# Contents



# Tables

## Schedule of study assessments

**Table S1. Study Assessments**

| | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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] | × | | | | | | | | | |
| Inclusion/exclusion criteria | × | × | | | | | | | | |
| Demographics | × | | | | | | | | | |
| Weight | × | × pre-dose | | | | | | × D1 pre-dose | | |
| Medical History | × | | | | | | | | | |
| Physical Examination | × | × pre-dose | × pre-dose | | | × | × | × D1, 8, 15 pre-dose | | |
| Performance Status (ECOG) | × | × | | | | × | × | × D1 | | |
| Radiologic examination[6] and tumor assessment | × | × | | | | × (if >6 weeks post last scan) | × (if >6 weeks post last scan) | × D1 every other cycle | × | × |
| Historic biopsy sample (if available) | × | | | | | | | | | |
| Tumor antigen assessment (CEACAM)[7] | | × pre-dose Cycle 2 only | × pre-dose Cycle 4 only | | | × (only if not done on C4D8) | × (only if not done on C4D8) | | | |
| Vital Signs (temp/HR/BP/RR/ pulse oximetry)[8,20] | × | × pre- & post-dose | × pre- & post-dose | × | | × | × | × D1, 8, 15 | | |
| Electrocardiogram[9,20] | × | × pre- & post-dose | × pre- & post-dose | | | × | × | × D1 and 8 pre-dose & post-dose (optional[10]) | | |
| Clinical lab tests[4] Hematology Chemistry Coagulation | × | × pre-dose | × pre-dose | | | × | × | × D1, 8, 15 pre-dose | | |
| Urinalysis[5] | × | × pre-dose | × pre-dose | | | × | × | × D1, 8, 15 pre-dose | | |
| Pregnancy test[11] | × | × pre-dose | | | | × | × | × D1 pre-dose | | |
| L-DOS47 administration[12] | | × | × | × | | | | × D1, 8, 15 | | |
| Pemetrexed/Carboplatin administration[13] | | × | | | | | | | | |

**Table S1. Study Assessments**

| | 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 | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 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] | | × | × | | | | | | | |
| Serum collection for anti-L-DOS47 antibody testing[15] | | × pre-dose | × pre-dose C1 only | | | × | × | × Day 1 pre-dose | × | |
| Concomitant medications | × | ×[16] pre-dose | ×[16] pre-dose | | | × | × | × D1, 8, 15 pre-dose | × | |
| Adverse events | | ×[17] | ×[17] | ×[17] | ×[17] | × | × | × D1, 8, 15 pre-dose & post-dose | × | |
| Disease progression and survival[18] | | | | | | | | | | × |

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

1. Informed consent was obtained before any experimental procedure or test was performed.
2. All patients were administered up to four cycles of L-DOS47 during the study treatment period. Treatment cycles were 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; (ii) at the time of discontinuation from the study. Note: All patients who were withdrawn from the study completed 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, 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 (pre-dose [0 hours]) on Day 1 (pre-dose [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: pre-dose and 10 and 20 minutes (during infusion), and 30 minutes (prior to end of infusion) and 1, 2, and 4 hours post-dose; Cycle 2, Days 1 and 8: pre-dose and 15 minutes (during infusion), and 30 minutes (prior to end of infusion). Cycle 2, Day 1 at 1 and 2 hours post-dose; Cycle 2, Day 8 at 1, 2, and 4 hours post-dose; Cycles 3 and 4, Days 1 and 8: pre-dose 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 as follows: pre-dose and at 1 and 1.5 hours post-dose.
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 was 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: pre-dose and serially post-dose (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 post-dose; Cycles 2 and 4, Day 8: pre-dose and serially post-dose (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 post-dose; Cycle 2, Day 1; Cycle 3, Days 1 and 8; Cycle 4, Day 1: pre-

dose and 30 minutes* post-dose (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 to be no change in the PK sampling timepoints, which are all relative to the start of L-DOS47 infusion. PK samples collected at 30 minutes and 45 minutes would be considered 'during infusion' samples and PK sample collected at 60 minutes (1 hour) would be a 'prior to end of infusion' sample. All other timepoints would remain the same.

15. Serum samples were collected (2 mL/ in SST tubes) for anti-L-DOS47 antibody testing on Cycle 1 (Day 1 [pre-dose; baseline] and Day 8 [pre-dose]), Cycles 2 through 4 (Day 1 [pre-dose]), all additional cycles (i.e., Cycle 5 and beyond, Day 1 [pre-dose], at the End-of-Treatment Visit or Early Termination Visit, and 30 days after the last dose.
16. Concomitant medications were recorded pre-dose on Days 1 and 8 of each cycle
17. AEs were recorded pre-dose and post-dose on Days 1, 8, and 15 of each cycle, and the Cycle 4 End-of-Treatment Visit. On non-visit days, AEs were monitored by telephone contact. AE monitoring on Day 21 only occurred under the circumstance that 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 one of the following occurred: 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 the acceptable lapse in assessment/sample collection.

## Definition of Dose Limiting Toxicity

In the standard dose escalation phase (cohorts 1, 2, 6 and 7), a Dose-limiting toxicity (DLT) was defined as the occurrence of any of the following events (according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) that occurred within 21 days after commencing study drug treatment and were considered to be possibly, probably or definitely related to L-DOS47 by the Investigator.

- Hematologic AEs Grade ≥4
- Non hematologic AEs Grade ≥3

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 to be considered a DLT.

In the accelerated dose escalation phase of the study (cohorts 3 – 5), DLT was defined as the occurrence of any of the following events (according to NCI CTCAE v4.0) 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:

- Hematologic adverse events (AEs) Grade ≥4
- Non hematologic AEs Grade ≥3
- One instance each of any two unique Grade 2 AEs

## Criteria for delayed dosing or withdrawal of L-DOS47 treatment

If a patient experienced a DLT, the patient was to be withdrawn from the study and not receive further doses of L-DOS47.

To meet the criteria for re-treatment, all toxicities considered by the Investigator to be related to therapy with L-DOS47 (excluding alopecia or anemia), had to 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 re-treatment criteria, the dose was to be held and the patient reassessed weekly (or sooner if deemed clinically appropriate), for possibility of re-treatment. 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 delay/modifications

Dose modifications for subsequent cycles were required when any of the dose delay conditions in Table S2 or L-DOS47 toxicity criteria in in Table S3 were met. Only one dose level reduction was allowed, to the dose level of the previous cohort (or 0.46 µg/kg for patients in cohort 1). If making the decision for dose modification, the worst-case scenario was to be used.

**Table S2. Dose Delay Definitions**

| 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 * |
| 8 to 14 days | 1st | Dose reduction |
| 8 to 14 days | 2nd | Withdrawn * |

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

**Table S3. Toxicity Criteria for L-DOS47 Dose Modification**

| 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 [a] |
| **Thrombocytopenia[(b)]** | 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 [a] |
| **Bleeding** | 1 or 2 | 1st | Possible, probable, definite | Dose reduction |
| | 1 or 2 | Any, prior dose reduction | Possible, probable, definite | Withdrawn [a] |
| | 3 or 4 | 1st | Possible, probable, definite | Withdrawn [a] |
| **Non-hematological** | | | | |
| | 3 | 1st | Possible, probable, definite | Dose reduction |
| | 3 | 2nd, prior dose reduction | Possible, probable, definite | Withdrawn [a] |
| | 4 | 1st | Possible, probable, definite | Withdrawn [a] |

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

[(b)] Without bleeding or platelet transfusion.

## Criteria for dose reduction/modification for pemetrexed and carboplatin

Doses were to be reduced for hematological and other AEs. Dose adjustments were to be made according to the system showing the greatest degree of toxicity, graded using the NCI CTCAE v4.0.

Any patient requiring a dose reduction was to continue to receive a reduced dose for the remainder of the study. Any patient with two 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 to be based on platelet and neutrophils nadir (lowest value) counts from the preceding cycle of therapy. Absolute neutrophil count (ANC) had to be $\geq 1.5 \times 10^9$/L and platelets $\geq 100 \times 10^9$/L prior to the start of any cycle. Treatment was to be delayed to allow sufficient time for recovery. Upon recovery, if treatment was resumed, it was to be done according to the guidelines shown in Table S4.

**Table S4. Dose Adjustments for Pemetrexed and Carboplatin based on Nadir Hematologic Values for Preceding Cycle**

| Platelets ($\times 10^9$/L) Nadir | | ANC ($\times 10^9$/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 two dose reductions | | Recurrence of Grade 3 or 4 neutropenia after two dose reductions | Discontinue pemetrexed and carboplatin |

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 had resolved before proceeding. Treatment with pemetrexed was to be resumed at 75% of the previous dose level. The carboplatin was to remain the same.

For other non-hematologic effects greater than or equal to Grade 3, with the exception of alopecia and mucositis, treatment was 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.

**Table S5. 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 | Discontinue pemetrexed | Discontinue carboplatin |

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

**Table S6. 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) | Discontinue pemetrexed | Discontinue carboplatin |

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

## Concomitant medications

| **Table S7. WHO-DD ATC Class Category Level II** | **Overall (N=14)** |
|---|---|
| Antianemic preparations | 13 (92.9%) |
| Antiemetics and antinauseants | 10 (71.4%) |
| Corticosteroids for systemic use | 10 (71.4%) |
| Analgesics | 9 (64.3%) |
| Antithrombotic agents | 9 (64.3%) |
| Vitamins | 8 (57.1%) |
| Drugs for acid related disorders | 7 (50.0%) |
| Drugs for constipation | 7 (50.0%) |
| Lipid modifying agents | 7 (50.0%) |
| Agents acting on the renin-angiotensin system | 6 (42.9%) |
| Antiinflammatory and antirheumatic products | 6 (42.9%) |
| Psychoanaleptics | 6 (42.9%) |
| Antihistamnines for systemic use | 5 (35.7%) |
| Psycholeptics | 5 (35.7%) |
| All other therapeutic products | 4 (28.6%) |
| Antibacterials for systemic use | 4 (28.6%) |
| Beta blocking agents | 4 (28.6%) |
| Blood substitutes and perfusion solutions | 4 (28.6%) |
| Calcium channel blockers | 4 (28.6%) |
| Cough and cold preparations | 4 (28.6%) |
| Diuretics | 4 (28.6%) |
| Drugs for obstructive airway diseases | 4 (28.6%) |
| Drugs used in diabetes | 4 (28.6%) |
| Mineral supplements | 4 (28.6%) |
| Urologicals | 4 (28.6%) |
| Nasal preparations | 3 (21.4%) |
| Thyroid therapy | 3 (21.4%) |
| Antidiarrheals, intestinal antiinflammatory | 2 (14.3%) |
| Corticosteroids, dermatological preparations | 2 (14.3%) |
| Drugs for functional gastrointestinal disorders | 2 (14.3%) |
| Drugs for treatment of bone diseases | 2 (14.3%) |
| Other nervous system drugs | 2 (14.3%) |
| Stomatological preparations | 2 (14.3%) |
| Unspecified herbal and traditional medicine | 2 (14.3%) |
| Anesthetics | 1 (7.1%) |
| Antifungals for dermatological use | 1 (7.1%) |
| Antigout preparations | 1 (7.1%) |
| Antiprotozoals | 1 (7.1%) |
| Antipruritics, including antihistamines, anesthetics | 1 (7.1%) |

| Table S7. WHO-DD ATC Class Category Level II | Overall (N=14) |
|---|---|
| Antivirals for systemic use | 1 (7.1%) |
| Cardiac therapy | 1 (7.1%) |
| General nutrients | 1 (7.1%) |
| Immunostimulants | 1 (7.1%) |
| Immunosuppressants | 1 (7.1%) |
| Muscle relaxants | 1 (7.1%) |
| Other alimentary tract and metabolism products | 1 (7.1%) |
| Peripheral vasodilators | 1 (7.1%) |

## Safety data

**Table S8. Summary of Treatment Emergent Adverse Events (All Grades)**

| MedDRA System Organ Class[1] | Overall (N=14) |
|---|---|
| Gastrointestinal disorders | 13 (92.9%) |
| General disorders and administration site conditions | 10 (71.4%) |
| Metabolism and nutrition disorders | 10 (71.4%) |
| Respiratory, thoracic and mediastinal disorders | 8 (57.1%) |
| Blood and lymphatic system disorders | 7 (50.0%) |
| Skin and subcutaneous tissue disorders | 7 (50.0%) |
| Investigations | 6 (42.9%) |
| Vascular disorders | 6 (42.9%) |
| Musculoskeletal and connective tissue disorders | 5 (35.7%) |
| Nervous system disorders | 5 (35.7%) |
| Infections and infestations | 4 (28.6%) |
| Psychiatric disorders | 4 (28.6%) |
| Renal and urinary disorders | 4 (28.6%) |
| Cardiac disorders | 1 (7.1%) |

[1] MedDRA version 17.1
[2] Number of Patients used as denominator to calculate percentages.
[3] Patients with multiple 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.

**Table S9. Summary of L-DOS47-Related TEAEs**

| MedDRA System Organ Class<br>MedDRA Preferred Term [1] | Overall (N=14) |
|---|---|
| Number of patients with any L-DOS47-related [4], TEAEs [2,3] | 7 (50.0%) |
| **General disorders and administration site conditions** | **4 (28.6%)** |
| Pyrexia | 2 (14.3%) |
| Chills | 1 (7.1%) |
| Fatigue | 1 (7.1%) |
| Oedema peripheral | 1 (7.1%) |
| **Skin and subcutaneous tissue disorders** | **3 (21.4%)** |
| Rash | 2 (14.3%) |
| Alopecia | 1 (7.1%) |
| Rash generalised | 1 (7.1%) |
| **Blood and lymphatic system disorders** | **2 (14.3%)** |
| Neutropenia | 1 (7.1%) |
| Thrombocytopenia | 1 (7.1%) |
| **Gastrointestinal disorders** | **2 (14.3%)** |
| Constipation | 2 (14.3%) |
| Abdominal pain | 1 (7.1%) |
| **Vascular disorders** | **2 (14.3%)** |
| Flushing | 1 (7.1%) |

**Table S9. Summary of L-DOS47-Related TEAEs**

| MedDRA System Organ Class<br>MedDRA Preferred Term [1] | Overall (N=14) |
|---|---|
| Hypertension | 1 (7.1%) |
| **Investigations** | **1 (7.1%)** |
| Alanine aminotransferase increased | 1 (7.1%) |
| Neutrophil count decreased | 1 (7.1%) |
| White blood cell count decreased | 1 (7.1%) |
| **Metabolism and nutrition disorders** | **1 (7.1%)** |
| Decreased appetite | 1 (7.1%) |
| Hypomagnesaemia | 1 (7.1%) |
| **Nervous system disorders** | **1 (7.1%)** |
| Headache | 1 (7.1%) |
| **Respiratory, thoracic and mediastinal disorders** | **1 (7.1%)** |
| Cough | 1 (7.1%) |
| Pneumonitis | 1 (7.1%) |

[1] MedDRA version 17.1
[2] Number of patients used as denominator to calculate percentages.
[3] Patients with multiple 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.
[4] Considered to have a possible, probable or definite relationship to L-DOS47.

**Table S10. Summary of Grade ≥3 TEAEs Occurring in the Study**

| MedDRA System Organ Class<br>MedDRA Preferred Term [1] | Overall (N=14) |
|---|---|
| Number of patients with any ≥ Grade 3 [4], TEAEs [2,3] | 12 (85.7%) |
| **Blood and lymphatic system disorders** | **5 (35.7%)** |
| Neutropenia | 3 (21.4%) |
| Anaemia | 2 (14.3%) |
| Febrile neutropenia | 1 (7.1%) |
| **Investigations** | **5 (35.7%)** |
| Neutrophil count decreased | 4 (28.6%) |
| White blood cell count decreased | 3 (21.4%) |
| Platelet count decreased | 2 (14.3%) |
| **Gastrointestinal disorders** | **2 (14.3%)** |
| Abdominal pain | 1 (7.1%) |
| Nausea | 1 (7.1%) |
| **Metabolism and nutrition disorders** | **2 (14.3%)** |
| Hyperglycaemia | 1 (7.1%) |
| Hypokalaemia | 1 (7.1%) |
| **Nervous system disorders** | **2 (14.3%)** |
| Syncope | 2 (14.3%) |
| Loss of consciousness | 1 (7.1%) |
| **Respiratory, thoracic and mediastinal disorders** | **2 (14.3%)** |
| Pulmonary embolism | 2 (14.3%) |
| Dyspnoea | 1 (7.1%) |
| Pleural effusion | 1 (7.1%) |
| **Vascular disorders** | **2 (14.3%)** |
| Hypertension | 1 (7.1%) |
| Superior vena cava syndrome | 1 (7.1%) |
| **General disorders and administration site conditions** | **1 (7.1%)** |
| Chest pain | 1 (7.1%) |
| **Infections and infestations** | **1 (7.1%)** |
| Bacteraemia | 1 (7.1%) |

[1] MedDRA version 17.1
[2] Number of patients used as denominator to calculate percentages.
[3] Patients with multiple TEAEs were only counted once within a summary category: system organ class, preferred term or maximum grade. 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.

## Efficacy data

**Table S11. Best Overall Response Summary (Efficacy Evaluable Population)**

| Best Overall Response | L-DOS47 Dose Cohort (µg/kg) + Pemetrexed/Carboplatin | | | | Overall |
|---|---|---|---|---|---|
| | 0.59 | 0.78 | 1.5/3.0/6.0 [5] | 9.0 | |
| Number of patients [1] | 1 | 6 | 3 | 2 | 12 |
| Partial response (PR) | 1 (100.0%) | 3 (50.0%) | 1 (33.3%) | 0 | 5 (41.7%) |
| Stable disease (SD) | 0 | 1 (16.7%) | 1 (33.3%) | 2 (100.0%) | 4 (33.3%) |
| Progressive disease (PD) | 0 | 2 (33.3%) | 1 (33.3%) | 0 | 3 (25.0%) |
| Objective response rate (CR+PR) [2,4] | 1 (100.0%) | 3 (50.0%) | 1 (33.3%) | 0 (0.0%) | 5 (41.7%) |
| Lower 95% confidence limit | (2.5%) | (11.8%) | (0.8%) | (0.0%) | (15.2%) |
| Upper 95% confidence limit | (100.0%) | (88.2%) | (90.6%) | (84.2%) | (72.3%) |
| Clinical benefit (CR+PR+SD) [3,4] | 1 (100.0%) | 4 (66.7%) | 2 (66.7%) | 2 (100.0%) | 9 (75.0%) |
| Lower 95% confidence limit | (2.5%) | (22.3%) | (9.4%) | (15.8%) | (42.8%) |
| Upper 95% confidence limit | (100.0%) | (95.7%) | (99.2%) | (100.0%) | (94.5%) |

[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.
[5] BOR was SD in the patient in the 1.5 µg/kg dose cohort (patient 003-011), PR in the patient in the 3.0 µg/kg dose cohort (patient 003-012), and PD in the patient in the 6.0 µg/kg dose cohort (patient 003-013).

## Pharmacokinetic data

**Table S12. Summary L-DOS47 Pharmacokinetic Parameters**

| L-DOS47 Dose (µg/kg) | Cycle/Day | $T_{max}$[a] (hr) | $C_{max}$[b] (ng/mL) | $T_{½}$[b] (hr) | $AUC_{tlast}$[b] (hr·ng/mL) |
|---|---|---|---|---|---|
| 0.59 | 1/1 | 0.5 (0.5 - 0.5) | 15.5 ±5.17 | NC | 47.1 ±27.2 |
| | 1/8 | 0.75 (0.5 - 1) | 12.9 ±ID | NC | 37.6 ±ID |
| 0.78 | 1/1 | 0.75 (0.5 - 0.75) | 21.5 ±4.61 | NC | 73.9 ±15.2 |
| | 1/8 | 0.5 (0.5 - 0.75) | 20.9 ±5.93 | NC | 53.2 ±22.6 |
| | 2/8 | 0.5 (0.5 - 0.5) | 12.3 ±ID | NC | 18.7 ±ID |
| | 4/8 | 1 (1 - 1) | 12.0 ±ID | NC | 21.0 ±ID |
| 1.5 | 1/1 | 0.75 (0.75 - 0.75) | 41.5 ±ID | 9.21 ±ID | 398 ±ID |
| 3.0 | 1/1 | 0.75 (0.75 - 0.75) | 72.6 ±ID | 6.59 ±ID | 588 ±ID |
| | 1/8 | 0.75 (0.75 - 0.75) | 78.2 ±ID | NC | 186 ±ID |
| | 2/8 | 0.75 (0.75 - 0.75) | 8.97 ±ID | NC | 4.50 ±ID |
| 6.0 | 1/1 | 0.5 (0.5 - 0.5) | 104 ±ID | 7.30 ±ID | 958 ±ID |
| | 1/8 | 0.5 (0.5 - 0.5) | 62.5 ±ID | NC | 128 ±ID |
| 9.0 | 1/1 | 0.63 (0.5 - 0.75) | 179 ±ID | 7.00 ±ID | 1550 ±ID |
| | 1/8 | 0.75 (0.75 - 0.75) | 148 ±ID | 7.16 ±ID | 1140 ±ID |
| | 2/8 | 0.5 (0.5 - 0.5) | 98.3 ±ID | 1.95 ±ID | 150 ±ID |

[a] Median (Min – Max)
[b] Arithmetic mean ± standard deviation
ID, insufficient data; NC, not calculable.

## Assessment of immunogenicity

The immunogenicity of L-DOS47 was evaluated from serum samples collected on Cycle 1, Day 1 (pre dose; baseline) and Day 8 (pre dose), Cycles 2 through 4 (Day 1, pre dose), all additional cycles (i.e., Cycle 5 and beyond, Day 1 (pre dose), at the End of Treatment or early termination visit, and at the follow-up visit (30 days after the last dose).

Anti-L-DOS47 antibodies in human serum were detected using an electrochemiluminescence (ECL) immunoassay. The assay employs a bridging format in which samples are pretreated with

acid to induce dissociation of immune complexes prior to analysis then incubated with both biotinylated L-DOS47 (bL-DOS47) and ruthenylated L-DOS47 (RuL-DOS47), where any ADA bind to both the bL-DOS47 and RuL-DOS47 molecules to form an antigen-antibody bridge complex. The samples are then transferred to a streptavidin (SA) plate where the bL-DOS47 in the complex binds to the SA in the wells. After washing and Read Buffer addition, voltage is applied which causes the RuL DOS47 to produce an ECL signal in which the amount of light produced is proportional to the amount of antigen-antibody complexes. The method was developed and validated by Charles River (Montreal).