELECTROCARDIOGRAM (EG).

PROGRAMMER'S NOTES:
When "Not done" is indicated, enter "NOT DONE" in the 'Time' column.
Add records for "Other unscheduled timepoints" within a day if necessary.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Date Performed" in ascending order within "Patient". Sort "Time" in ascending order within "Date".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

Appendix 16.2.9.5
Immunogenicity Data of L-DOS47
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle Day (day)	Date Collected	Time Collected	Titer	ELISA Result
ccc-ppp	xxx	x/xx (xx)	ddmmmyyyy	HH:MM	xxxx	Negative
			ddmmmyyyy	HH:MM	xxxx	Positive
ccc-ppp	xxx	x/xx (xx)	ddmmmyyyy		xxxx	Inconclusive

[1] Day relative to the first dose of study medication.
[2] WHO-DD version June 2013.
Cross-References: Case Report Form ANTIBODY TESTING (AT).

PROGRAMMER'S NOTES:
When "None" is indicated, enter "NO CONCOMITANT MEASURES" in the 'Drug Name or Treatment' column.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Start Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Present only data is available.

Appendix 16.2.9.6
Immunogenicity Data of Tumour Antigen (CEACAM6)
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Cycle Day (day)	Date Collected	Time Collected	Titer	ELISA Result
ccc-ppp	xxx	x/xx (xx)	ddmmmyyyy	HH:MM	xxxx	Negative
			ddmmmyyyy	HH:MM	xxxx	Positive
ccc-ppp	xxx	x/xx (xx)	ddmmmyyyy		xxxx	Inconclusive

[1] Day relative to the first dose of study medication.
[2] WHO-DD version June 2013.
Cross-References:

PROGRAMMER'S NOTES:
When "None" is indicated, enter "NO CONCOMITANT MEASURES" in the 'Drug Name or Treatment' column.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Start Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.
Present only data is available.

Appendix 16.2.10.1
Concomitant Measures
Safety Evaluable (N=n)

Patient	L-DOS47 Dose Level (µg/kg)	Start Date Stop Date	Start Day Stop Day [1]	Drug Name or Treatment (WHO-DD Preferred Term) (WHO-DD ATC Class Category Level II)[2]	Route	Reason For Use
ccc-ppp	xxx	ddmmmyyyy Ongoing	-xx	Concomitant Measure (WHO-DD Preferred Term) (WHO-DD ATC Class Category Level II)	Route	Reason
		ddmmmyyyy ddmmmyyyy	xx xx	Concomitant Measure (WHO-DD Preferred Term) (WHO-DD ATC Class Category Level II)	Route	Reason
		ddmmmyyyy ddmmmyyyy	xx xx	Concomitant Measure (WHO-DD Preferred Term) (WHO-DD ATC Class Category Level II)	Route	Reason
ccc-ppp	xxx	ddmmmyyyy Ongoing	-xx	Concomitant Measure (WHO-DD Preferred Term) (WHO-DD ATC Class Category Level II)	Route	Reason

[1] Day relative to the first dose of study medication.
[2] WHO-DD version June 2013.
Cross-References: Case Report Form CONCOMITANT MEASURES (CM).

PROGRAMMER'S NOTES:
When "None" is indicated, enter "NO CONCOMITANT MEASURES" in the 'Drug Name or Treatment' column.
Data will be presented in mixed case for formatted variables and upper case only for unformatted variables.
Sort "Patient" in ascending order using "ppp", and then "ccc" portion of patient number.
Sort "Start Date" in ascending order within "Patient".
L-DOS47 Dose Level = 0.59, 0.78, 1.5, 3.0, 6.0, 9.0, 12.0 µg/kg.

List of CSR Appendices

The following appendices apply to the CSR. This RAP provides the listings for Appendix 16.2.

Appendix	Description
16.1	**Study Information**
16.1.1	Protocol and protocol amendments
16.1.2	Sample case report form
16.1.3	List of IECs or IRBs and representative written information for patient and sample consent forms
16.1.4	List and description of investigators and other important participants in the study + CVs
16.1.5	Signatures of principal investigator(s) and sponsor representatives
16.1.6	Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used
16.1.7	Randomization scheme and codes
16.1.8	Audit certificates
16.1.9	Documentation of statistical methods
16.1.10	Documentation of inter-laboratory standardization methods and quality assurance procedures if used
16.1.11	Publications based on the study
16.1.12	Important publications referenced in the report
16.2	**Patient Data Listings**
16.2.1	Patient accountability (includes Discontinued Patients and Inclusion/Exclusion Criteria)
16.2.3	Patients excluded from the efficacy analysis
16.2.4	Demographic data and baseline characteristics
16.2.5	Compliance and/or drug concentration data
16.2.6	Individual efficacy response data
16.2.7	Adverse event listings
16.2.8	Individual laboratory measurements by patient
16.2.9	Other safety listings (Vital Signs, ECG, Physical Exam etc.)
16.2.10	Concomitant medications