# CLINICAL STUDY PROTOCOL
# IND: 118108

## A Phase 1b/2 Dose Escalation and Expansion Trial of NC-6004 (Nanoparticle Cisplatin) plus Gemcitabine in Patients with Advanced Solid Tumors or Squamous Non-Small Cell Lung, Biliary Tract, and Bladder Cancer

## NC-6004-004A

**Sponsor:** NanoCarrier Co, Ltd
144-15 Chuo Gaiku, 226-39 Wakashiba Kashiwa
Chiba, 277-0871, Japan

**Sponsor Contact:**
Director of International Clinical Development
NanoCarrier Co, Ltd
Telephone: +81-3-3241-0551

**Medical Monitor:**
Medical Director, Pharmacovigilance
PPD, Inc.
929 North Front Street
Wilmington, North Carolina, 28401-3331, USA
Telephone: 800-201-8725

**Current Version and Date of Protocol:** Amendment 4, Version 5.0: 13 March 2017

**Previous Dates and Versions:**
Original, Version 1.2: 17 October 2013 (US only)
Amendment 1, Version 2.0: 31 December 2014 (US only)
Amendment 2, Version 3.0: 07 July 2015 (US only)
Amendment 3, Version 4.0: 31 July 2016 (US only)
Amendment 3, Version 4.1: 31 August 2016 (EU only)
Amendment 3, Version 4.2: 12 December 2016 (US and EU; harmonizes versions 4.0 and 4.1)

# CONFIDENTIAL



The study will be conducted according to the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice.

# Protocol Approval - Sponsor Signatory

| | |
|---|---|
| Study Title | A Phase lb/2 Dose Escalation and Expansion Trial of NC-6004 (Nanoparticle Cisplatin) plus Gemcitabine in Patients with Advanced Solid Tumors or Squamous Non-Small Cell Lung, Biliary Tract, and Bladder Cancer |
| Protocol Number | NC-6004-004A |
| Protocol Date | Protocol Version Final 5.0 incorporating Amendment 4 -13 March 2017 |

Protocol accepted and approved by:

[redacted]

144-15 Chuo Gaiku, 226-39 Wakashiba Kashiwa
Chiba, 277-0871, Japan

[redacted]

Sign Date

# Declaration of Investigator

I have read and understood all sections of the protocol entitled "A Phase 1b/2 Dose Escalation and Expansion Trial of NC-6004 (Nanoparticle Cisplatin) plus Gemcitabine in Patients with Advanced Solid Tumors or Squamous Non-Small Cell Lung, Biliary Tract, and Bladder Cancer" and the accompanying investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the Final Protocol Version 5.0, dated 13 March 2017, the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations. I will not make changes to the protocol before consulting with NanoCarrier Co, Ltd. or implement protocol changes without independent ethics committee approval except to eliminate an immediate risk to patients. I agree to administer study treatment only to patients under my personal supervision or the supervision of a subinvestigator.

I will not supply the investigational drug to any person not authorized to receive it. Confidentiality will be protected. Patient identity will not be disclosed to third parties or appear in any study reports or publications.

I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from NanoCarrier Co, Ltd.

| | |
|---|---|
| Signature of Principal Investigator | Date |

Printed Name of Principal Investigator

# Table of Contents

# List of Tables

# Protocol Synopsis

| | |
|---|---|
| **Protocol Number:** | NC-6004-004A |
| **Title:** | A Phase 1b/2 Dose Escalation and Expansion Trial of NC-6004 (Nanoparticle Cisplatin) plus Gemcitabine in Patients with Advanced Solid Tumors or Squamous Non-Small Cell Lung, Biliary Tract, and Bladder Cancer |
| **Sponsor:** | NanoCarrier Co, Ltd |
| **Study Phase:** | 1b/2 |
| **Study Sites:** | At least 20 sites in the United States and Europe |
| **Indication:** | Part 1: Advanced solid tumors<br>Part 2: First-line metastatic squamous non-small cell lung cancer (NSCLC); first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and first-line metastatic or locally advanced transitional cell carcinoma (TCC) of the urinary tract (bladder cancer) |
| **Rationale:** | NC-6004 is a polymeric micelle containing cisplatin as an active moiety. The nanoparticle provides sustained release of the cisplatin and utilizes the enhanced permeability retention-effect to target the release of platinum to tumors. Synergistic effects of cisplatin and gemcitabine have been evaluated extensively in various types of tumor cell lines, including NSCLC cell lines, and nonclinical studies have demonstrated that, in tumors in which the combination of cisplatin and gemcitabine exhibit synergistic effects, the combined effects of NC-6004 and gemcitabine also are synergistic. This study will establish a maximum-tolerated dose (MTD) and recommended Phase 2 (RPII) dose of NC-6004 in combination with gemcitabine and evaluate the initial activity and tolerability profile. |
| **Objectives:** | The primary objectives of this study are:<br>• In the dose-escalation phase of the study (Part 1), to determine the dose-limiting toxicities (DLTs), MTD, and RPII dose of NC-6004 in combination with gemcitabine;<br>• In the expansion phase of the study (Part 2), to evaluate the activity of NC-6004 in combination with gemcitabine in patients with first-line Stage IV squamous NSCLC, first-line advanced or metastatic biliary tract cancer, and first-line metastatic or locally advanced bladder cancer compared with historical control as measured by local |

investigator/radiologist-assessed progression-free survival (PFS), according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

The secondary objectives of this study are:

- To evaluate overall response rate (ORR), disease control rate (DCR = complete response + partial response + stable disease), duration of response (DOR), PFS, overall survival (OS)
- To evaluate therapy-related adverse events (AEs)
- To evaluate the safety and tolerability of NC-6004 when combined with gemcitabine
- To evaluate quality of life using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
- To evaluate acute and delayed symptoms using the MD Anderson Symptom Inventory (MDASI) and a nausea and vomiting patient diary

The exploratory objective of this study is:

- To assess the pharmacokinetic and pharmacodynamic effects of NC-6004.

**Patient Population:**

**Inclusion Criteria**

Each patient must meet all of the following criteria to be enrolled in this study:

1. Provide signed written informed consent prior to the initiation of any study-specific procedures.
2. (Part 1 only) Have a histologically or cytologically confirmed diagnosis of advanced solid tumor that has relapsed or is refractory to standard curative or palliative therapy or has a contraindication to standard therapy.

   (Part 2 only) Cohort 1: Have histologically or cytologically confirmed diagnosis of Stage IV squamous NSCLC and have not received prior chemotherapy or immunotherapy for metastatic disease and are not known to be PD-L1 positive (known high PD-L1 expression defined as Tumor Proportion Score [TPS] greater than or equal to 50%). Patients with known sensitizing mutation in the epidermal growth factor receptor (EGFR) gene or anaplastic lymphoma kinase (ALK) fusion oncogene must have received at least 1 and up to

2 targeted therapies prior to enrollment.

- A patient with stable, treated brain metastases is eligible, provided that there is no evidence of progression after treatment and the patient does not require corticosteroids, or, if the patient requires corticosteroids, has been receiving a stable dose of corticosteroids for at least 14 days prior to assignment to treatment.
- Patients whose tumors are known to harbor an exon 19 deletion or exon 21 L858R EGFR mutation must have had intolerance or have progressed on at least 1 and up to 2 EGFR tyrosine kinase inhibitors.
- Patients whose tumors are known to harbor an ALK translocation must have had intolerance or have progressed on at least 1 and up to 2 ALK inhibitors.

(Part 2 only) Cohort 2: Have histologically or cytologically confirmed diagnosis of nonresectable, recurrent, or metastatic biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma) and have not received prior systemic anticancer therapy for advanced or metastatic disease.

(Part 2 only) Cohort 3: Have histologically or cytologically confirmed diagnosis of metastatic or locally advanced TCC of the urinary tract (bladder, urethra, ureter, renal pelvis) (T3b-T4 N0 M0, Tany N1-N3 M0, or Tany Nany M1) and are not candidates for surgery.

- Patients must not have received prior treatment with systemic anticancer therapy for metastatic or locally advanced urinary tract cancer.
- Certain mixed histologies that are predominantly (>50%) TCC are eligible: squamous, adenocarcinoma, and undifferentiated. Mixed undifferentiated histology requires immunohistochemistry consistent with a TCC origin. Predominantly squamous or neuroendocrine tumors are excluded.

3. Have measurable disease per RECIST version 1.1.
4. Are males or females aged ≥18 years.
5. Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 1, with the exception of patients in Part 2 (Cohort 3, unfit bladder cancer patients) who

may have an ECOG PS of 2.

6. Have adequate bone marrow reserve defined as:
   - Absolute neutrophil count of at least $1.5 \times 10^9$/L,
   - Platelet count of at least $100 \times 10^9$/L, and
   - Hemoglobin level of at least 10 g/dL (transfusion is allowed to achieve hemoglobin level of at least 10 g/dL).
7. Have adequate liver function defined as:
   - Total serum bilirubin <1.5 × upper limit of normal (ULN) and
   - Baseline alanine transaminase and aspartate transaminase <2.0 × ULN or, in patients with documented hepatic metastasis <5.0 × ULN and
   - Serum albumin ≥3.5 g/dL
8. Prothrombin time within normal limits
9. In Part 1 and in Part 2 in Cohorts 1 and 2: have adequate renal function defined as a creatinine clearance (CrCl) ≥50 mL/minute (calculated according to the formula of Cockcroft and Gault 1976) or serum creatinine <1.5 mg/dL. In Part 2, patients in Cohort 3 (bladder cancer) must have a CrCl of ≥30 mL/min.
   - Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 and ≥60 mL/min and ECOG PS 0 to 1. If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.
10. Have a negative pregnancy test result at screening (for females of childbearing potential; not applicable to patients who are unable to become pregnant, including those with bilateral oophorectomy and/or hysterectomy or postmenopausal [no menses for the previous 12 months]). The test must be performed within 1 week before Day 1 of treatment.
11. Male patients must agree to use a condom during treatment and for 90 days after dosing. Male patients must agree not to donate sperm for 90 days after dosing.

12. For women of childbearing potential*: are willing to follow 1 of the following effective methods of birth control from the time of study entry to 6 months after the last day of treatment:
    - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
    - Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
    - Intrauterine devices
    - Intrauterine hormone-releasing system
    - Vasectomized partner who has received medical assessment of surgical success
    - Bilateral tubal occlusion
    - True sexual abstinence**

    *Patients not of childbearing potential include those who are surgically sterile or postmenopausal (no menses for the previous 12 months). For women not currently taking contraceptive methods at screening, low user-dependency contraceptive methods (eg, implantable progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner) are recommended.

    **The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.
13. Have reasonably recovered from preceding major surgery as judged by the investigator or have had no major surgery within 4 weeks prior to Day 1 treatment.

**Exclusion Criteria**

Patients meeting any of the following criteria will be excluded from the study:

1. Have received prior platinum therapy in the past 3 months (Part 1) or 6 months in the adjuvant or neoadjuvant setting (Part 2).

2. Have received prior cisplatin and gemcitabine concomitantly within the last 6 months or are refractory to cisplatin and gemcitabine.

3. Are unable to receive platinum-based therapy due to previous

toxicity.

4. Have unresolved toxicity from prior radiation, chemotherapy, or other targeted treatment, including investigational treatment, with the exception of alopecia and ≤Grade 1 peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE version 4.03. Clinical judgment by the investigator is allowed to determine if Grade 1 fatigue at screening is residual toxicity from prior treatment or is a symptom of the patient's general condition or disease. The investigator and Medical Monitor will discuss the eligibility of patients with baseline toxicity.

5. Have evidence suggesting pulmonary fibrosis or interstitial pneumonia.

6. Have a history of thrombocytopenia with complications including hemorrhage or bleeding of ≥Grade 2 per NCI CTCAE version 4.03 that required medical intervention or have any hemolytic condition or coagulation disorder that would make participation unsafe in the opinion of the investigator.

7. Have known hypersensitivity to platinum compounds or gemcitabine.

8. Have uncontrolled diabetes or have hypertension requiring more than 3 medications for control of hypertension.

9. Have known active hepatitis B (defined as a known positive hepatitis B surface antigen [HBsAg] result) or hepatitis C (defined by a known positive hepatitis C antibody result and known quantitative HCV RNA results greater than the lower limits of detection of the assay).

10. Are pregnant or breast-feeding.

11. Have signs or symptoms of organ failure, major chronic illnesses other than cancer, or any concomitant medical or social condition that, in the opinion of the investigator, make it undesirable for the patient to participate in the study or that could jeopardize compliance with the protocol.

12. Have pre-existing alcoholic liver injury or significant liver disease.
13. Are regularly consuming alcohol within 6 months of Screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 8 g of alcohol: a half-pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.
14. Have experienced any of the following within the 6-month period prior to screening: angina pectoris, coronary artery disease, cerebrovascular accident, transient ischemic attack, cardiac failure with known ejection fraction less than 40%, or cardiac arrhythmia requiring medical therapy.
15. Are unwilling or unable to comply with study procedures or are planning to take a vacation for 7 or more consecutive days during the treatment phase of the study without prior consent from the Medical Monitor.

**Study Design:**

This study will consist of 2 parts; Part 1 is a Phase 1b, continual reassessment method dose-escalation trial, and Part 2 is a Phase 2, adaptive, open-label, expansion trial evaluating activity, safety, and tolerability at the RPII dose identified in Part 1.

In Part 1, patients will receive intravenous infusion of NC-6004 at escalating doses on Day 1 in combination with gemcitabine at the fixed dose of 1250 mg/m$^2$ on Days 1 and 8 of a 21-day cycle. The dose-escalation part of the trial will begin with a single-patient run-in phase. In the run-in phase, 1 patient will be enrolled sequentially at the following dose levels: 60, 75, 90, 105, 120, 135, 150, 165, and 180 mg/m$^2$ until a DLT is observed or until a patient is treated at 180 mg/m$^2$ for 1 cycle without a DLT. During the single-subject run-in phase, after enrollment of the initial patient at 60 mg/m$^2$, the first patient in each cohort will not be enrolled until the patient at the immediately lower cohort has completed at least 1 full cycle. A Bayesian continual-reassessment method per Neuenschwander et al 2008 (N-CRM) model will be used for dose escalation. The N-CRM will model the starting dose for the remainder of the escalation using the run-in data. For the remainder of Part 1 of the study, 4 patients will be enrolled as a cohort at each dose level predicted

by the N-CRM model. If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.

On Day 1 of each cycle, patients will receive NC-6004 over 1 hour (+10-minute window) followed by an infusion of gemcitabine 1250 mg/m$^2$ over 30 minutes. All patients will receive gemcitabine 1250 mg/m$^2$ alone on Day 8 of each cycle. In Part 1, patients will continue to receive treatment until they experience disease progression, experience unacceptable toxicity (UT), or withdraw voluntarily. If the investigator and the patient request continuation of NC-6004 administration until progressive disease or until the drug is no longer tolerated (whichever occurs first), the sponsor may agree to supply the drug after discussion of the request with the investigator.

In subsequent cohorts, the NC-6004 dose will be increased in 15 mg/m$^2$ increments based on the toxicity profile of the previous cohort. The dose-toxicity relationship will be re-evaluated at the completion of the first treatment cycle in each cohort until the MTD is identified. At any time, in the absence of an MTD from the N-CRM model, NanoCarrier can recommend a RPII dose less than or equal to the maximum administered dose based on efficacy, full safety, and/or pharmacokinetic (PK) data.

Part 2 of the study (Phase 2 portion) will begin after the RPII dose of NC-6004 is identified for use in combination with gemcitabine. All patients will receive NC-6004 at the RPII dose (135 mg/m$^2$, established in Part 1) in combination with gemcitabine 1250 mg/m$^2$ by the same regimen as in Part 1.

Three cohorts of patients are eligible (Cohort 1: first-line metastatic squamous NSCLC; Cohort 2: first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and Cohort 3: first-line metastatic or locally advanced TCC of the urinary tract (bladder cancer). Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 (unfit) and ≥60 mL/min and ECOG 0 to 1 (fit). If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.

Part 2 will enroll up to 50 patients each in Cohorts 1 and 2, and

up to 60 patients (ie, 30 unfit and 30 fit patients) in Cohort 3, for a total of up to 160 patients in Part 2.The primary endpoint (PFS) will be continuously updated and compared with the historical PFS from Phase 3 pivotal cisplatin and gemcitabine trials within each cohort. The PFS hazard model will be updated as PFS data accrue. A hazard ratio (HR) for PFS for each cohort versus historical control will be obtained.

| **Cohort** | **Biliary** | **Bladder (CrCl: ≥60 mL/min and ECOG PS 0-1; fit)** | **Bladder (CrCl: ≥30 to <60 mL/min and/or ECOG PS 2; unfit)** | **Squamous NSCLC** |
|---|---|---|---|---|
| Historical Median Duration of PFS | 8.8 months | 7.6 months | 5.8 months | 5 months |
| Historical PFS Weekly Hazard | 0.01795 | 0.020755 | 0.02711 | 0.031377 |

Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance status.

Once 10 PFS events have been observed, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort.

- Futility – 10 PFS events have been observed in each cohort and at least 1 of the following conditions is true:
    - Probability (Promising HR*) <0.4
    - Probability (Phase 3 Success*) <0.4
- Success – 25 PFS events have been observed in each 50-patient cohort and 15 PFS events in each 30-patient bladder cancer cohort and:

- Probability (Phase 3 Success*) >0.8
- Inconclusive – neither futility nor success.

*Phase 3 success is defined as success in a Phase 3 clinical trial with 381 events - enough to provide 80% power to detect an HR of 0.75. A promising HR is defined as one less than 0.85.

*Futility can only be declared for a cohort after 10 PFS events have been observed in that cohort. Success can only be declared for a cohort after 25 or 15 PFS events have been observed in that 50-patient cohort (Cohort 1 and 2) or 30-patient bladder cancer cohort (Cohort 3, fit and unfit), respectively. Accrual will stop for any cohort identified as futile or successful at interim. The conclusion of this Phase 2 trial will be that a Phase 3 trial with 381 events should be conducted for each cohort that is a success.

If any indication is declared a success, the combination of NC-6004 and gemcitabine advances to a Phase 3 randomized, controlled trial with sample size sufficient to observe 381 events.

After completion of 6 cycles of treatment (Cohorts 1 and 3) or 8 cycles of treatment (Cohort 2), patients will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

Patients who discontinue treatment and have not progressed will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone. Patients who discontinue treatment due to disease progression will have an End-of-Treatment visit and be contacted for survival every 12 weeks by phone.

**Estimated Study Duration:**

Part 1 of the study will include a screening period (up to 28 days); as many cycles until progressive disease or until the drug is no longer tolerated (whichever occurs first); tumor assessments for response and disease progression with scans every 6 weeks; and telephone calls for survival every 12 weeks. The cycles are 21 days in duration.

Part 2 of the study will include a screening period (up to 28 days); 6 treatment cycles (Cohorts 1 and 3) or 8 treatment cycles (Cohort 2) that are 21 days in duration; tumor assessments for response and disease progression with scans every 6 weeks; and telephone calls for survival every 12 weeks.

Patients will receive study treatment until any of the following

occur:

- Progressive disease is observed (Part 1) or completion of 6 cycles of treatment (Part 2; Cohorts 1 and 3) or 8 cycles of treatment (Part 2; Cohort 2)
- Unacceptable toxicity experienced
- Grade 4 liver enzyme elevation
- Withdrawal of consent
- Major protocol violation
- Required treatment delay >14 days (except in case of potential patient benefit, then the duration of the delay is to be approved by the sponsor)
- Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal
- For Cohort 3 only, unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart)
- Lost to follow-up
- Other (eg, pregnancy, development of contraindications of use of the study drug)
- The investigator or sponsor determines it is in the best interest of the patient to discontinue the patient's participation in the study.

**Efficacy Assessments:** Disease response assessment will occur every 6 weeks until disease progression and will include radiological assessments per RECIST version 1.1 for ORR, DCR, PFS, DOR, and OS. Patients who have obtained a response (partial response or complete response) will have a confirmatory scan at a minimum of 4 weeks following the initial scan. Data will be collected continuously for OS while patients are receiving study drug. After the discontinuation or completion of treatment, patients without disease progression will be followed for progression with scans every 9 weeks and for survival (by telephone contact) every 12 weeks.

Quality of life will be assessed before treatment on Day 1 and Day 8 of each cycle and at the End-of-Treatment visit using the EORTC QLQ-C30.

Symptoms will be assessed before treatment on Day 1 and Day 8

of each cycle and at the End-of-Treatment visit using the core MD Anderson Symptom Inventory or the MDASI-lung cancer (Part 1 only).

**Pharmacokinetic or Pharmacodynamic Assessments:**

The concentration-versus-time profile of micellar platinum in plasma and of total platinum in plasma and plasma ultrafiltrate (ie, free platinum) will be determined in Part 1 and in Part 2.

**Part 1 Pharmacokinetic Time Points**

Pharmacokinetic plasma and plasma ultrafiltrate samples will be collected at the following times in Part 1:

- Before the start of the NC-6004 infusion on Day 1 of Cycles 1 through 6
- At the end of NC-6004 infusion in Cycles 1, 3, and 5
- After the start of NC-6004 infusion at Hours 3, 6, 12, 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 (Day 8, prior to gemcitabine infusion), and 336 (Day 15) in Cycles 1, 3, and 5
- At End-of-Treatment visit

**Part 2 Pharmacokinetic Time Points**

Pharmacokinetic plasma and plasma ultrafiltrate will be collected at the following times in Part 2 for up to 6 cycles:

- Before the start of the NC-6004 infusion on Day 1
- At the end of NC-6004 infusion
- Before gemcitabine infusion on Day 8
- At End-of-Treatment visit

**Safety Assessments:**

Adverse events will be evaluated at each visit during every cycle and graded according to the NCI CTCAE version 4.03 dated June 14, 2010 (only abnormal laboratory results deemed to be clinically significant will be recorded as AEs or SAEs). Hematology and coagulation and biochemistry tests will be performed at screening and on Days 1, 8, and 15 of each cycle (before any study drug infusions), and at the End-of-Treatment visit. Urinalyses will be performed at screening and at the End-of-Treatment visit. A 12-lead electrocardiogram will be performed at screening, before and at various time points after NC-6004 infusions in selected cycles, before and after gemcitabine infusions in selected cycles, and at the End-of-Treatment visit. Physical examinations will be performed and vital signs will be measured at screening, before the start of treatment on Day 1 of each cycle (or can be completed on

| | |
|---|---|
| | Day -1), and at the End-of-Treatment visit. Additionally, on Day 1 of Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the infusion. Starting in Cycle 2, vital signs will be measured before the NC-6004 infusion and at the completion of the NC-6004 infusion on Day 1 of each cycle. Vital signs will be measured before and after gemcitabine infusion on Day 8 of each cycle. Audiometry will be performed at screening and only as clinically indicated before treatment on Day 1 of each cycle and as clinically indicated at the End-of-Treatment visit.<br>Nausea severity and vomiting incidence will be assessed and recorded using a patient diary. |
| **Definition of DLT** | A DLT (monitored in Part 1 only) is defined as the following treatment-related AEs or laboratory abnormalities, graded according to NCI CTCAE version 4.03:<br>• Grade 3 or 4 febrile neutropenia or neutropenic infection<br>• Grade 4 neutropenia of duration longer than 7 days and unresponsive to growth factor support per institutional guidelines or American Society of Clinical Oncology guidelines<br>• Grade 4 thrombocytopenia<br>• Grade 3 thrombocytopenia with clinically significant bleeding or Grade 3 thrombocytopenia requiring a platelet transfusion<br>• Grade 4 life-threatening anemia<br>• Grade 3 or Grade 4 nonhematological toxicity (excluding alopecia and Grade 3 nausea, vomiting, diarrhea, and electrolyte imbalances lasting less than 48 hours or with suboptimal prophylactic and suboptimal curative treatment)<br>• Grade 3 nausea, vomiting, diarrhea, or electrolyte imbalances lasting greater than 48 hours despite optimal prophylactic and curative treatment<br>• Grade 4 vomiting, diarrhea, or electrolyte imbalances (life-threatening consequences) of any duration despite optimal prophylactic and curative treatment<br>• ≥Grade 3 hypersensitivity reaction<br>• Dosing delay >14 days due to toxicity |
| **Study Drug, Dosage,** | NC-6004 is provided in vials of 5 mL containing the equivalent of |

| | |
|---|---|
| **and Route of Administration:** | 50 mg cisplatin. After the administration of premedications, NC-6004 should be mixed with 500 mL of 5% dextrose solution. **Saline must not be used for any dilution of NC-6004 before infusion because cisplatin is released easily from the micelle in the chloride-rich environment. Saline must not be used for flushing infusion lines immediately before or immediately after NC-6004 administration.**<br>In each part of the study, NC-6004 will be administered as a 1-hour (+10-minute window) intravenous infusion on Day 1 of each cycle. The potential dosage levels of NC-6004 in this study include 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, and 240 mg/m$^2$. A full safety review of all AEs for all cycles as well as an optional PK analysis will be conducted by the investigators, the Medical Monitor, and NanoCarrier before increasing the NC-6004 dose beyond 240 mg/m$^2$. Gemcitabine 1250 mg/m$^2$ will be administered as a 30-minute intravenous infusion on Day 1 after the completion of the NC-6004 infusion. Gemcitabine 1250 mg/m$^2$ will also be administered as a 30-minute intravenous infusion on Day 8. The duration of each cycle will be 21 days. |
| **Dose Escalation Design:** | A Bayesian continual reassessment method per Neuenschwander et al 2008 (N-CRM) model is used for dose escalation and determination of MTD. The initial NC-6004 dose for evaluation will be 60 mg/m$^2$. Sequential doses selected for evaluation are 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, and 240 mg/m$^2$.<br>The dose-escalation part of the trial will begin with a single-patient run-in phase. In the run-in, 1 patient will be enrolled sequentially at each dose level until a DLT is observed. Dose escalation in the run-in phase will only occur after a patient at a given dose level has experienced a DLT or has completed the first cycle. The N-CRM will model the starting dose for the remainder of the escalation using the run-in data. For the remainder of the escalation, 4 patients will be enrolled as a cohort at each dose level predicted by the N-CRM model. For the remainder of Part 1 of the study, dose escalation will only occur after all patients in a cohort have either experienced a DLT or completed the first cycle. If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$. |
| **Sample Size:** | Up to 49 patients with solid tumors will be enrolled in Part 1 of the study. Simulations were performed assuming scenarios with |

different dose-toxicity relationships. The associated mean sample size in these scenarios ranged from 17.22 patients to 25.79 patients.

Part 2 is a 3-cohort study with an overall sample size of up to 160 patients with no more than 50 patients each in Cohorts 1 and 2 and no more than 60 patients in Cohort 3 (30 unfit and 30 fit bladder cancer patients). The total sample size will depend on the results of interim futility and superiority analyses. In order to evaluate the overall sample size, simulations were performed assuming scenarios with different HRs for PFS for each cohort compared with historical control and different sample sizes for a subsequent Phase 3 clinical trial. The associated mean sample size for this trial in these scenarios ranged from 92.7 to 116.8 patients.

Patients who receive study drug will not be replaced.

**Statistical Methods:** Ninety-five percent confidence intervals may be calculated for selected safety and exploratory variables. Dose escalation will be based on the N-CRM model and the incidence of DLTs. Adverse events and serious AEs will be tabulated by system organ class and preferred term. Laboratory test results after the first dose will be summarized with regard to shifts from baseline values and the grade per NCI CTCAE version 4.03. Overall survival, PFS, and DOR will be summarized using Kaplan-Meier methods. The ORR and DCR will be summarized and 95% confidence intervals for both will be created.

In Part 2, the following posterior probabilities will be derived using a Bayesian model updated every 6 weeks after 10 PFS have occurred within a cohort:

- Probability (Promising HR)
- Probability (Phase 3 Success)

If any cohort at interim or final analyses has a probability (success in a Phase 3 trial with 381 PFS events) >0.8, that indication will be declared a success, and the combination of NC-6004 and gemcitabine advances to a Phase 3 randomized, controlled trial with a sample size sufficient to observe 381 PFS events.

**Date of Protocol:** 13 March 2017

# List of Abbreviations

| Abbreviation | Definition |
|---|---|
| ADL | activities of daily living |
| AE | adverse event |
| AI | accumulation index |
| ALK | anaplastic lymphoma kinase |
| ASCO | American Society of Clinical Oncology |
| $AUC_{0-\tau}$ | area under the concentration-time curve from time zero to the end of the dosing interval |
| $AUC_{last}$ | area under the concentration-time curve from time zero to the last quantifiable concentration |
| $AUC_{0-\infty}$ | area under the concentration-time curve from time zero to infinity |
| BSA | body surface area |
| CFR | Code of Federal Regulations |
| CL | clearance |
| $C_{max}$ | maximum concentration |
| CR | complete response |
| CRA | clinical research associate |
| CrCl | creatinine clearance |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DCR | disease control rate |
| DLT | dose-limiting toxicity |
| DOR | duration of response |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic case report form |
| EDC | electronic data capture |
| EGFR | epidermal growth factor receptor |
| EMA | European Medicines Agency |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |

| Abbreviation | Definition |
|---|---|
| GCP | Good Clinical Practice |
| HR | hazard ratio |
| ICF | informed consent form |
| ICH | International Council for Harmonisation |
| IEC | independent ethics committee |
| IRB | institutional review board |
| $\lambda_z$ | terminal elimination phase rate constant |
| MDSAI | MD Anderson Symptom Inventory |
| MDSAI-LC | MD Anderson Symptom Inventory module specific for lung cancer |
| MRT | mean residence time |
| MTD | maximum-tolerated dose |
| NCI | National Cancer Institute |
| N-CRM | Bayesian continual reassessment method design per Neuenschwander et al 2008 |
| NSCLC | non-small cell lung cancer |
| ORR | overall response rate |
| OS | overall survival |
| PEG-pGlu | polyethylene glycol-polyglutamate copolymer, also written as α-(methoxy-ω-aminopropyl, polyethylene glycol)-block-poly(sodium L-glutamate) copolymer |
| PFS | progression-free survival |
| PK | pharmacokinetic |
| PR | partial response |
| PS | performance status |
| QoL | quality of life |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RPII | recommended Phase 2 |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | stable disease |
| $T_{½}$ | terminal half-life |
| TCC | transitional cell carcinoma |
| TEAE | treatment-emergent adverse event |

| Abbreviation | Definition |
|---|---|
| $T_{max}$ | time to maximum concentration |
| ULN | upper limit of normal |
| UT | unacceptable toxicity |
| VHP | Voluntary Harmonisation Procedure |
| $V_{ss}$ | volume of distribution at steady-state |
| $V_z$ | volume of distribution |

# 1 Introduction

Platinum compounds are well established agents in the treatment of cancer (Kelland and Sharp 1999). The leading platinum compounds in cancer chemotherapy are cisplatin, carboplatin, and oxaliplatin. They share a number of common structural chemical characteristics; however, they exhibit marked interanalogue differences in pharmacokinetics, adverse effect profiles, and optimal therapeutic indication.

Cisplatin has been widely used for the treatment of cancer including lung cancer (both small cell and non-small cell lung cancer [NSCLC]), head and neck cancer, germ-cell tumors (testicular, ovarian, and extragonadal germ cell tumor), ovarian cancer, testicular tumor, bladder cancer, renal pelvis/ureter tumor, prostate cancer, esophageal cancer, cervical cancer, neuroblastoma, stomach cancer, osteosarcoma, and pleura malignant mesothelioma in monotherapy and including malignant bone tumor, endometrial cancer (adjuvant chemotherapy and chemotherapy for metastasis/recurrence), recurrent/refractory malignant lymphoma, and pediatric malignant solid tumor (rhabdomyosarcoma, neuroblastoma, hepatoblastoma and other primary malignant liver tumor, and medulloblastoma) in combination therapy. The mechanism of action of cisplatin is the inhibition of DNA synthesis induced by the platinum-DNA adduct formed by cross-linking between cisplatin and specific base sequences. This cross-linking inhibits DNA replication and transcription and activates signal transduction pathways leading to apoptosis and cell death (Pinto and Lippard 1985).

As described above, cisplatin-based regimens represent the mainstay of treatment in a number of indications; however, its use is associated with irreversible ototoxicity and renal toxicity, which necessitates the use of pre-hydration regimens using mannitol and excludes its use in patients with less than normal renal function. Continuous administration of cisplatin is associated with neurotoxicity, myelotoxicity, and gastrointestinal toxicity, including nausea and vomiting. Decreased appetite, alopecia, and general disorder such as fatigue, which are common toxicological features of platinum compounds affecting patient's quality of life (QoL), are also associated with cisplatin therapy (Hartmann and Lipp 2003).

Nonclinical studies have indicated that NC-6004 (1) is preferentially distributed to tumors, (2) demonstrates significantly lower toxicity compared to cisplatin at an equivalent dose, and (3) has increased antitumor activity (Uchino et al 2005). Preferential tumor accumulation of polymer micelles with an average diameter of 30 nm can be explained by the mechanism of

the enhanced permeability and retention effect, characterized by marked vascular hyperpermeability to the circulating macromolecular carrier (≥40 kilodalton) and impaired lymphatic drainage in the tumor (Matsumura and Maeda 1986). Furthermore, polymer micelles successfully avoid glomerular filtration (threshold diameter of 8 nm), and the hydrophilic outer shell composed of polyethylene glycol greatly extends the circulation time of micelles by preventing the micelles from being captured by the reticuloendothelial system, enhancing the specific tumor accumulation. These micelles progressively break down in the presence of chloride to release cisplatin and the copolymer. The cytotoxic activity of NC-6004 is considered to be exerted by the formation of cellular DNA adducts with released cisplatin. The slow release of cisplatin from NC-6004 achieves a long-period systemic exposure to cisplatin, leading to its continuous antitumor effect with a toxicity profile similar to that of cisplatin.

Results of in vitro cytotoxicity studies of NC-6004 in combination with gemcitabine, showed a synergistic effect in MOR/CPR cisplatin-refractory lung adenocarcinoma, MDA-MB-231 breast adenocarcinoma, LS174T colon adenocarcinoma, and BxPC-3 pancreas adenocarcinoma cells; and an additive effect was observed in K562 chronic myelogenous leukemia, HT1376 bladder carcinoma, HepG2 hepatocellular carcinoma, and NCI-N87 gastric carcinoma cells. In in vivo studies of NC-6004 in combination with gemcitabine, significant antitumor effects were observed in MDA-MB-231, MOR/CPR, BxPC-3, and PC-3 prostate cancer xenograft models.

The results of a Phase 1 study of NC-6004 as monotherapy in patients with solid tumors (Study NC-6004-001) suggested that NC-6004 monotherapy has potential activity for the treatment of solid tumors. The pharmacokinetic (PK) analysis indicated prolonged circulation of NC-6004 in the blood and delayed and sustained release of the potentially active platinum species, cisplatin, after the administration of NC-6004 (Plummer et al 2011).

In the first part of the Phase 1/2 study performed in Asia in patients with pancreatic cancer (Study NC-6004-002), NC-6004 and gemcitabine combination therapy exhibited an improved efficacy profile with prolonged administration period compared to that in Study NC-6004-001. Although, this is partly due to the aggressive prophylactic regimen for hypersensitivity reactions, NC-6004 is well tolerated even in combination with gemcitabine, and further clinical results are anticipated.

Based on these results, it is concluded that further clinical study should proceed aiming at the development of a new micelle formulation of cisplatin for out-patient-based therapy without serious toxicity.

This study will determine the maximum tolerated dose (MTD) and recommended Phase 2 (RPII) dose of NC-6004 in combination with gemcitabine and evaluate the activity, safety, and tolerability of NC-6004 in combination with gemcitabine in patients with advanced solid tumors and first-line metastatic squamous NSCLC; first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and first-line metastatic or locally advanced transitional cell carcinoma (TCC) of the urinary tract (bladder cancer). The study will also evaluate the overall response rate (ORR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), QoL, and therapy-related adverse events (AEs). In addition, the study will assess the PK and pharmacodynamic effects of NC-6004.

# 2 Study Objectives

## 2.1 Primary Objectives

The primary objectives of this study are:

- In the dose-escalation phase of the study (Part 1), to determine the dose-limiting toxicities (DLTs), MTD, and RPII dose of NC-6004 in combination with gemcitabine;
- In the expansion phase of the study (Part 2), to evaluate the activity of NC-6004 in combination with gemcitabine in patients with first-line Stage IV squamous NSCLC, first-line advanced or metastatic biliary tract cancer, and first-line metastatic or locally advanced bladder cancer compared with historical control as measured by local investigator/radiologist-assessed progression-free survival (PFS), according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

## 2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate ORR, DCR (DCR = complete response [CR] + partial response [PR] + stable disease [SD]), DOR, PFS, and OS
- To evaluate therapy-related AEs
- To evaluate the safety and tolerability of NC-6004 when combined with gemcitabine
- To evaluate QoL using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
- To evaluate acute and delayed symptoms using the MD Anderson Symptom Inventory (MDASI) and a nausea and vomiting patient diary

## 2.3 Exploratory Objectives

The exploratory objectives of this study are:

- To assess the PK and pharmacodynamic effects of NC-6004

# 3 Investigational Plan

## 3.1 Study Design

This study will consist of 2 parts; Part 1 is a Phase 1b, continual reassessment method dose-escalation trial in patients with any advanced solid tumor, and Part 2 is a Phase 2, adaptive, open-label, expansion trial in patients with squamous NSCLC, biliary tract, and bladder cancer evaluating activity, safety, and tolerability at the RPII dose identified in Part 1.

In Part 1, patients will receive intravenous infusion of NC-6004 and gemcitabine in 3-week treatment cycles. NC-6004 will be administered on Day 1 of each cycle and gemcitabine 1250 mg/m$^2$ will be administered on Day 1 of each cycle (after the administration of NC-6004) and on Day 8 of each cycle. Patients will be treated until disease progression. If the investigator and the patient request continuation of NC-6004 administration until progressive disease or until the drug is no longer tolerated (whichever occurs first), the sponsor may agree to supply the drug after discussion of the request with the investigator.

A Bayesian continual-reassessment method per Neuenschwander et al 2008 (N-CRM) model will be used for dose escalation and determination of MTD (as described in Section 6.3.1.2). The initial NC-6004 dose for evaluation will be 60 mg/m$^2$. Sequential doses selected for evaluation are listed in Table 3-1.

**Table 3-1 Dose Levels of NC-6004**

| Dose Level Name | NC-6004 Dose Level (mg/m$^2$) |
|---|---|
| 1 | 60 |
| 2 | 75 |
| 3 | 90 |
| 4 | 105 |
| 5 | 120 |
| 6 | 135 |
| 7 | 150 |
| 8 | 165 |
| 9 | 180[a] |
| 10 | 195 |
| 11 | 210 |
| 12 | 225 |
| 13 | 240[b] |

[a] If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.

[b] A formal review by the safety committee will take place to decide if the dose can be increased beyond 240 mg/m$^2$.

Part 1 will begin with a single-patient run-in phase. In the run-in phase, 1 patient will be enrolled sequentially at each dose level of NC-6004 until a DLT is observed. Dose escalation in the run-in phase will only occur after a patient at a given dose level has experienced a DLT or has completed the first cycle. The N-CRM will model the starting dose for the remainder of Part 1 using the run-in data. For the remainder of Part 1, 4 patients will be enrolled as a cohort at each dose level as predicted by the N-CRM model. The N-CRM model may enroll the next cohort at the previous dose level, the current dose level, or the next dose level. The N-CRM model will only be updated after all patients in a cohort have either experienced a DLT or completed the first cycle. If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.

Once the MTD (or RPII dose) of NC-6004 is identified, dose escalation within Part 1 will cease. Patients in Part 1 who were not assigned to the NC-6004 dose identified as the RPII dose will continue treatment cycles at their assigned dose level.

Part 2 of the study (Phase 2 portion) will begin after the RPII dose of NC-6004 is identified for use in combination with gemcitabine. All patients will receive NC-6004 at the RPII dose (135 mg/m$^2$, established in Part 1) in combination with gemcitabine 1250 mg/m$^2$ by the same regimen as in Part 1. Cohort 3 will stratify patients by creatinine clearance (CrCl) to assess study drug in patients with reduced kidney function (ie, CrCl of ≥30 to <60 mL/min [unfit] and ≥60 mL/min [fit]) in a controlled manner and with the stipulation that enrollment will stop if 2 of 6 patients in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart).

Three cohorts of patients are eligible (Cohort 1: first-line metastatic squamous NSCLC; Cohort 2: first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer [biliary tract cancer]; and Cohort 3: first-line metastatic or locally advanced TCC of the urinary tract [bladder cancer]). Part 2 will enroll up to 50 patients each in Cohorts 1 and 2 and up to 60 patients (ie, 30 unfit and 30 fit bladder cancer patients) in Cohort 3, for a total of up to 160 patients in Part 2. The primary endpoint (PFS) will be continuously updated and compared with the historical PFS from Phase 3 pivotal cisplatin and gemcitabine trials within each cohort. The PFS hazard model will be updated as PFS data accrue. A hazard ratio (HR) for PFS for each cohort versus historical control will be obtained.

| **Cohort** | **Biliary** | **Bladder (CrCl: ≥60 mL/min and ECOG PS 0-1; fit)** | **Bladder (CrCl: ≥30 to <60 mL/min and/or ECOG PS 2; unfit)** | **Squamous NSCLC** |
|---|---|---|---|---|
| Historical Median Duration of PFS | 8.8 months | 7.6 months | 5.8 months | 5 months |
| Historical PFS Weekly Hazard | 0.01795 | 0.020755 | 0.02711 | 0.031377 |

Abbreviations: CrCl: creatinine clearance; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance status.

Once 10 PFS events have been observed, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort.

- Futility – 10 PFS events have been observed in each cohort and at least 1 of the following conditions is true:
    - Probability (Promising HR*) <0.4
    - Probability (Phase 3 Success*) <0.4
- Success – 25 PFS events have been observed in each 50-patient cohort and 15 PFS events in each 30-patient bladder cancer cohort and:
    - Probability (Phase 3 Success*) >0.8
    - Inconclusive – neither futility nor success.

*Phase 3 success is defined as success in a Phase 3 clinical trial with 381 events - enough to provide 80% power to detect an HR of 0.75. A promising HR is defined as one less than 0.85.

*Futility can only be declared for a cohort after 10 PFS events have been observed in that cohort. Success can only be declared for a cohort after 25 or 15 PFS events have been observed in that 50-patient cohort (Cohort 1 and 2) or 30-patient bladder cancer cohort (Cohort 3, fit and unfit), respectively. Accrual will stop for any cohort identified as futile or successful at interim. The conclusion of this Phase 2 trial will be that a Phase 3 trial with 381 events should be conducted for each cohort that is a success.

If any indication is declared a success, the combination of NC-6004 and gemcitabine advances to a Phase 3 randomized, controlled trial with sample size sufficient to observe 381 events.

In Part 1, patients will continue to receive treatment until they experience disease progression. The maximum number of cycles a patient undergoes is at the discretion of the investigator and depends on response as described in the American Society of Clinical Oncology (ASCO) guidelines (Azzoli et al 2011). Patients who complete 4 or more cycles will be considered as having completed the treatment. Subject to sponsor approval, individual patients will be treated until progressive disease. If the investigator and the patient request continuation of NC-6004 administration until progressive disease or until the drug is no longer tolerated (whichever occurs first), the sponsor may agree to supply the drug after discussion of the request with the investigator. In Part 2, patients will continue to receive treatment for up to 6 cycles (Cohorts 1 and 3) or 8 cycles (Cohort 2).

After progressive disease is observed (Part 1) or the completion of 6 cycles (Part 2; Cohorts 1 and 3) or 8 cycles (Part 2; Cohort 2), patients will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone. Patients who discontinue treatment and have not progressed will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone. Patients who discontinue treatment due to disease progression will have an End-of-Treatment visit and be contacted for survival every 12 weeks by phone.

Disease assessment will be performed using RECIST version 1.1 (Eisenhauer et al 2009) and the same imaging method used at screening should be used for all subsequent assessments.

**Screening Period (Day -28 to -1)**

The following procedures will be performed during the screening period within 28 days prior to the first study treatment:

- Signed informed consent can be obtained within 28 days of dosing and prior to performing any study evaluations.
- Disease assessment will be evaluated with a baseline scan (see Section 6.1.1 for imaging methods) and should be performed within the 28 days before the start of study treatment.

**Screening Period (Day -14 to -1)**

The following procedures will be performed during the screening period within 14 days prior to the first study treatment:

- Assessment of eligibility criteria
- Patient demography
- Medical history (to include a complete history of all surgeries and significant diagnoses)
- Complete history of all cancer treatment (including surgery, radiation therapy, chemotherapy, etc.)
- Physical examination
- Height and weight

- Vital sign measurements
- Eastern Cooperative Oncology Group (ECOG) performance status (PS)
- Audiometry
- Urinalysis
- Cardiac risk factors (history of angina pectoris, coronary artery disease or cerebrovascular accident, transient ischemic attack, cardiac failure with known ejection fraction less than 40%, or cardiac arrhythmia requiring medical therapy)
- Concomitant medication use (including prescription or over-the-counter medication, herbal or naturopathic products) within the past 30 days

**Screening Period (Day -7 to -1)**

The following procedures will be performed during the screening period within 7 days prior to the first study treatment:

- Pregnancy test (serum or urine, only for women of childbearing potential)
- Hematology and coagulation
- Biochemistry
- 12-lead electrocardiogram (ECG)
- Safety assessments scheduled for Day 1 (physical examination, ECOG PS, and review of AEs and concomitant medication use) can be completed on Day –1 (not to be conducted in place of screening assessments)

**Day 1 of Cycle**

The following procedures will be performed on Day 1 prior to NC-6004 infusion in each treatment cycles unless otherwise specified:

- Pregnancy test (serum or urine) on Day 1 of each cycle (at Cycle 1, serum or urine; test is not required on Day 1 of Cycle 1 if pregnancy test at screening was performed using serum)
- Physical examination (if not performed on Day –1)

- Height, weight, and calculation of body surface area using the Mosteller formula (Mosteller 1987)
- Vital sign measurements (For additional vital sign assessments following dosing, refer to Section 6.3.8.)
- ECOG PS (if not performed on Day –1)
- Disease assessment will be evaluated beginning in Cycle 3 and continuing through the remainder of the treatment cycles every 6 (±1) weeks (ie, every other cycle), and at the End-of-Treatment visit or until disease progression
- Audiometry (only as clinically indicated)
- Hematology and coagulation
- Biochemistry
- EORTC QLQ-C30
- Part 1 only: Core MDASI or MDASI module specific for lung cancer (MDASI-LC) (Section 6.1.3)
    - MDASI-LC will only be performed by patients with NSCLC in Part 1 and will not be performed in Part 2
- Nausea and vomiting patient diary completion (completed in all cycles in Part 1 and only for 2 cycles in Part 2 of the study)
- 12-lead ECG (For additional ECGs following NC-6004 dosing, refer to Section 6.3.6.)
- PK blood sample collection (For additional PK samples following dosing, refer to Section 6.2)
- Adverse events (if not performed on Day –1)
- Concomitant medication use (if not performed on Day –1)
- Prophylactic administrations

**Day 8 of Each Cycle**

The following procedures will be performed on Day 8 prior to gemcitabine infusion in each treatment cycle:

- Vital signs
- Hematology and coagulation
- Biochemistry
- EORTC QLQ-C30
- Part 1 only: Core MDASI or MDASI-LC
    - MDASI-LC will only be performed by patients with NSCLC in Part 1 and will not be performed in Part 2
- Nausea and vomiting patient diary completion (completed in all cycles in Part 1 and only for 2 cycles in Part 2 of the study)
- 12-lead ECG (at Cycle 1 only, for additional ECGs following gemcitabine dosing refer to Section 6.3.6)
- PK blood sample collection
- Adverse events
- Concomitant medication use

**Day 15 of Each Cycle (Part 1: required; Part 2: if clinically indicated)**

The following procedures will be performed on Day 15 in each treatment cycle:

- Hematology and coagulation
- Biochemistry
- Nausea and vomiting patient diary completion (completed in all cycles in Part 1 and is not collected at Day 15 in Part 2 of the study)
- PK blood sample collection (Cycles 1, 3, and 5 of Part 1 only)

- Adverse events
- Concomitant medication use

**End-of-Treatment Visit**

The following procedures will be performed within 28 days after treatment discontinuation:

- Pregnancy test (serum or urine)
- Physical examination
- Vital sign measurements
- ECOG PS
- Disease assessment if scan has not previously shown disease progression
- Audiometry (only as clinically indicated)
- Hematology and coagulation
- Biochemistry
- Urinalysis
- EORTC QLQ-C30
- Part 1 only: Core MDASI or MDASI-LC
- 12-lead ECG
- PK blood sample collection
- Adverse events (All AEs will be followed until it meets criteria outlined in Section 6.3.2.6.)
- Concomitant medication use

**Follow-Up**

Patients who complete treatment or discontinue treatment without disease progression will continue to be followed until disease progression with scans every 9 weeks. Following

disease progression, patients will be contacted by telephone every 12 (±1) weeks to collect the following data:

- Survival
- Adverse events (All AEs will be followed until resolution, Section 6.3.2.6)
- New treatments (targeted therapy or chemotherapy used after study disease progression and treatment completion)

### 3.1.1 Rationale of Study Design

NC-6004 is a polymeric micelle containing cisplatin as an active moiety. The nanoparticle provides sustained release of the cisplatin and utilizes the enhanced permeability-retention effect to target the release of platinum to tumors. Synergistic effects of cisplatin and gemcitabine have been evaluated extensively in various types of tumor cell lines, including NSCLC cell lines, and nonclinical studies have demonstrated that, in tumors in which the combination of cisplatin and gemcitabine exhibit synergistic effects, the combined effects of NC-6004 and gemcitabine are synergistic.

This study will determine the DLTs, MTD, and RPII of NC-6004 in combination with gemcitabine in patients with advanced solid tumors and first-line Stage IV squamous NSCLC, first-line advanced or metastatic biliary tract cancer, and first-line metastatic or locally advanced bladder cancer for use in future efficacy studies. The initial dose level in this study was selected as 60 mg/m$^2$ based on the dose escalation and extension trial (Study NC-6004-002) where NC-6004 and gemcitabine were administered to Asian patients with pancreatic cancer. In Study NC-6004-002, the MTD and recommended dose of NC-6004 were determined to be 120 mg/m$^2$ and 90 mg/m$^2$, respectively, and the gemcitabine dose was 1000 mg/m$^2$ × 2, one week apart, every 3 weeks for pancreatic cancer, whereas in the current study in the United States the gemcitabine dose is 1250 mg/m$^2$ × 2, one week apart, every 3 weeks. Based upon these differences, as well as consideration of the differences in demographics between an Asian and a United States population, it is determined that the starting dose of NC-6004 in the current study should be one-half of the MTD and two-thirds the recommended dose determined in Study NC-6004-002.

Dose escalation of subsequent cohorts will be performed at 15 mg/m$^2$ increments to more precisely identify the actual MTD than has been performed in previous clinical trials. Dose

escalation in this study will follow an N-CRM which models the relationship between toxicities and dose level. This methodology allocates the fewest number of patients to doses with unacceptable toxicities and, based on our modeling, is better at identifying the correct MTD compared to a traditional 3 + 3 trial design. At any time, in the absence of an MTD from the N-CRM model, NanoCarrier can recommend a RPII dose less than or equal to the maximum administered dose based on efficacy, full safety, and/or PK data.

The study will evaluate the safety and tolerability of NC-6004 in combination with gemcitabine in these patients by assessment of therapy-related AEs (particularly DLTs). These events are commonly associated with cisplatin therapy and the intent of this design is to assess the frequency of these events using nanoparticle technology in comparison to historical data of cisplatin therapy. The study will also evaluate tolerability by assessing the severity of nausea and incidence of vomiting, commonly associated with cisplatin therapy, using a patient diary designed specifically for this purpose.

The study will also evaluate the activity of NC-6004 in combination with gemcitabine in terms of ORR, DCR, DOR, PFS, and OS. These are standard parameters for evaluating cancer chemotherapies.

The EORTC QLQ-C30 will be used to evaluate QoL. The EORTC QLQ-C30 is a QoL questionnaire specific for cancer patients. It has been translated and validated into 81 languages and has been used in more than 3000 studies worldwide.

The MDASI is a multisymptom patient-reported outcome measure for clinical and research use. In Part 1 only, the MDASI will be used to evaluate symptoms related to QoL during treatment. The MDASI's 13 core symptom items include those found to have the highest frequency and/or severity in patients with various cancers and treatment types. The MDASI has several advantages over other symptom-assessment scales in that it applies broadly across cancer types and treatments, is easy for patients to complete, includes items related to symptom interference with daily life, and it is easily translated into other languages. The MDASI-LC questionnaire is designed specifically for patients with lung cancer and will be used by patients with NSCLC in Part 1 of this study.

This clinical trial will also assess the pharmacokinetics of NC-6004 in terms of micellar platinum and total platinum to determine the pharmacodynamic relationships for both of these forms of circulating platinum.

# 4 Patient Selection and Withdrawal Criteria

## 4.1 Selection of Study Population

Approximately 209 patients (up to 49 patients in Part 1 and up to 160 patients in Part 2) will be enrolled in at least 20 sites in the United States and Europe. Patients will be assigned to a study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

### 4.1.1 Inclusion Criteria

Each patient must meet all of the following criteria to be enrolled in this study:

1. Provide signed written informed consent prior to the initiation of any study-specific procedures.

2. (Part 1 only) Have a histologically or cytologically confirmed diagnosis of advanced solid tumor that has relapsed or is refractory to standard curative or palliative therapy or has a contraindication to standard therapy.

   (Part 2 only) Cohort 1: Have histologically or cytologically confirmed diagnosis of Stage IV squamous NSCLC and have not received prior chemotherapy or immunotherapy for metastatic disease and are not known to be PD-L1 positive (known high PD-L1 expression defined as Tumor Proportion Score [TPS] greater than or equal to 50%). Patients with known sensitizing mutation in the epidermal growth factor receptor (EGFR) gene or anaplastic lymphoma kinase (ALK) fusion oncogene must have received at least 1 and up to 2 targeted therapies prior to enrollment.

   - A patient with stable, treated brain metastases is eligible, provided that there is no evidence of progression after treatment and the patient does not require corticosteroids, or, if the patient requires corticosteroid, has been receiving a stable dose of corticosteroids for at least 14 days prior to assignment to treatment.

   - Patients whose tumors are known to harbor an exon 19 deletion or exon 21 L858R EGFR mutation must have had intolerance or have progressed on at least 1 and up to 2 EGFR tyrosine kinase inhibitors.

- Patients whose tumors are known to harbor an ALK translocation must have had intolerance or have progressed on at least 1 and up to 2 ALK inhibitors.

(Part 2 only) Cohort 2: Have histologically or cytologically confirmed diagnosis of nonresectable, recurrent, or metastatic biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma) and have not received prior systemic anticancer therapy for advanced or metastatic disease.

(Part 2 only) Cohort 3: Have histologically or cytologically confirmed diagnosis of metastatic or locally advanced TCC of the urinary tract (bladder, urethra, ureter, renal pelvis) (T3b-T4 N0 M0, Tany N1-N3 M0, or Tany Nany M1) and are not candidates for surgery.

- Patients must not have received prior treatment with systemic anticancer therapy for metastatic or locally advanced urinary tract cancer.
- Certain mixed histologies that are predominantly (>50%) TCC are eligible: squamous, adenocarcinoma, and undifferentiated. Mixed undifferentiated histology requires immunohistochemistry consistent with a TCC origin. Predominantly squamous or neuroendocrine tumors are excluded.

3. Have measurable disease per RECIST version 1.1.
4. Are males or females aged ≥18 years.
5. Have an ECOG PS of 0 to 1, with the exception of patients in Part 2 (Cohort 3, unfit bladder cancer patients) who may have an ECOG PS of 2.
6. Have adequate bone marrow reserve defined as:
    - Absolute neutrophil count of at least $1.5 \times 10^9$/L,
    - Platelet count of at least $100 \times 10^9$/L, and
    - Hemoglobin level of 10 g/dL (transfusion is allowed to achieve hemoglobin level of at least 10 g/dL).

7. Have adequate liver function defined as:
    - Total serum bilirubin <1.5 × upper limit of normal (ULN) and
    - Baseline alanine transaminase, and aspartate transaminase <2.0 × ULN or, in patients with documented hepatic metastasis <5.0 × ULN and
    - Serum albumin ≥3.5 g/dL
8. Prothrombin time within normal limits
9. In Part 1 and in Part 2 in Cohorts 1 and 2: have adequate renal function defined as a CrCl ≥50 mL/min (calculated according to the formula of Cockcroft and Gault 1976) or serum creatinine <1.5 mg/dL. In Part 2, patients in Cohort 3 (bladder cancer) must have a CrCl of ≥30 mL/min.
    - Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 and ≥60 mL/min and ECOG PS 0 to 1. If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.
10. Have a negative pregnancy test result at screening (for females of childbearing potential; not applicable to patients who are unable to become pregnant, including those with bilateral oophorectomy and/or hysterectomy or postmenopausal [no menses for the previous 12 months]). The test must be performed within 1 week before Day 1 of treatment.
11. Male patients must agree to use a condom during treatment and for 90 days after dosing. Male patients must agree not to donate sperm for 90 days after dosing.
12. For women of childbearing potential*: are willing to follow 1 of the following effective methods of birth control from the time of study entry to 6 months after the last day of treatment:
    - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)

- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine devices
- Intrauterine hormone-releasing system
- Vasectomized partner who has received medical assessment of surgical success
- Bilateral tubal occlusion
- True sexual abstinence**

*Patients not of childbearing potential include those who are surgically sterile or postmenopausal (no menses for the previous 12 months). For women not currently taking contraceptive methods at screening, low user-dependency contraceptive methods (eg, implantable progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner) are recommended.

**The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

13. Have reasonably recovered from preceding major surgery as judged by the investigator or have had no major surgery within 4 weeks prior to Day 1 treatment.

### 4.1.2 Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Have received prior platinum therapy in the past 3 months (Part 1) or 6 months in the adjuvant or neoadjuvant setting (Part 2).
2. Have received prior cisplatin and gemcitabine concomitantly within the last 6 months or are refractory to cisplatin and gemcitabine.
3. Are unable to receive platinum-based therapy due to previous toxicity.

4. Have unresolved toxicity from prior radiation, chemotherapy, or other targeted treatment, including investigational treatment, with the exception of alopecia and ≤Grade 1 peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 (National Cancer Institute 2010). Clinical judgment by the investigator is allowed to determine if Grade 1 fatigue at screening is residual toxicity from prior treatment or is a symptom of the patient's general condition or disease. The investigator and Medical Monitor will discuss the eligibility of patients with baseline toxicity

5. Have evidence suggesting pulmonary fibrosis or interstitial pneumonia.

6. Have a history of thrombocytopenia with complications including hemorrhage or bleeding of ≥Grade 2 according to the NCI CTCAE version 4.03 that required medical intervention or have any hemolytic condition or coagulation disorders that would make participation unsafe in the opinion of the investigator.

7. Have known hypersensitivity to platinum compounds or gemcitabine.

8. Have uncontrolled diabetes or have hypertension requiring more than 3 medications for control of hypertension.

9. Have known active hepatitis B (defined as a known positive hepatitis B surface antigen [HBsAg] result) or hepatitis C (defined by a known positive hepatitis C antibody result or known quantitative HCV RNA results greater than the lower limits of detection of the assay).

10. Are pregnant or breast-feeding.

11. Have signs or symptoms of organ failure, major chronic illnesses other than cancer, or any concomitant medical or social conditions that, in the opinion of the investigator, make it undesirable for the patient to participate in the study or that could jeopardize compliance with the protocol.

12. Have pre-existing alcoholic liver injury or significant liver disease.

13. Are regularly consuming alcohol within 6 months of Screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 8 g of alcohol:

a half-pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.

14. Have experienced any of the following within the 6-month period prior to screening: angina pectoris, coronary artery disease or cerebrovascular accident, transient ischemic attack, cardiac failure with known ejection fraction less than 40%, or cardiac arrhythmia requiring medical therapy.

15. Are unwilling or unable to comply with study procedures or are planning to take a vacation for 7 or more consecutive days during the treatment phase of the study without prior consent from the Medical Monitor.

## 4.2 Withdrawal of Patients From the Study

The duration of the study for each patient is defined as the time from the date of signed written informed consent through the End-of-Treatment visit or until death.

### 4.2.1 Reasons for Withdrawal/Discontinuation

Patients may withdraw from the study at any time and for any reason without prejudice to their future medical care by the investigator or others at the study site. Every effort should be made to keep patients in the study. The reasons for patients not completing the study will be recorded. A patient may be withdrawn from the study for any of the following reasons:

- Disease progression
- Unacceptable toxicity experienced
- Grade 4 liver enzyme elevation
- Withdrawal of consent
- Major protocol violation
- Required treatment delay >14 days (except in case of potential patient benefit, which must be approved by the sponsor)
- Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal

- For Cohort 3 only, unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart)
- Lost to follow-up
- Other (eg, pregnancy, development of contraindications of use of the study drug)
- The investigator or sponsor determines it is in the best interest of the patient to discontinue the patient's participation in the study.

The investigator also will withdraw a patient if NanoCarrier terminates the study. Upon occurrence of a serious or intolerable AE, the investigator will confer with the sponsor. If a patient is discontinued because of an AE, then the event will be followed until it is resolved.

### 4.2.2 Handling of Withdrawals

Patients who discontinue study treatment or active participation in the study will no longer receive the study drug. When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the electronic case report form (eCRF). Whenever possible, all patients who discontinue study treatment or withdraw from the study prematurely will undergo all end-of-treatment assessments. Patients who fail to return for final assessments will be contacted by the site. Following a minimum of 2 documented unsuccessful telephone calls, a registered letter will be sent to the patient in a final attempt to ensure protocol compliance.

It is vital to obtain follow-up data on any patient withdrawn because of an AE or serious AE (SAE). In every case, efforts must be made to undertake protocol-specified, safety, follow-up procedures.

### 4.2.3 Replacements

Patients in Part 1 who discontinue treatment without DLT before completion of the first cycle will be replaced. No other patients will be replaced.

# 5 Study Treatments

## 5.1 Method of Assigning Patients to Treatment Groups

This is an open-label study that will be conducted in 2 parts. In both parts, NC-6004 will be administered as a 1-hour (+10-minute window) intravenous infusion on Day 1 of each cycle. Gemcitabine 1250 mg/m$^2$ will be administered as a 30-minute intravenous infusion on Day 1 of each cycle (after the administration of NC-6004) and on Day 8 of each cycle. The duration of each cycle will be 21 days.

In Part 1, patients will be assigned to receive gemcitabine 1250 mg/m$^2$ in combination with NC-6004 at doses of 60, 75, 90, 105, 120, 135, 150, 165, or 180 mg/m$^2$ by the N-CRM model (as described in Section 6.3.1.2).

In Part 2, all patients will receive the RPII dose (135 mg/m$^2$) of NC-6004 identified in Part 1. Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 (unfit) and ≥60 mL/min and ECOG PS 0 to 1 (fit). If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.

## 5.2 Prophylactic Treatments

All patients will receive the following medications before administration of NC-6004 on Day 1 of each cycle:

- Patients will be instructed to take 20 mg of dexamethasone orally at 12 hours and 6 hours before the start of NC-6004 infusion on Day 1 of each cycle. When necessary, 12 and 6 hours before the first infusion may be defined as “immediately before sleeping” and “immediately after waking up.”
- Patients will be given 50 mg of diphenhydramine hydrochloride intravenously 30 minutes before the start of the NC-6004 infusion on Day 1 of each cycle.
- Patients will be given 50 mg of ranitidine intravenously or 20 mg famotidine intravenously 30 minutes before the start of NC-6004 infusion on Day 1 of each cycle.

- Pre-hydration will be administered over 1 to 3 hours, as outlined by institutional standards. A minimum of 1 L of 0.9% sodium chloride solution will be infused intravenously over 1 to 3 hours prior to NC-6004 administration, and a minimum of 500 mL of 0.9% sodium chloride solution will be infused over 2 hours following NC-6004 administration. The 0.9% sodium chloride is changeable to 0.45% sodium chloride at investigator discretion based on the patient's condition. When gemcitabine only is infused, hydration is not required.

- At all cycles, 8 mEq (1 g) of magnesium sulfate will be added to the 1-L 0.9% sodium chloride pre-hydration regimen for all patients. Once a patient's magnesium level drops to <1.8 mg/dL or <lower limit of normal (Grade 1 hypomagnesemia), the investigator may treat as clinically warranted by supplementing with oral and/or intravenous magnesium.

- For 2 days after administration of NC-6004, dexamethasone 4 mg (twice per day) will be taken orally by all patients.

Prophylactic antiemetic medications may be administered according to standard treatment center protocols for cisplatin-based treatments. The use of prophylactic growth factor support medications is also allowed according to ASCO guidelines (Smith et al 2006) and is encouraged in patients who have experienced myelosuppression on treatment and/or in patients at high risk for experiencing febrile neutropenia.

## 5.3 Treatments Administered

The duration of each treatment cycle will be 21 days in both parts of the study. NC-6004 will be administered on Day 1 of each cycle as a 1-hour (+10-minute window) intravenous infusion**. Note: NC-6004 nanoparticles degrade in the presence of chloride ions. Therefore, it is imperative that saline is never used as either a diluent for NC-6004 or to flush cannulas immediately before or immediately after the NC-6004 infusion.** Gemcitabine 1250 mg/m$^2$ will be administered as a 30-minute intravenous infusion on Day 1 after the completion of the NC-6004 infusion and on Day 8 of each cycle.

In Part 1 of the study, patients will receive treatment until disease progression. In Part 2 of the study, patients will receive treatment for 6 cycles (Cohorts 1 and 3) or 8 cycles (Cohort 2). Antiemetic medications may be administered according to standard treatment center protocols. The use of growth factor support medications is also allowed according to ASCO guidelines (Smith et al 2006) and is encouraged in patients who have experienced

myelosuppression on treatment and/or in patients at high risk for experiencing febrile neutropenia.

The dose level may escalate to 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 225, or 240 mg/m$^2$ according to observations of DLTs and the dose-level toxicity relationship (Section 6.3.1.2). A full safety review of all AEs for all cycles as well as an optional PK analysis will be conducted by the investigators, the Medical Monitor, and NanoCarrier before increasing the NC-6004 dose beyond 240 mg/m$^2$.

In Part 1, cohorts will receive one of the following treatments shown in Table 5-1 as identified by the N-CRM model (as described in Section 6.3.1.2).

**Table 5-1 Dose Level Cohorts**

| Dose Level | Day 1 of Each Cycle | Day 8 of Each Cycle |
|---|---|---|
| 60 mg/m$^2$ | 60 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 75 mg/m$^2$ | 75 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 90 mg/m$^2$ | 90 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 105 mg/m$^2$ | 105 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 120 mg/m$^2$ | 120 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 135 mg/m$^2$ | 135 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 150 mg/m$^2$ | 150 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 165 mg/m$^2$ | 165 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 180 mg/m$^{2,\,a}$ | 180 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 195 mg/m$^2$ | 195 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 210 mg/m$^2$ | 210 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 225 mg/m$^2$ | 225 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 240 mg/m$^2$ | 240 mg/m$^2$ NC-6004; 1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |

[a] If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.

In Part 2, on Day 1 of each cycle, all patients will receive NC-6004 at the RPII dose (135 mg/m$^2$) identified in Part 1 and 1250 mg/m$^2$ gemcitabine. On Day 8 of each cycle, all patients in Part 2 of the study will receive 1250 mg/m$^2$ gemcitabine.

## 5.4 Dose Delays and Modifications

The doses for NC-6004 and gemcitabine will be calculated in milligrams per square meter (mg/m$^2$) at screening and will not be changed in subsequent cycles unless the patient's body weight has increased or decreased by ≥10% from the patient's weight measurement at screening. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs (Note: This threshold should not be confused with a change in the patient's body surface area [BSA] [m$^2$]). Weight will be measured before treatments on Day 1 of each cycle, with calculation of BSA before dosing on Day 1 of each cycle (using the Mosteller formula [Mosteller 1987]).

Patients experiencing significant toxicities must be immediately and permanently withdrawn from treatment with NC-6004 and gemcitabine as follows:

- Any patient who experiences a Grade 3 or 4 hypersensitivity reaction during any cycle of treatment
- Any patient who experiences 2 protocol-defined DLTs during treatment
- Any patient who experiences a recurrent Grade 3 or 4 toxicity (recurrence of the same AE) after a dose reduction
- Any patient who requires a dosing delay >14 days at any time during treatment (except in case of potential patient benefit, which must be approved by the sponsor)
- Any patient who experiences a Grade 4 liver enzyme elevation

### 5.4.1 NC-6004 Dose Delay and Modification

During any treatment cycle, investigators should suspend further dosing with NC-6004 for up to 14 days after the scheduled dose in the event of a protocol-defined DLT or any Grade 4 hematologic toxicity or Grade 3 or 4 nonhematologic toxicity that is possibly, probably, or definitely related to NC-6004 (excluding alopecia and Grade 3 nausea, vomiting, diarrhea, and electrolyte imbalances lasting less than 48 hours or with suboptimal prophylactic and

suboptimal curative treatment). Any patient experiencing a Grade 3 liver enzyme elevation should have their next dose of NC-6004 suspended until improvement to Grade 1 or lower. At the discretion of the investigator, the dose may also be delayed for up to 14 days for any toxicity possibly or probably related to NC-6004 that does not meet DLT criteria. A delay of more than 14 days will require the patient to be removed from the study (except in case of potential patient benefit, which must be approved by the sponsor). The toxicity for which the dose was suspended must have improved to Grade 1 or lower prior to NC-6004 infusion.

Following recovery to Grade 1 or lower, treatment may resume at the investigator's discretion. Patients who resume treatment following a dose delay will have the dose of study drug reduced by 50% for the remainder of study treatment. If toxicities persist or recur to Grade 3 or 4 (recurrence of the same AE) after the dose reduction, study treatment will be terminated.

### 5.4.2 Gemcitabine Dose Delay and Modification

For gemcitabine, investigators should withhold (for up to 14 days of the scheduled dose) or reduce (by 50%) the gemcitabine dose in the event of any Grade 3 or 4 nonhematologic toxicity that is possibly, probably, or definitely related to gemcitabine (excluding alopecia, nausea, and vomiting) until it is resolved to Grade 1 or lower prior to gemcitabine infusion. Once resolved, the dose can be reinstated at the full-dose level. Any patient who experiences any unexplained dyspnea or other evidence of severe pulmonary toxicity, severe hepatic toxicity, hemolytic-uremic syndrome, or capillary leak syndrome during any cycle of treatment must immediately and permanently discontinue treatment with gemcitabine.

For hematologic toxicities, the recommended dose reductions for gemcitabine are shown in the following table:

| **Absolute Granulocyte Count ($\times 10^6$/L)** | | **Platelet Count ($\times 10^6$/L)** | **% of Full Dose** |
|---|---|---|---|
| ≥1000 | And | ≥100 000 | 100 |
| 500-999 | Or | 50 000-99 999 | 75 |
| <500 | Or | <50 000 | hold |

## 5.5 Identity of Investigational Product

NanoCarrier will provide NC-6004 to PPD, Inc (PPD) and PPD will distribute adequate supplies of NC-6004 to the study sites.

The following drug supplies will be used in the study:

| Product | Supplied As: |
|---|---|
| NC-6004 | 5-mL solution of drug product in a vial (equivalent of 50 mg cisplatin) |
| Gemcitabine | 200 mg vial for injection or 1 g vial for injection |

### 5.5.1 NC-6004 Drug Product

NC-6004 stock solution defined as the drug substance is colorless or pale yellow, clear solution with no visible contaminants. The mean diameter of a micellar nanoparticle is approximately 30 nm. The number of cisplatin residues in a micellar nanoparticle is approximately 720.

NC-6004 is a sterile formulation containing cisplatin-incorporated micellar nanoparticles, derived from the α-(methoxy-ω-aminopropyl, polyethylene glycol)-block-poly(sodium L-glutamate) copolymer, also written as polyethylene glycol-polyglutamate copolymer, (PEG-pGlu) and cisplatin. It is provided preformulated in amber vials containing 5 mL of NC-6004 formulation containing the equivalent of 50 mg cisplatin.

Each vial of NC-6004 drug product contains 32.5 mg of platinum (corresponding to 50 mg of cisplatin), 250 mg of D-mannitol to adjust tonicity, and water for injection.

**Saline must not be used for any dilution of the NC-6004 or for flushing infusion lines immediately before or immediately after NC-6004 administration because cisplatin is released easily from the micelle in the chloride-rich environment.** After the administration of premedications, NC-6004 should be mixed with 500 mL of 5% dextrose solution for intravenous infusion. If necessary, NC-6004 may be diluted in 5% dextrose prior to the preparation of final infusion 500 mL.

### 5.5.2 Gemcitabine Drug Product

Gemzar® (gemcitabine for injection, USP), is available in sterile single-use vials individually packaged in a carton containing: 200 mg white to off-white, lyophilized powder in a 10-mL size sterile single-use vial or 1 g white to off-white, lyophilized powder in a 50-mL size sterile single-use vial. Vials of gemcitabine contain either 200 mg or 1 g of gemcitabine hydrochloride (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

## 5.6 Management of Clinical Supplies

### 5.6.1 Study Drug Packaging and Storage

NC-6004 will be prepared in vials and shipped by PPD.

All study drugs must be stored in a secure area (eg, a locked cabinet). NC-6004 should be protected from light and stored refrigerated (2° to 8°C). Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C that allows for excursions between 15° and 30°C.

### 5.6.2 Test Article Accountability

The investigator will maintain accurate records of receipt of all test articles that are centrally provided, including dates of receipt. In addition, accurate records will be kept regarding when and how much test article is dispensed and used by each patient in the study. Reasons for departure from the expected dispensing regimen must also be recorded. At the completion of the study, to satisfy regulatory requirements regarding drug accountability, all study drugs will be reconciled and retained or destroyed according to applicable regulations.

## 5.7 Overdose Management

An overdose is any dose of study treatment given to a patient or taken by a patient that exceeds the dose described in the protocol. Any overdose, with or without associated AEs, must be promptly reported to the PPD Drug Safety Center. Overdoses without signs or

symptoms do not need to be recorded as AEs; in case of any AEs associated with the overdose, these should be reported on relevant AE or SAE sections in the eCRF.

### 5.7.1 Treatment of Overdose

There is no clinically proven antidote available for NC-6004. The expected manifestations of overdose are likely to be an exaggerated form of the adverse drug reactions anticipated with the administration of the drug. Therefore, patients should be carefully monitored for signs of immunosuppression. Symptomatic treatment and standard supportive care measures for the management of this toxicity should be applied.

## 5.8 Prophylaxis and Management of Hypersensitivity Reactions

All patients must receive the following prophylactic treatment at each cycle to reduce the risk of hypersensitivity reactions:

- Dexamethasone 20 mg taken orally at 12 and 6 hours before the infusion of NC-6004. When necessary, 12 and 6 hours before the infusion of NC-6004 may be defined as "immediately before sleeping" and "immediately after waking up."
- Diphenhydramine hydrochloride 50 mg and either ranitidine 50 mg or 20 mg famotidine will be administered intravenously 30 minutes before the infusion of NC-6004.
- For 2 days after administration of NC-6004, dexamethasone 4 mg twice per day will be taken orally.

If a Grade 1 or Grade 2 hypersensitivity occurs in a patient, the following medications should be administered for 48 hours after NC-6004 infusion:

- Ranitidine 150 mg orally given 2 times per day or 40 mg famotidine orally given once per day
- Diphenhydramine hydrochloride 50 mg orally given 3 times per day

If a Grade 3 or higher hypersensitivity occurs, the patient should be discontinued from the study and must be treated immediately with hydrocortisone 20 mg administered intravenously and/or other appropriate medications. In these cases, patients must be carefully observed after the treatment. Additional therapy per institution standard of care should also be followed.

## 5.9 Treatment Compliance

Administration of the study treatments will be performed by the investigator or a qualified designee; therefore, compliance will be verified by the study drug administration information.

## 5.10 Prior, Concomitant, and Subsequent Therapy

(Part 2 only) Cohort 1: For patients with Stage IV NSCLC, they may not have received prior chemotherapy or immunotherapy for metastatic disease. Patients with known sensitizing mutation in the EGFR gene or ALK fusion oncogene must have received at least 1 and up to 2 targeted therapies prior to enrollment. If a patient with treated, stable brain metastases is otherwise eligible and requires corticosteroids, the patient must have been receiving a stable dose of corticosteroids for at least 14 days prior to assignment to treatment. Patients whose tumors are known to harbor an exon 19 deletion or exon 21 L858R EGFR mutation must have had intolerance or have progressed on at least 1 and up to 2 EGFR tyrosine kinase inhibitors. Patients whose tumors are known to harbor an ALK kinase translocation must have had intolerance or have progressed on at least 1 and up to 2 ALK inhibitors. Patients with eligible biliary tract carcinoma must not have received prior systemic anticancer therapy for advanced or metastatic disease. Patients with eligible TCC of the urinary tract must not have received prior treatment with systemic anticancer therapy for metastatic or locally advanced urinary tract cancer.

All patients must receive prophylactic treatment at each cycle to reduce the risk of hypersensitivity reactions and nausea and/or vomiting (Section 5.8).

The use of antiemetic medications according to the site's standard of care is allowed. The use of prophylactic growth factor support medications is also allowed according to ASCO guidelines (Smith et al 2006) and is encouraged in patients who have experienced myelosuppression on treatment and/or in patients at high risk for experiencing febrile neutropenia.

Use of all concomitant medications, including antiemetic medications and those required for administration before the infusion on Day 1 of each cycle, will be recorded in the patient's eCRF. The minimum requirement is that drug name and the dates of administration are to be recorded. This will include all prescription drugs, herbal products, vitamins, minerals, and

over-the-counter medications. Any changes in concomitant medications will also be recorded in the patient's eCRF.

Any concomitant medication deemed necessary for the welfare of the patient during the study may be given at the discretion of the investigator. However, it is the responsibility of the investigator to ensure that details regarding the medication are recorded in full in the eCRF.

## 5.11 Prohibited Medications

The following products should be avoided during study treatment with NC-6004 and for 1 month following treatment due to known interactions with the released cisplatin.

- Bacillus Calmette-Guerin
- Clozapine
- Natalizumab
- Tacrolimus (Topical)
- Tofacitinib
- Live vaccines

This list is not comprehensive and a physician or a pharmacist should evaluate other concomitant medications used during the trial.

# 6 Study Assessments and Procedures

Before performing any study procedures, all potential patients will sign an informed consent form (ICF). Patients will have the opportunity to have any questions answered before signing the ICF. The investigator must address all questions raised by the patient. The investigator will also sign the ICF.

The Schedule of Events is presented in Appendix 12.1.

Disease assessment is to be performed within the 28 days prior to the start of study treatment. For patients with advanced solid tumors, disease assessment will be performed according to RECIST version 1.1. Patients who have obtained a response (PR or CR) will have a confirmatory scan at a minimum of 4 weeks following the initial scan.

## 6.1 Efficacy Assessments

Efficacy assessments include disease response assessments, QoL assessments, and symptom changes assessments. Disease response assessments (Section 6.1.1) will occur every 6 weeks (±1 week), at the End-of-Treatment visit, and every 9 weeks after discontinuation or completion of treatment until disease progression. Quality of life will be assessed using the EORTC QLQ-C30 version 3 (Section 6.1.2) on Days 1 and 8 of each cycle and at the End-of-Treatment visit. Symptom changes will be assessed using the core MDASI (Part 1 only) or MDASI-LC (only in patients with NSCLC in Part 1) (Section 6.1.3) on Days 1 and 8 of each cycle and at the End-of-Treatment visit. A schedule of the efficacy assessments is provided in Appendix 12.1.

### 6.1.1 Disease Response Definitions

- ORR: Defined as percentage of patients with CR or PR assessed using RECIST version 1.1
- DCR: Defined as the percentage of patients with CR, PR, or SD assessed using RECIST version 1.1
- PFS: Defined as the time from the beginning of NC-6004 treatment until objective tumor progression or death assessed using RECIST version 1.1
- OS: Defined as the time from the beginning of NC-6004 treatment until death or last contact

The rate of confirmed response and tumor growth control will be determined according to RECIST version 1.1 in solid tumor patients for patients evaluable for response using the following imaging methods:

Timing

Disease assessment will occur at Screening and every 6 weeks (±1 week) until disease progression. Patients who have obtained a response (PR or CR) will have a confirmatory scan at a minimum of 4 weeks following the initial scan.

Anatomic Coverage

Imaging should include a computed tomography scan of the chest, abdomen, and pelvis. In addition, areas of known predisposition for metastases (eg, the brain for NSCLC) and any areas identified by the clinician as probable sites of metastasis based on clinical evaluation should be included in imaging if clinically indicated. Other imaging may be performed at the investigator's discretion as standard of care.

Imaging Method

The preferred method for imaging is computed tomography with IV contrast. If the patient is allergic to contrast media or has another medical contraindication, magnetic resonance imaging with contrast can be used at the clinician's discretion. **It is critical that the same method of imaging is used throughout the study for a given patient**.

Slice Thickness

The preferred slice thickness is 5 mm. If a larger slice thickness is used (eg, 7 mm), the smallest tumor measurement that can be reported is twice the thickness of the slice.

### 6.1.2 European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30

The EORTC QLQ-C30 (version 3) is a questionnaire developed to assess the QoL of cancer patients (Appendix 12.2). It is a copyrighted instrument which has been translated and validated into 81 languages and is used in more than 3000 studies worldwide. The questionnaire for this study is supplemented by a disease-specific validated module for lung

cancer. The questionnaire will be administered by the site before study treatments on Days 1 and 8 of each cycle and at the End-of-Treatment visit.

### 6.1.3 MD Anderson Symptom Inventory

The MDASI (Cleeland et al 2000) is a multisymptom patient-reported outcome measure for clinical and research use. The MDASI's 13 core symptom items include those found to have the highest frequency and/or severity in patients with various cancers and treatment types. The MDASI has several advantages over other symptom-assessment scales in that it applies broadly across cancer types and treatments, is easy for patients to complete, includes items related to symptom interference with daily life, and it is easily translated into other languages. This study will use the core MDASI (Appendix 12.3) for all patients in Part 1 of the study except those patients with NSCLC.

For patients with NSCLC in Part 1 only, a specific MDASI module designed for patients with lung cancer will be used, MDASI-LC (Appendix 12.3). The MDASI-LC is a site-specific module. Along with the core MDASI's 13 symptom items and 6 interference items, the MDASI-LC also assesses 3 lung cancer-specific symptom items: coughing, constipation, and sore throat.

The MDASI-LC module includes the following:

- Purpose: To assess the severity of multiple lung cancer-related symptoms and the impact of these symptoms on daily functioning
- Population: Patients with symptoms caused by lung cancer and its treatment
- Assessment areas: Severity of multiple symptoms and the impact of symptoms on daily functioning during the last 24 hours
- Time required: 5 minutes

The core MDASI and the MDASI-LC will be administered as a self-report paper-and-pencil form given to the patient at the site before study treatments on Days 1 and 8 of each cycle in Part 1 only.

## 6.2 Pharmacokinetic and Pharmacodynamic Assessments

Pharmacokinetic samples will be collected and processed according to the instructions provided by the bioanalytical laboratory to the clinical sites. Pharmacokinetic samples will be analyzed according to the bioanalytical laboratory protocol. The concentration profiles of micellar platinum in plasma and total platinum in plasma and plasma ultrafiltrate (ie, free platinum) will be characterized. The concentration-versus-time profile will be determined in Part 1 and in Part 2.

Pharmacokinetic plasma and plasma ultrafiltrate samples will be collected at the following times in Part 1:

- Before the start of the NC-6004 infusion on Day 1 of Cycles 1 through 6
- At the end of NC-6004 infusion in Cycles 1, 3, and 5
- After the start of NC-6004 infusion at Hours 3, 6, 12, 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 (Day 8, prior to gemcitabine infusion), and 336 (Day 15) in Cycles 1, 3, and 5
- At End-of-Treatment visit

Pharmacokinetic plasma and plasma ultrafiltrate samples will be collected at the following times in Part 2 for up to 6 cycles:

- Before the start of the NC-6004 infusion on Day 1
- At the end of NC-6004 infusion
- Before gemcitabine infusion on Day 8
- At End-of-Treatment visit

Additional PK blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed.

Pharmacokinetics blood sampling should occur within 10% of nominal time for Days 1 and 2, ±4 hours of nominal time for all other time points, and should occur within 10 minutes after the 12-lead ECGs performance at time-matched visits (Section 6.3.6). All PK samples will be evaluable as long as the actual collection times are recorded.

Pharmacodynamics will be assessed based on $C_{max}$ (maximum concentration) values and nephrotoxicity as assessed by reports of AEs and from clinical laboratory data.

## 6.3 Safety and Tolerability Assessments

Safety will be assessed using frequent collection of AE reports (Section 6.3.2) and clinical hematology and coagulation, biochemistry, and urinalysis test results (Section 6.3.5). Adverse events will be graded according to the NCI CTCAE version 4.03 (National Cancer Institute 2010). Additional safety assessments include, periodic 12-lead ECG recordings (Section 6.3.6), physical examination findings (Section 6.3.7), vital sign measurements (Section 6.3.8), ECOG PS (Section 6.3.9), and audiometry (Section 6.3.10). A schedule of the safety assessments is provided in Appendix 12.1.

### 6.3.1 Dose-Limiting Toxicities and Dose Escalation Scheme

#### 6.3.1.1 Definition of Dose-Limiting Toxicities

A DLT (monitored in Part 1 only) is defined as the following treatment-related AEs or laboratory abnormalities, graded according to the NCI CTCAE version 4.03:

- Grade 3 or 4 febrile neutropenia or neutropenic infection
- Grade 4 neutropenia of duration longer than 7 days and unresponsive to growth factor support per institutional guidelines or ASCO guidelines
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with clinically significant bleeding or Grade 3 thrombocytopenia requiring a platelet transfusion
- Grade 4 life-threatening anemia
- Grade 3 or Grade 4 nonhematological toxicity (excluding alopecia and Grade 3 nausea, vomiting, diarrhea, and electrolyte imbalances lasting less than 48 hours or with suboptimal prophylactic and suboptimal curative treatment)
- Grade 3 nausea, vomiting, diarrhea or electrolyte imbalances lasting greater than 48 hours despite optimal prophylactic and curative treatment

- Grade 4 vomiting, diarrhea, or electrolyte imbalances (life-threatening consequences) of any duration despite optimal prophylactic and curative treatment
- ≥Grade 3 hypersensitivity reaction
- Dosing delay >14 days due to toxicity

### 6.3.1.2 Dose Escalation Scheme

To determine the MTD of NC-6004, an adaptive approach using an N-CRM model based on the paper by Neuenschwander et al 2008 will be used. The standard dose selection in a Bayesian N-CRM model is based on point estimates for the probability of a DLT at each dose. The uncertainty of the probability estimate is ignored. When this uncertainty is high, the risk of overdosing can be unacceptably high. The N-CRM classifies the probability of a DLT into 4 categories:

- Under-dosing: $p \in (0, 0.20]$
- Targeted toxicity: $p \in (0.20, 0.33]$
- Excessive toxicity: $p \in (0.33, 0.60]$
- Unacceptable toxicity: $p \in (0.60, 1.00]$

The N-CRM is updated with the dose level and DLT status of each patient. Updates occur after each patient experiences a DLT or completes the first cycle in the single-patient run-in phase. In the remainder of Part 1, updates occur after all 4 patients enrolled in the most recent cohort either experience a DLT or complete the first cycle. Each time the N-CRM is updated, the posterior distribution of the probability of a DLT will be summarized for each dose for the 4 toxicity categories and the estimated dose-toxicity relationship curve is updated. The dose selection relies on maximizing the probability of targeted toxicity while controlling the probability of excessive or unacceptable toxicity to be no more than 25%. The interval between dose levels is prespecified (Table 3-1) and is not determined by the N-CRM algorithm.

In the run-in phase, 1 patient will be enrolled sequentially at the following dose levels: 60, 75, 90, 105, 120, 135, 150, 165, and 180 mg/m$^2$ until a DLT is observed or until a patient is treated at 180 mg/m$^2$ for 1 cycle without a DLT. During the run-in phase of Part 1, if no DLT

is observed at a dose level, the next patient will be enrolled at the next higher dose level. If a DLT is observed at the current dose level or if the current dose level of the run-in phase is 180 mg/m$^2$, the first cohort of 4 patients will be enrolled at the dose level with the greatest posterior probability of targeted toxicity that controls the posterior probability of excessive or unacceptable toxicity to be no more than 25%, given the run-in data. If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.

After each patient in each cohort of 4 patients either completes the first cycle or experiences a DLT, the next cohort of 4 patients will be enrolled at one of the following 3 dose levels, unless Part 1 of the trial is stopped: the next lower dose level, the current dose level, or the next higher dose level. When the current dose level is the lowest dose level, the next dose level is restricted to 2 levels: the current dose level and the next higher dose level. Similarly, when the current dose level is the highest dose level, the next dose level is restricted to the next lower dose level and the current dose level. Of the 2 or 3 possible next dose levels, the dose level with the greatest posterior probability of targeted toxicity that controls the posterior probability of excessive or unacceptable toxicity to be no more than 25%, given all of the data from Part 1 collected through the current cohort is selected for the next cohort.

Part 1 of the trial will be stopped when:

1. 10 cohorts are completed, or
2. 2 cohorts are treated at the MTD, or
3. No dose level controls the posterior probability of excessive or unacceptable toxicity to be no more than 25%

The dose level with the greatest posterior probability of targeted toxicity that controls the posterior probability of excessive or unacceptable toxicity to be no more than 25% when Part 1 is stopped is identified as the MTD.

It is important to note that Part 1 of the study will not be stopped during the single-patient run-in phase, even if the first patient enrolled experiences a DLT. At least 2 cohorts of 4 patients each must be enrolled in order to stop Part 1. Finally, Part 1 will not be stopped for any reason other than 10 cohorts completing unless at least 2 DLTs are observed. It is therefore possible that more than 2 cohorts are dosed at a single dose level.

More conservative dose escalation, evaluation of intermediate doses, and expansion of an existing dose level are all permissible following discussions between the sponsor and the investigators, if such measures are needed for patient safety or for a better understanding of the dose–related toxicity, exposure, or pharmacodynamics of NC-6004.

After determination of the MTD, patients who are in cohorts receiving a lower dose of NC-6004 will continue at the previously assigned dose.

#### 6.3.1.2.1 Safety Monitoring in Part 2

During Part 2 of the study, patients treated with NC-6004 at the RPII dose from Part 1 will be monitored for safety. Dose delay and modification rules for both NC-6004 and gemcitabine apply in Part 2 as in Part 1.

In Part 2 (Cohort 3), if 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort. In addition, in Part 2 (Cohort 3), if an unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart) he or she may be withdrawn from the study (Section 4.2.1).

NC-6004-related Grade 3 or higher related AEs (excluding toxicities related to the underlying disease, alopecia and Grade 3 peripheral neuropathy) resulting in study drug withdrawal prior to cycle 4 will be considered UTs.

The cumulative UT incidence rate is defined as the number of patients experiencing at least one UT divided by the number of patients treated in Part 2 through the current date. The cumulative UT incidence rate will be updated monthly. If at any time in Part 2 after a minimum of 10 patients have been treated the cumulative UT incidence rate exceeds 30%, enrollment will be stopped pending a formal safety review by the sponsor, PPD Medical Monitor, and the investigators, who will ultimately decide whether to stop the trial.

### 6.3.2 Adverse Events

#### 6.3.2.1 Definitions of Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study drug or their clinical significance.

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study drug. Patients will be instructed to contact the investigator at any time after randomization if any symptoms develop.

A treatment-emergent AE (TEAE) is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

An SAE is defined as any event that results in death, is immediately life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Hospitalization for elective procedures or for protocol compliance is not considered an SAE. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

#### 6.3.2.2 Eliciting and Documenting Adverse Events

Adverse events will be assessed from the time the patient signs the ICF until 30 days after the last dose of study drug.

Serious AEs that occur more than 30 days after the last dose of study drug need not be reported unless the investigator considers them related to study drug.

At every study visit, patients will be asked a standard nonleading question to elicit any medically related changes in their well-being. They also will be asked if they have been

hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (both prescription and over-the-counter medications).

In addition to patient observations, AEs will be documented from any data collected on the AE page of the eCRF (eg, laboratory values, physical examination findings, ECG changes) or identified from review of other documents (eg, patient diaries) that are relevant to patient safety.

### 6.3.2.3 Reporting Adverse Events

All AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes drug treatment, dose, event terminology, date of onset, NCI CTCAE version 4.03 assessment of severity and relationship to study drug, date of resolution of the event, seriousness, any required treatment or evaluations, and outcome. With the exception of disease progression, adverse events resulting from concurrent illnesses, reactions to concurrent illnesses, and reactions to concurrent medications also must be reported. All AEs will be followed to adequate resolution (Section 6.3.2.6). The NCI CTCAE version 4.03 will be used to grade all AEs. The CTCAE includes 5 grades (1-5), with Grade 5 being death.

Any AE that meets SAE criteria (Section 6.3.2.1) must be reported to PPD immediately (ie, within 24 hours after the time site personnel first learn about the event). The event is reported via the electronic data capture (EDC) system where site personnel complete as much of the respective AE page (eCRF) as they are able.

If the EDC system is unavailable, the AE information must be recorded on the manual SAE report form and immediately (ie, within 24 hours of awareness) sent to PPD by one of the following methods (refer to the "SAE Guidelines" document for WorldReach toll-free access numbers if necessary):

**Pharmacovigilance Department**
**United States SAE Hotline:** +1 800-201-8725
**United States SAE Fax line:** +1 888-488-9697
**Europe SAE Hotline:** +44 1223 374 240 (to be used for questions concerning SAEs)
**Europe SAE Fax line:** +44 1223 374 102 (to be used for reporting SAEs)

Once the EDC system becomes available again, the site needs to transfer all data to the respective eCRF page of the patient.

### 6.3.2.4 Assessment of Severity

The severity, or intensity, of an AE refers to the extent to which an AE affects the patient's daily activities. The intensity of the AE graded on a scale of 1 to 5 as follows:

| | |
|---|---|
| 1: | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated |
| 2: | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a] |
| 3: | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b] |
| 4: | Life-threatening consequences; urgent intervention indicated |
| 5: | Death related to AE |

a Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

b Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent do not require documentation of onset and duration of each episode.

### 6.3.2.5 Assessment of Causality

The investigator's assessment of an AE's relationship to study drug (combination of NC-6004 and gemcitabine) is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the test article in causing or contributing to the AE will be characterized using the following classification and criteria:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE, ie, the event follows a reasonable temporal sequence from the time of drug administration or follows a known response pattern to the study drug, but could also have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the investigator's clinical experience, the association of the event with the study drug seems likely. The event disappears or decreases on cessation or reduction of the dose of study drug.

Definite: This relationship suggests that a definite causal relationship exists between drug administration and the AE, and other conditions (concurrent illness, progression/expression of disease state, or concurrent medication reaction) do not appear to explain the event. The event reappears or worsens if the study drug is re-administered.

### 6.3.2.6 Follow-up of Patients Reporting Adverse Events

All AEs must be reported in detail on the appropriate page of the eCRF and followed to satisfactory resolution, until the investigator deems the event to be chronic or not clinically significant, or until the patient is considered to be stable.

### 6.3.2.7 Management Guidelines for NC-6004-Related Liver Dysfunction

At the onset of Grade 4 liver enzyme elevation, NC-6004 must be immediately and permanently discontinued. Patients should be referred promptly to a hepatologist/gastroenterologist/specialist to be further evaluated. Patients with Grade 4 liver enzyme elevation should have a physical examination performed and should be assessed for signs of fever, rash and jaundice. Liver function tests including serum transaminases, alkaline

phosphatase, γ-glutamyl transpeptidase, and total bilirubin (including direct and indirect), albumin choline esterase, total cholesterol, as well as hematological tests including prothrombin time (PT), PT/international normalized ratio (INR) and eosinophil count should be performed. Other testing including a serological test may be performed at the hepatologist/gastroenterologist/specialist's discretion. Patients should then be monitored on a bi-weekly basis (or more frequent if indicated by the hepatologist/gastroenterologist/specialist) until improvement to Grade 2 or below and clinical stability. Section 5.4.1 provides details for management of Grade 3 liver enzyme elevation.

### 6.3.3 Assessment of Nausea and Vomiting

Before dosing on Day 1 of Cycle 1, the patient will rate the worst severity of their nausea and the number of emetic episodes (vomiting or retching) occurring over the last 24 hours.

For Parts 1 and 2, each patient will be given a nausea and vomiting patient diary to take home. This diary will be used to record the severity of nausea and incidence of emetic episodes over the previous 24 hours daily on Days 2 through 21. The first 7 days of the diary will be recorded verbatim in the eCRF. The patient will be given the diary and instructed on how and when to complete the diary before discharge from the site on Day 1 of each cycle.

Part 1: The investigator will collect the nausea and vomiting patient diary from each patient on Day 8 and Day 15 for Cycle 1. For all subsequent cycles, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle), Day 8, and Day 15. The investigator will record the worst severity of the patient's nausea and the total number of emetic episodes occurring over the previous 7 days in the eCRF for Day 8, Day 15, and Day 21.

Part 2: The investigator will collect the nausea and vomiting patient diary from each patient at the site on Day 8 for Cycle 1. For Cycle 2, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle) and Day 8. Note that nausea and vomiting patient diaries will not be collected past Cycle 2. The investigator will record the worst severity of the patient's nausea and the total number of emetic episodes occurring over the previous 7 days in the eCRF for Day 8 and Day 21.

Nausea will be rated on the following scale of 0 to 3:

0 None (no nausea)

1 Loss of appetite with change in eating habits

2 Less eating and drinking than normal but without much weight loss

3 Not able to eat food or drink, or tube feedings are given, or hospitalization is required for treatment of nausea

### 6.3.4 Pregnancy

Pregnancy is not regarded as an adverse event unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. Any pregnancy that occurs during study participation must be reported using a clinical study pregnancy form. To ensure patient safety, each pregnancy must be reported to PPD as described for reported SAEs in Section 6.3.2.3 within 2 weeks of learning of its occurrence. The pregnancy must be followed-up to determine outcome (including spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) and status of mother and child, even if the patient was discontinued from the study. Pregnancy complications and elective terminations for medical reasons should not be reported as an AE or SAE. Spontaneous miscarriages must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the patient has completed the study and considered by the investigator as possibly related to the study treatment must be promptly reported to PPD (Section 6.3.2.3).

### 6.3.5 Clinical Laboratory Analyses

Samples for hematology and coagulation, biochemistry, and urinalysis will be collected at the time points specified in Appendix 12.1, Schedule of Events. All samples for clinical laboratory analyses will be collected according to standard procedures.

Only abnormal laboratory test results (hematology and coagulation, biochemistry, or urinalysis) that are deemed clinically significant by the PI will be recorded as AEs or SAEs per the NCI CTCAE version 4.03.

#### 6.3.5.1 Hematology and Coagulation

Hematology will include hemoglobin, reticulocytes, red blood cell count, differential white blood cell count, and platelets. Coagulation will include prothrombin time and international normalized ratio. Hematology and coagulation tests will be performed during the screening period on Day -7 to -1, prior to dosing on Day 1 of Cycle 1 (if they were last performed more than 24 hours before the start of the study drug administration), weekly at each study visit prior to any treatments, and at the End-of-Treatment visit.

#### 6.3.5.2 Biochemistry

Biochemistry will include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, sodium, potassium, calcium, magnesium, urea, creatinine, CrCl (calculated using the Cockcroft and Gault 1976 formula), total protein, albumin, and lactate dehydrogenase. Biochemistry tests will be performed during the screening period on Day -7 to -1, prior to dosing on Day 1 of Cycle 1 (if they were last performed more than 24 hours before the start of the study drug administration), weekly at each study visit prior to any treatments, and at the End-of-Treatment visit.

#### 6.3.5.3 Urinalysis

Urinalysis will be performed and will include: leukocyte esterase, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose. Urinalysis will be performed during the screening period on Day -14 to -1 and at the End-of-Treatment visit.

### 6.3.6 Electrocardiograms

All 12-lead ECGs will be performed after the patient has adequately rested in the supine position.

A 12-lead ECG will be performed during the screening period at Day -7 to -1. On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 hours (Day 2) after start of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the completion of gemcitabine infusion, and at 1 hour after

completion of gemcitabine infusion. Twelve-lead ECGs will also be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion and at the End-of-Treatment visit. All 12-lead ECGs should be performed within a ±30-minute window.

Any assessments, including those that worsen from baseline, believed to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs per the NCI CTCAE version 4.03.

### 6.3.7 Physical Examination

A complete physical examination will be performed during the screening period at Day -14 to -1, before study treatments on Day –1 or Day 1 of each cycle, and at the End-of-Treatment visit. Height and weight will also be assessed at the time of the screening period physical examination and before treatments on Day 1 of each cycle. Calculation of BSA will be done before each dosing on Day 1 of each cycle (using the Mosteller formula [Mosteller 1987]. (***Note***: Dose will only be recalculated if there is a ≥10% increase or decrease in the patient's weight from the patient's weight measurement at screening. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs. This threshold should not be confused with a change in the patient's BSA [$m^2$]).

Any abnormal assessments, including those that worsen from baseline, are to be recorded as AEs or SAEs as per the NCI CTCAE version 4.03.

### 6.3.8 Vital Sign Measurements

Vital sign measurements will include arterial blood pressure, heart rate, respiratory rate, and temperature. Vital signs will be measured after the patient has adequately rested in the supine position.

Vital signs will be measured during the screening period on Day -14 to -1. On Day 1 of Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the NC-6004 infusion. Starting in Cycle 2, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion on Day 1 of each cycle. Vital signs will be measured before and after gemcitabine infusion on Day 8 of each cycle. Vital signs will also be measured at the End-of-Treatment visit.

Any abnormal assessments, including those that worsen from baseline, are to be recorded as AEs or SAEs as per the NCI CTCAE version 4.03.

### 6.3.9 Eastern Cooperative Oncology Group Performance Status

The patient's PS will be assessed during the screening period on Day -14 to -1 and before dosing on Day –1 or Day 1 of each cycle using the ECOG PS grades (Oken et al 1982) below:

0 Fully active, able to carry on all predisease performance without restriction

1 Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work

2 Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair

5 Dead

### 6.3.10 Audiometry

Audiometry will be performed to assess for ototoxicity during the screening period at Day -14 to -1. On Day 1 of each cycle prior to study treatments and at the End-of-Treatment visit, audiometry will be performed only as clinically indicated.

Any abnormal assessments, including those that worsen from baseline, are to be recorded as AEs or SAEs per the NCI CTCAE version 4.03.

# 7 Statistical and Analytical Plan

## 7.1 Safety Endpoints

The safety endpoints for this study are the incidence and severity of AEs and laboratory abnormalities, according to the NCI CTCAE version 4.03, the occurrence of SAEs and treatment discontinuations due to AEs, and nausea severity and vomiting incidence obtained from the patient diary.

## 7.2 Exploratory Endpoints

The exploratory endpoints of this study include exploratory safety endpoints of the occurrence of AEs and SAEs after 6 cycles of treatment and the following PK endpoints for micellar platinum in plasma and total platinum in plasma and plasma ultrafiltrate calculated for all patients using noncompartmental analysis:

- $C_{max}$ (maximum concentration)
- $T_{max}$ (time to maximum concentration)
- $AUC_{last}$ (area under the concentration-time curve from time zero to the last quantifiable concentration)
- $AUC_{0-\tau}$ (area under the concentration-time curve from time zero to the end of the dosing interval)
- $AUC_{0-\infty}$ (area under the concentration-time curve from time zero to infinity)
- AI (accumulation index)
- $V_{ss}$ (volume of distribution at steady-state)
- MRT (mean residence time)
- $\lambda_z$ (terminal elimination phase rate constant)
- $T_{½}$ (terminal half-life)
- CL (clearance)
- $V_z$ (volume of distribution)

## 7.3 Sample Size Calculations

This is a Phase 1b/2 study with an overall sample size of up to 209 patients (up to 49 patients in Part 1 and up to 160 patients in Part 2). The total sample size will depend on the number of

cohorts required to establish an RPII dose and the number of patients with NSCLC enrolled at the RPII dose in Part 1.

Simulations were performed assuming scenarios with different dose-toxicity relationships to evaluate the sample size for Part 1 (Phase 1b). The associated mean sample size in these scenarios ranged from 17.22 to 25.79 patients.

Part 2 is a 3-cohort study with an overall sample size of up to 160 patients with no more than 50 patients each in Cohorts 1 and 2 and no more than 60 patients in Cohort 3 (30 unfit and 30 fit bladder cancer patients). The total sample size will depend on the results of interim futility and superiority analyses. In order to evaluate the overall sample size, simulations were performed assuming scenarios with different HRs for PFS for each cohort compared with historical control and different sample sizes for a subsequent Phase 3 clinical trial. The associated mean sample size for this trial in these scenarios ranged from 92.7 to 116.8 patients.

No formal efficacy analysis will be performed and no inference regarding efficacy will be drawn based on the response rate of the overall study.

Patients who receive study drug will not be replaced.

## 7.4 Analysis Sets

Four analysis sets will be used in this study:

- The DLT-evaluable analysis set consists of all patients in Part 1 who either experience a DLT in the first cycle or complete the first cycle without a DLT.
- The safety analysis set consists of all patients in Part 1 or Part 2 who receive study product.
- The Full Analysis Set (FAS) consists of all patients treated at RPII dose in Part 1 or Part 2 who receive study product.
- The PK analysis set consists of all patients in the safety analysis set who have sufficient concentration data for PK analysis.

## 7.5 Description of Subgroups to be Analyzed

No subgroup analyses are planned.

## 7.6 Statistical Analysis Methodology

Ninety-five percent confidence intervals may be calculated for selected safety and exploratory variables. Dose escalation will be based on N-CRM model and DLT incidence. Adverse events and SAEs will be tabulated by system organ class and preferred term. Laboratory test results after the first dose will be summarized with regard to shifts from baseline values and grade per NCI CTCAE version 4.03. Overall survival, PFS, and DOR will be summarized using Kaplan-Meier methods. Ninety-five percent confidence intervals for ORR and DCR will be constructed. All safety analyses will be performed on the safety analysis set. All efficacy analyses will be performed on the FAS. All summaries will present data by dose level, for patients with NSCLC dosed at the MTD, and overall.

In Part 2, the following posterior probabilities will be derived using a Bayesian model updated every 6 weeks after 10 PFS have occurred within a cohort:

- Probability (Promising HR)
- Probability (Phase 3 Success)

If any cohort at interim or final analyses has a probability (success in a Phase 3 trial with 381 PFS events) >0.8, that indication will be declared a success, and the combination of NC-6004 and gemcitabine advances to a Phase 3 randomized, controlled trial with a sample size sufficient to observe 381 PFS events.

### 7.6.1 Efficacy Analysis

#### 7.6.1.1 Progression–Free Survival

Progression-free survival will be defined as the time from first dose of study product until the first date of either disease progression or death due to any cause and will be evaluated for each dose level and for all patients in the FAS. The date of disease progression will be defined as the earliest date of radiological disease progression as assessed by the investigator using RECIST version 1.1 or clinical disease progression. For patients who have not

progressed or died at the time of the analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, patients with disease progression or death after an extended loss to follow-up will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up. Further details on censoring rules will be outlined in the statistical analysis plan (SAP).

#### 7.6.1.2 Overall Survival

Overall survival will be defined as the time from first dose of study product until the date of death due to any cause and will be evaluated for each dose level and for all patients in the FAS. For patients who have not died at the time of the analysis, censoring will be performed using the date the patient was last known to be alive. Further details on censoring rules will be outlined in the SAP.

#### 7.6.1.3 Duration of Response

Duration of response will be defined as the time from the earliest date of confirmed response until the first date of either disease progression or death due to any cause and will be evaluated for each dose level and for all patients in the FAS. The date of disease progression will be defined as the earliest date of radiological disease progression as assessed by the investigator using RECIST version 1.1, or clinical disease progression. For patients who have not progressed or died at the time of the analysis, censoring will be performed using the date of the last adequate disease assessment. In addition, patients with disease progression or death after an extended loss to follow-up will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up. Further details on censoring rules will be outlined in the SAP.

#### 7.6.1.4 Disease Control Rate

Disease control rate is defined as the proportion of patients with best overall response of SD longer than 7 weeks, confirmed PR, or confirmed CR at the time each patient discontinues study treatment.

### 7.6.1.5 Overall Response Rate

Overall response rate is defined as the proportion of patients with best overall response of confirmed PR or confirmed CR at the time each patient discontinues NC-6004 and gemcitabine.

### 7.6.1.6 Quality of Life Analyses

Quality of life will be assessed using the EORTC QLQ-C30. Analyses will be based on the FAS.

Each of the 30 scores of the EORTC QLQ-C30, as well as the 5 functional scales (physical, role, emotional, cognitive, social), and 9 symptom scales (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial difficulties) will be summarized by visit. Changes from baseline will be summarized by dose level, for all patients dosed at MTD (or RPII dose), and overall.

The calculation of scores and methods to deal with missing data will be handled according to the respective questionnaires' standard scoring guidelines. Full details of all the QoL analyses will be provided in the SAP.

### 7.6.1.7 Symptoms Assessment Analyses

The MDASI core 13 symptom items and 6 interference items plus the 3 lung cancer-specific symptom items (MDASI-LC) will be summarized by visit. Analyses will be based on the FAS. Changes from baseline will be summarized by dose level, for all patients with NSCLC dosed at MTD (or RPII dose), and overall.

The calculation of scores and methods to deal with missing data will be handled according to the respective questionnaires' standard scoring guidelines. Full details of all the QoL analyses will be provided in the SAP.

## 7.6.2 Safety Analyses

### 7.6.2.1 Analyses of Adverse Events

An AE will be considered to be a TEAE if it begins or worsens on or after first dose date and before last dose date + 28 days. The following summaries of TEAEs by system organ class and preferred term will be provided:

- All TEAEs
- All serious TEAEs
- All treatment-related TEAEs
- All treatment-related serious TEAEs
- All TEAEs resulting in study drug discontinuation
- All TEAEs by NCI CTCAE grade
- All TEAEs by relationship to study drug

The following summaries of TEAEs by preferred term will be provided:

- TEAEs with at least 5% incidence in all patients
- Treatment-related TEAEs with at least 5% incidence in all patients
- TEAEs with at least 5% incidence in all patients with NSCLC dosed at the MTD or RPII dose
- Treatment-related TEAEs with at least 5% incidence in all patients with NSCLC dosed at the MTD or RPII dose

The incidence of deaths and the primary cause of death will be summarized.

### 7.6.2.2 Severity of Nausea and Incidence of Vomiting

The severity of nausea and incidence of vomiting as captured in the diary data will be summarized.

### 7.6.2.3 Clinical Laboratory Results

Clinical hematology and coagulation, biochemistry, and urinalysis data will be summarized at each scheduled assessment. Numeric hematology and coagulation and biochemistry results will be summarized using change from baseline. All results will be summarized using shift from baseline. Shifts for laboratory results that are can be graded with NCI CTCAE version 4.03 will be summarized by NCI CTCAE grade. Shifts for other numeric laboratory results will be by high/normal/low flag. Shifts for all other laboratory results will be by normal/abnormal flag.

Summaries by visit will include data from scheduled assessments only, and all data will be reported according to the nominal visit date for which it was recorded (ie, no visit windows will be applied). Unscheduled data will be included in "worst case postbaseline" summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. Further details will be provided in the SAP.

Numeric clinical hematology and coagulation, biochemistry, and urinalysis results will be summarized using change from baseline. All results will be summarized using shift from baseline.

### 7.6.2.4 Additional Safety Assessments

The results of scheduled assessments of vital signs, ECOG PS, and 12-lead ECG will be summarized. Summaries by visit will include data from scheduled assessments only. All data will be reported according to the nominal visit date for which it was recorded (ie, no visit windows will be applied). Unscheduled data will be included in "worst case" summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment. All data will be listed. Further details will be provided in the SAP.

## 7.6.3 Pharmacokinetic and Pharmacodynamic Analyses

Noncompartmental analysis will be used to calculate the following PK parameters for total platinum in plasma and plasma ultrafiltrate:

- $C_{max}$
- $T_{max}$
- $AUC_{last}$

- $AUC_{0-\tau}$
- $AUC_{0-\infty}$
- AI
- $V_{ss}$
- MRT
- $\lambda z$
- $T_{½}$
- CL
- $V_z$

Data for PK parameters will be summarized in tables and individual data will be listed.

### 7.6.4 Study Drug Exposure

Study drug exposure will be summarized by dose level and overall for the safety analysis set. Duration of treatment and total number of cycles dosed will be summarized for combination therapy. Total dose received (mg) will be summarized for NC-6004 and gemcitabine separately. The number of patients dosed by cycle will also be summarized using frequency counts and percentages.

Duration of treatment, in days, will be calculated as (date of last dose of study product – date of first dose of study product + 1).

## 7.7 Data Quality Assurance

Steps to be taken to ensure the accuracy and reliability of data include the selection of a qualified investigator and appropriate study center, review of protocol procedures with the investigator and associated personnel before the study, and periodic monitoring visits by the clinical research associate (CRA). Written instructions will be provided for collection, preparation, and shipment of blood and plasma samples.

The eCRFs will be provided to the clinical contact and the CRA will review them with site personnel.

The CRA will review eCRFs for accuracy and completeness by remote monitoring, during on-site monitoring visits, and after transmission to the sponsor; any discrepancies will be

resolved with the investigator or designee, as appropriate. After entry of the data into the clinical study database they will be verified for accuracy.

### 7.7.1 Data Management

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate case histories for the patients treated as part of the research under this protocol. The investigator agrees to maintain accurate eCRFs and source documentation as part of the case histories. These source documents may include laboratory reports, ECG strips, and patient diaries.

Investigative site personnel will enter patient data into Medidata Rave. The analysis data sets will be a combination of these data and data from other sources (eg, laboratory data).

Clinical data management will be performed in accordance with applicable PPD standards and data cleaning procedures to ensure the integrity of the data (eg, removing errors and inconsistencies in the data). Adverse events will be coded using MedDRA version 16.0. Concomitant medications will be coded using WHO Drug Dictionary, version 01-Jun-2013.

After database lock, each study site will receive a CDROM containing all of their site specific eCRF data as entered into Oracle Clinical Remote Data Capture for the study, including full discrepancy and audit history. Additionally, a CDROM copy of all of the study site's data from the study will be created and sent to the sponsor for storage. PPD will maintain a duplicate CDROM copy for its records. In all cases, patient initials will not be collected or transmitted to the sponsor.

# 8 Ethics

## 8.1 Independent Ethics Committee or Institutional Review Board

Federal regulations and the International Council for Harmonisation (ICH) guidelines require that approval be obtained from an institutional review board (IRB)/independent ethics committee (IEC) before participation of human patients in research studies. Before study onset, the protocol, informed consent, advertisements to be used for the recruitment of study patients, and any other written information regarding this study to be provided to the patient or the patient's legal guardian must be approved by the IRB/IEC. Documentation of all IRB/IEC approvals and of the IRB/IEC compliance with ICH harmonised tripartite guideline E6(R1): Good Clinical Practice (GCP) will be maintained by the site and will be available for review by the sponsor or its designee.

All IRB/IEC approvals should be signed by the IRB/IEC chairman or designee and must identify the IRB/IEC name and address, the clinical protocol by title or protocol number or both, and the date approval or a favorable opinion was granted.

The investigator is responsible for obtaining continued review of the clinical research at intervals not exceeding 1 year or otherwise specified by the IRB/IEC. The investigator must supply the sponsor or its designee with written documentation of continued review of the clinical research.

## 8.2 Ethical Conduct of the Study

The study will be performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, ICH GCP, and all applicable regulations.

## 8.3 Patient Information and Consent

A written informed consent in compliance with US Title 21 Code of Federal Regulations (CFR) Part 50 shall be obtained from each patient before entering the study or performing any unusual or nonroutine procedure that involves risk to the patient. An informed consent template may be provided by the sponsor to investigative sites. If any institution-specific modifications to study-related procedures are proposed or made by the site, the consent should be reviewed by the sponsor or its designee or both before IRB/IEC submission. Once

reviewed, the consent will be submitted by the investigator to his or her IRB/IEC for review and approval before the start of the study. If the ICF is revised during the course of the study, all active participating patients must sign the revised form.

Before recruitment and enrollment, each prospective patient or his or her legal guardian will be given a full explanation of the study and be allowed to read the approved ICF. Once the investigator is assured that the patient/legal guardian understands the implications of participating in the study, the patient/legal guardian will be asked to give consent to participate in the study by signing the ICF.

The investigator shall retain the signed original ICF(s) and give a copy of the signed original form to the patient or legal guardian.

# 9 Investigator's Obligations

The following administrative items are meant to guide the investigator in the conduct of the study but may be subject to change based on industry and government standard operating procedures, working practice documents, or guidelines. Changes will be reported to the IRB/IEC but will not result in protocol amendments.

## 9.1 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's legal guardian), except as necessary for monitoring and auditing by the sponsor, its designee, the Food and Drug Administration (FDA), or the IRB/IEC.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

## 9.2 Financial Disclosure and Obligations

Investigators are required to provide financial disclosure information to allow the sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

Neither the sponsor nor PPD is financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the sponsor nor PPD is financially responsible for further treatment of the patient's disease.

## 9.3 Investigator Documentation

Prior to beginning the study, the investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the CFR by providing the following essential documents, including but not limited to:

- IRB/IEC approval.
- Original investigator-signed investigator agreement page of the protocol.
- Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572.
- Curriculum vitae for the investigator and each subinvestigator listed on Form FDA 1572
- Financial disclosure information to allow the sponsor to submit complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigators must provide to the sponsor a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.
- IRB/IEC-approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardian,

## 9.4 Study Conduct

The investigator agrees that the study will be conducted according to the principles of ICH E6(R1). The investigator will conduct all aspects of this study in accordance with all national, state, and local laws or regulations. Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of patients begins.

## 9.5 Adherence to Protocol

The investigator agrees to conduct the study as outlined in this protocol in accordance with ICH E6(R1) and all applicable guidelines and regulations.

## 9.6 Adverse Events and Study Report Requirements

By participating in this study the investigator agrees to submit reports of SAEs according to the time line and method outlined in the protocol. In addition, the investigator agrees to submit annual reports to the study site IRB/IEC as appropriate.

## 9.7 Investigator's Final Report

Upon completion of the study, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the study's outcome and the sponsor and regulatory authority(ies) with any reports required.

## 9.8 Records Retention

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

## 9.9 Publications

After completion of the study, the data may be considered for reporting at a scientific meeting or for publication in a scientific journal. In these cases, the sponsor will be responsible for these activities and will work with the investigators to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted, and other related issues. The sponsor has final approval authority over all such issues.

Data are the property of the sponsor and cannot be published without prior authorization from the sponsor, but data and publication thereof will not be unduly withheld.

# 10 Study Management

## 10.1 Monitoring

### 10.1.1 Monitoring of the Study

The clinical monitor, as a representative of the sponsor, has the obligation to follow the study closely. In doing so, the monitor will visit the investigator and study site at periodic intervals, in addition to maintaining necessary telephone and letter contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the investigator and personnel.

All aspects of the study will be carefully monitored by the sponsor or its designee for compliance with applicable government regulation with respect to current GCP and current standard operating procedures.

### 10.1.2 Inspection of Records

Investigators and institutions involved in the study will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to all study records. In the event of an audit, the investigator agrees to allow the sponsor, representatives of the sponsor, or a regulatory agency access to all study records.

The investigator should promptly notify the sponsor and PPD of any audits scheduled by any regulatory authorities and promptly forward copies of any audit reports received to the sponsor.

## 10.2 Management of Protocol Amendments and Deviations

### 10.2.1 Modification of the Protocol

Any changes in this research activity, except those necessary to remove an apparent, immediate hazard to the patient, must be reviewed and approved by the sponsor or its designee. Amendments to the protocol must be submitted in writing to the investigator's IRB/IEC for approval before patients can be enrolled into an amended protocol.

### 10.2.2 Protocol Violations and Deviations

The investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard to study patients without prior IRB/IEC approval. As soon as possible after such an occurrence, the implemented deviation or change, the reasons for it, and any proposed protocol amendments should be submitted to the IRB/IEC for review and approval, to the sponsor for agreement, and to the regulatory authorities, if required.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

Protocol deviations will be documented by the clinical monitor throughout the course of monitoring visits. Principal investigators will be notified in writing by the monitor of deviations. The IRB/IEC should be notified of all protocol deviations in a timely manner.

## 10.3 Study Termination

Although NanoCarrier has every intention of completing the study, NanoCarrier reserves the right to discontinue the study at any time for clinical or administrative reasons.

The end of the study is defined as the date on which the last patient completes the last visit to the study site (includes any End-of Treatment visit to the site and any visit to the site to obtain confirmatory scan of response).

## 10.4 Final Report

Whether the study is completed or prematurely terminated, the sponsor will ensure that the clinical study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor will also ensure that the clinical study

reports in marketing applications meet the standards of the ICH harmonised tripartite guideline E3: Structure and content of clinical study reports.

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results.

Upon completion of the clinical study report, the sponsor will provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study patients, as appropriate. The study results will be posted on publicly available clinical trial registers.

# 11 Reference List

Azzoli CG, Baker S, Temin S, et al. 2011 Focused Update of 2009 American Society Clinical Oncology clinical practice guideline update on chemotherapy for Stage IV non-small cell lung cancer. J Clin Oncol. 2011;29(28):3825-31. Full guideline published (2009) in J Clin Oncol. 2009;27(36):6251-66.

Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer: the M. D. Anderson Symptom Inventory. Cancer. 2000;89(7):1634-46.

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.

Hartmann JT, Lipp HP. Toxicity of platinum compounds. Expert Opin Pharmacother. 2003;4(6):889-901.

Kelland LR, Sharp SY. Platinum compounds in cancer therapy. Curr Opin Oncol, Endocrine, Metabolic Invest Drugs. 1999;1:380-5.

Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res. 1986;46:6387-92.

Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987;317(17):1098.

National Cancer Institute. Common terminology criteria for adverse events (CTCAE) Version 4.0 (v4.03) 14 June 2010. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008;27(13):2420-39.

Oken MM, Creech RH, Tormey, DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55

Pinto AL, Lippard SJ. Binding of the antitumor drug *cis*-diamminedichloroplatinum(II) (Cisplatin) to DNA. Biochim Biophys Acta. 1985;780(3):167-80.

Plummer R, Wilson RH, Calvert H, et al.) A phase I clinical study of cisplatin-incorporated polymeric micelles (NC-6004) in patients with solid tumours. Br J Cancer. 2011;104(4):593-8.

Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol. 2006;24(19):3187-205.

Uchino H, Matsumura Y, Negishi T, et al. Cisplatin-incorporating polymeric micelles (NC-6004) can reduce nephrotoxicity and neurotoxicity of cisplatin in rats. Br J Cancer. 2005;93(6):678-87.

# 12 Appendices

## 12.1 Appendix: Schedule of Events

### Table 12-1 Schedule of Events

| Procedure | Screening | | | Cycle 1 | | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 2 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Informed consent | X | | | | | | | | | | | | | | | | | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | | |
| Demography | | X | | | | | | | | | | | | | | | | |
| Medical history | | X | | | | | | | | | | | | | | | | |
| Pregnancy test (serum or urine) | | | X | X[e] | | | | X | | | X | | | X | | | X | |
| Physical examination | | X[f] | | X[f] | | | | X | | | X | | | X | | | X | |
| Height, weight, and BSA calculation[g] | | X[g] | | X | | | | X | | | X | | | X | | | | |
| Vital signs[h] | | X | | X[h] | | X | | X | X | | X | X | | X | X | | X | |
| Performance status (ECOG) | | X[f] | | X[f] | | | | X | | | X | | | X | | | X | |
| Disease assessment[i] | X | | | | | | | | | | X[i] | | | X[i] | | | X | X |
| Audiometry | | X | | X[j] | | | | X[j] | | | X[j] | | | X[j] | | | X[j] | |
| Hematology and coagulation | | | X | X[k] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Biochemistry | | | X | X[k] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Urinalysis | | X | | | | | | | | | | | | | | | X | |
| EORTC QLQ-C30 | | | | X | | X | | X | X | | X | X | | X | X | | X | |
| MDASI or MDASI-LC [l] | | | | X | | X | | X | X | | X | X | | X | X | | X | |

Continued

## Table 12-1 Schedule of Events (Continued)

| Procedure | Screening | | | Cycle 1 | | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 2 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Part 1: Nausea and vomiting patient diary[m] | | | | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| Part 2 Nausea and vomiting patient diary[m] | | | | X | | X | | X | X | | | | | | | | | |
| Cardiac risk factors | | X | | | | | | | | | | | | | | | | |
| 12-lead ECG[n] | | | X | X | X | X | | X | | | X | | | | | | X | |
| Pharmacokinetic assessments (Part 1)[o] | | | | X | X[o] | X | X | X | | | X | X[o] | X[o] | | | | X | |
| Pharmacokinetic assessments (Part 2)[p] | | | | X | | X | | X | X | | X | X | | | | | X | |
| Adverse events | | | | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication | | X[f] | | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] |
| Prophylactic administrations | | | | X | | | | X | | | X | | | X | | | | |
| NC-6004 administration[a] | | | | X | | | | X | | | X | | | X | | | | |
| Gemcitabine administration | | | | X | | X | | X | X | | X | X | | X | X | | | |

Abbreviations: BSA, body surface area; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MDASI, MD Anderson Symptom Inventory; RECIST, Response Evaluation Criteria in Solid Tumors; MDASI-LC, MDASI-lung cancer.

a. In Part 1 of the study, patients will receive treatment until progressive disease. In Part 2 of the study, patients will receive treatment for 6 cycles (Cohorts 1 and 3) or 8 cycles (Cohort 2).

b. End-of-treatment assessments will be performed within 28 days after treatment discontinuation.

c. After patient discontinuation or completion of treatment without disease progression, patients will be followed with scans every 9 weeks until disease progression. Patients will be called every 12 (±1) weeks to collect data on patient survival, new treatments, and adverse events.
d. Day 15 visit is required in Part 1. In Part 2, Day 15 visit is only necessary if it is clinically indicated.
e. Not required if screening pregnancy test was performed using serum.
f. Safety assessments of physical examination, ECOG, review of adverse events, and concomitant medication use can be completed on Day -1 to allow for early morning dosing. These should not be conducted in place of screening assessments.
g. From Day -14 to -1 at screening, only height and weight will be measured. On Day 1 of each cycle, weight will be measured before treatments and BSA will be calculated before each dose using the Mosteller formula (Mosteller 1987). (***Note:*** Dose will only be recalculated if there is a ≥10% increase or decrease in the patient's weight from the patient's screening weight measurement. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs. This threshold should not be confused with a change in the patient's BSA [$m^2$]).
h. Vital signs will be performed after the patient has adequately rested in the supine position. On Day 1 of Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the NC-6004 infusion. Starting in Cycle 2, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion on Day 1 of each cycle. Vital signs will be measured before and after gemcitabine infusion on Day 8 of each cycle. Vital signs will also be measured at the End-of-Treatment visit.
i. Disease assessment will be performed using RECIST version 1.1 and the same imaging method used at screening should be used for all subsequent assessments. Beginning in Cycle 3 and continuing through the remainder of the treatment cycles, disease will be assessed every 6 (±1) weeks (ie, every other cycle) and at the End-of-Treatment visit or until disease progression. Patients who have obtained a partial response or complete response will have a confirmatory scan at a minimum of 4 weeks following the initial scan.
j. To be performed only as clinically indicated.
k. Hematology and coagulation and biochemistry tests will be repeated prior to dosing on Day 1 of Cycle 1 if they were last performed more than 24 hours before the start of the study drug administration.
l. Symptom changes will be assessed using the core MDASI (Part 1 only) or MDASI-LC (only in patients with NSCLC in Part 1).
m. Part 1: The investigator will collect the nausea and vomiting patient diary from each patient on Day 8 and Day 15 for Cycle 1. For all subsequent cycles, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle), Day 8, and Day 15. Part 2: The investigator will collect the nausea and vomiting patient diary from each patient at the site on Day 8 for Cycle 1. For Cycle 2, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle) and Day 8. Note that nausea and vomiting patient diaries will not be collected past Cycle 2. For additional details, see Section 6.3.3.
n. Twelve-lead ECGs will be performed after the patient has adequately rested in the supine position. A 12-lead ECG will be performed during the screening period at Day -7 to -1. On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 (Day 2) after the start of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the end of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion, and at the End-of-Treatment visit. All 12-lead ECGs should be performed within a ±30-minute window.
o. For Part 1, blood samples will be collected at the following times: before the start of the NC-6004 infusion on Day 1 of Cycles 1 through 6, at end of NC-6004 infusion in Cycles 1, 3, and 5, after the start of NC-6004 infusion at Hours 3, 6, 12, 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 (Day 8, prior to gemcitabine infusion), and 336 (Day 15) in Cycles 1, 3, and 5, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed. Blood samples will be collected within 10 minutes after the 12-lead ECGs performance.
p. For Part 2 (up to 6 cycles), on the day of NC-6004 infusion for each cycle, blood samples will be collected before the start of the NC-6004 infusion, at the end of the NC-6004 infusion, before gemcitabine infusion on Day 8, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed. Blood samples will be collected within 10 minutes after the 12-lead ECGs performance.

## 12.2 Appendix: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

**During the past week:**

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | | 2 | 3 | 4 |
| 18. Were you tired? | | 2 | 3 | 4 |
| 19. Did pain interfere with your family activities? | | 2 | 3 | 4 |
| 20. Have difficulty concentrating on things, like reading or watching television? | | 2 | 3 | 4 |
| 21 | | 2 | 3 | 4 |
| 22. | | 2 | 3 | 4 |
| 23. Did | | 2 | 3 | 4 |
| | : | : | : | : |
| 26. Has your physical condition or medical treatment interfered with your family life? | | | | |
| 27. Has your physical condition or medical treatment interfered with your social activities? | | 1 | 3 | 4 |
| 28 | | 1 | 2 | |

In the following questions please circle the one number that best applies to you

29. How would you rate your overall health during the past week?

4 5 6

Very Poor Excellent

## 12.3 Appendix: MD Anderson Symptom Inventory–Lung Cancer

Note: The core MDASI is the same as the MDASI-LC (shown below) with the exception that the core MDASI does not include questions 14, 15, and 16 of the MDASI-LC.

**Date:** _____ **Institution:** _____

**Participant Initials:** _____ **Hospital Chart #:** _____

**Participant Number:** _____

### M. D. Anderson Symptom Inventory - Lung Cancer (MDASI-LC)

**Part I.** How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please rate each of these symptoms from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be).

| **CORE Items** | Not Present 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | As Bad As You Can Imagine 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Your **pain** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 2. Your **fatigue (tiredness)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 3. Your **nausea** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 4. Your **disturbed sleep** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 5. Your feeling of being **distressed (upset)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 6. Your **shortness of breath** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 7. Your problem with **remembering things** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 8. Your problem with **lack of appetite** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 9. Your feeling **drowsy (sleepy)** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 10. Your having a **dry mouth** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 11. Your feeling **sad** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 12. Your **vomiting** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 13. Your **numbness or tingling** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Page 1 of 2**



MDASI-LC - December, 2010

**Date:** _____ **Institution:** _____

**Participant Initials:** _____ **Hospital Chart #:** _____

**Participant Number:** _____

| **Lung Cancer - Specific Items** | Not Present 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | As Bad As You Can Imagine 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 14. Your **coughing** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 15. Your **constipation** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 16. Your **sore throat** at its WORST? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |

**Part II.** How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items **in the last 24 hours**:

| | Did not Interfere 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | Interfered Completely 10 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 17. General **activity**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 18. **Mood**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 19. **Work** (including work around the house)? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 20. **Relations** with other people? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 21. **Walking**? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| 22. **Enjoyment** of life? | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |





MDASI-LC - December, 2010

## 12.4 Appendix: Protocol Amendments

### 12.4.1 Protocol Amendment 1–Protocol Version 2.0, Incorporating Amendment 1, Dated 31 December 2014

The following sections detail the changes made to the original protocol (Version 1.2) dated 17 October 2013. The integrated protocol, Version 2.0, including Amendment 1, was issued on 31 December 2014.

#### 12.4.1.1 Overview of Changes

The overview of significant changes includes the following:

***Title Page – Sponsor; Protocol Approval – Sponsor Signatory***

The sponsor address was updated to the following:
144-15 Chuo Gaiku, 226-39 Wakashiba Kashiwa
Chiba, 277-0871, Japan

***Title Page – Sponsor Contact***

The sponsor contact telephone was updated to the following:

+81-4-7197-7623

***Synopsis – Exclusion Criteria; Section 4.1.2 – Exclusion Criteria***

- Exclusion criterion #4 was updated to allow clinical judgment by the investigator to determine if Grade 1 fatigue at screening was residual toxicity from prior treatment or was a symptom of the patient's general condition or disease. The investigator and Medical Monitor were to discuss the eligibility of patients with baseline toxicity.

- Exclusion criterion #8 was updated to exclude patients who had hypertension requiring more than 3 medications for control of hypertension.

- Exclusion criterion #11 was updated to exclude patients who experienced any of the of the listed cardiac conditions within the 6-month period prior to screening (angina pectoris, coronary artery disease, cerebrovascular accident, transient ischemic attack, cardiac failure with known ejection fraction less than 40%, or cardiac arrhythmia requiring medical therapy). Previously, any history was exclusionary regardless of how long ago it had occurred.

***Synopsis - Study Design; Section 6.3.1.2 – Dose Escalation Scheme***

It was also added that in the run-in phase, 1 patient will be enrolled at the sequentially listed dose levels until either a DLT is observed or a patient is treated at 180 mg/m$^2$ for 1 cycle without a DLT.

***Synopsis – Study Design; Synopsis – Study Drug, Dosage, and Route of Administration; Synopsis – Dose Escalation Design; Section 3.1 – Study Design; Table 3-1 - Dose Levels of NC-6004; Table 5-1 - Dose Level Cohorts; Section 6.2 - Pharmacokinetic and Pharmacodynamics Assessments; Section 6.3.1.2 – Dose Escalation Scheme***

The study design was updated to include that if no DLT was observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase would end and the next cohort would enroll 4 subjects at 180 mg/m$^2$.

***Synopsis – Study Design; Synopsis – Estimated Study Duration; Section 3.1 - Study Design; Section 5.3 - Treatments Administered; Appendix 12.1 - Schedule of Events***

It was added that after completion of 4 to 6 cycles of treatment, individual patients could continue study drug, subject to sponsor approval, for an additional 4 to 6 cycles of treatment (up to a maximum of 10 total cycles) if they had clinical benefit, with monitoring the same as that in the treatment phase.

***Synopsis – Study Design; Section 3.1.1 – Rationale of Study Design***

It was added that at any time, in the absence of an MTD from the N-CRM model, NanoCarrier can recommend a recommended Phase 2 dose less than or equal to the maximum administered dose based on efficacy, safety, and/or PK data.

***Synopsis – Pharmacokinetic or Pharmacodynamic Assessments; Section 6.2 - Pharmacokinetic and Pharmacodynamic Assessments; Section 7.2 - Exploratory Endpoints; Section 7.6.3 – Pharmacokinetic and Pharmacodynamic Analyses; Appendix 12.1 - Schedule of Events***

Whole blood was removed from the PK assessments. Note: for the schedule of events table (footnotes “k” and “l”), “whole” was removed from “whole blood samples” to increase clarity.

***Synopsis – Safety Assessments; Section 6.3.8 – Vital Sign Measurements; Appendix 12.1 - Schedule of Events***

It was added that vital signs will be measured before NC-6004 infusion and at the completion of NC-6004 infusion in Cycles 2 through 6 (or up to 10). Previously, vital signs were only measured from Cycles 2 through 6.

***Synopsis – Definition of a DLT; Section 6.3.1.1 - Definition of Dose-Limiting Toxicities***

The definition of 1 of the listed DLT criteria was expanded to include Grade 4 neutropenia of duration longer than 7 days and unresponsive to growth factor support per institutional guidelines or American Society of Clinical Oncology guidelines.

***Synopsis – Study Drug, Dosage, and Route of Administration; Synopsis – Dose Escalation Design; Table 3-1 - Dose Levels of NC-6004; Section 5.3 - Treatments Administered; Table 5-1 - Dose Level Cohorts***

The following potential dosage levels were added to the study: 195, 210, 225, and 240 mg/m$^2$.

***Synopsis – Study Drug, Dosage, and Route of Administration; Table 3.1 – Dose Levels of NC-6004; Section 5.3 – Treatments Administered***

It was added that a full safety review of all AEs for all cycles as well as an optional PK analysis will be conducted by the investigators, the Medical Monitor, and NanoCarrier before increasing the NC-6004 dose beyond 240 mg/m$^2$.

***Synopsis – Sample Size; Section 7.3 - Sample Size Calculation***

The description for sample size calculation was updated to provide further clarification.

***Section 3.1 - Study Design; Appendix 12.1 - Schedule of Events***

It was clarified in the study design that the patient's signed informed consent can be obtained within 28 days of dosing and prior to performing any study evaluations.

***Synopsis – Safety Assessments; Section 3.1 - Study Design; Section 6.3.7 - Physical Examination; Section 6.3.9 – Eastern Cooperative Oncology Group Performance Status; Appendix 12.1 - Schedule of Events***

It was confirmed that safety assessments scheduled for Day 1 (physical examination, ECOG performance status, and review of AEs and concomitant medication use) can be completed on Day –1 to allow for early morning dosing. These should not be conducted in place of screening assessments.

***Section 5.2 – Prophylactic Treatment***

- Pre-hydration will be administered over 1 to 3 hours, as outlined by institutional standards. This change would increase the allowable window for the pre-hydration infusion time.

- The text for pre-hydration was updated to indicate that the 0.9% sodium chloride is changeable to 0.45% sodium chloride at investigator discretion based on the patient's condition.

- It was added that 8 mEq (1 g) of magnesium sulfate was to be added to the 1-L 0.9% sodium chloride pre-hydration regimen for all patients at all cycles. Once a patient's magnesium level dropped to <1.8 mg/dL or <lower limit of normal (Grade 1 hypomagnesemia), the investigator could treat as clinically warranted by supplementing with oral and/or intravenous magnesium.

***Section 7.4 – Analysis Sets***

The definition of the Full Analysis Set was updated to include all patients treated at MTD in Part 1 or Part 2 who received study product.

### 12.4.1.2 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in **bold** and deletions are shown in ~~strikethrough~~ text. Minor or obvious editorial and grammatical corrections are not highlighted.

***Title Page – Sponsor***

~~Yaesu Yamagata Bldg, 3-2-2 Nihonbashi Chuo-ku,~~
~~Tokyo 103-0027, Japan~~
**144-15 Chuo Gaiku, 226-39 Wakashiba Kashiwa**
**Chiba, 277-0871**, Japan

***Title Page – Sponsor Contact***

Telephone: +81~~-3-3548-0213~~**4-7197-7623**

***Protocol Approval – Sponsor Signatory***

~~Yaesu Yamagata Bldg, 3-2-2 Nihonbashi Chuo-ku,~~
~~Tokyo 103-0027,~~ Japan
**144-15 Chuo Gaiku, 226-39 Wakashiba Kashiwa**
**Chiba, 277-0871**, Japan

***Synopsis – Exclusion Criteria***

…

4. Have unresolved toxicity from prior radiation, chemotherapy, or other targeted treatment, including investigational treatment, with the exception of alopecia and ≤Grade 1 peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events NCI CTCAE version 4.03. **Clinical judgment by the investigator is allowed to determine if Grade 1 fatigue at screening is residual toxicity from prior treatment or is a symptom of the patient's general condition or disease. The investigator and Medical Monitor will discuss the eligibility of patients with baseline toxicity.**

…

8. Have uncontrolled diabetes or have hypertension requiring more than ~~2~~**3** medications for control of hypertension.

…

11. Have ~~a history of~~ **experienced any of the following within the 6-month period prior to screening:** angina pectoris, coronary artery disease or cerebrovascular accident, transient ischemic attack, cardiac failure with known ejection fraction less than 40%, or cardiac arrhythmia requiring medical therapy.

***Synopsis – Study Design***

…

The dose-escalation part of the trial will begin with a single patient run-in phase. In the run-in phase, 1 patient will be enrolled sequentially at the following dose levels: 60, 75, 90, 105, 120, 135, 150, 165, and 180 mg/m$^2$ until a DLT is observed **or until a patient is treated at 180 mg/m$^2$ for 1 cycle without a DLT.** During the **single-subject** run-in phase, after enrollment of the initial patient at 60 mg/m$^2$, the first patient in each cohort will not be enrolled until the patient at the immediately lower cohort has completed at least 1 full cycle. A Bayesian continual-reassessment method per Neuenschwander et al 2008 (N-CRM) design will be used for dose escalation. The N-CRM will model the starting dose for the remainder of the escalation using the run-in data. For the remainder of Part 1 of the study, 4 patients will

be enrolled as a cohort at each dose level predicted by the N-CRM model. **If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.**

…

Patients will continue to receive treatment until they experience disease progression, experience unacceptable toxicity (UT), withdraw voluntarily, or complete a maximum of ~~4 to 6~~ **10 total** cycles **of treatment (4 to 6 cycles followed by an additional 4 to 6 cycles, if they have clinical benefit)**, whichever occurs first.

…

**At any time, in the absence of an MTD from the N-CRM model, NanoCarrier can recommend a recommended Phase 2 dose less than or equal to the maximum administered dose on efficacy, full safety, and/or pharmacokinetic (PK) data.**

…

After completion of 4 to 6 cycles of treatment **(or up to 10 cycles)**, patients will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

***Synopsis – Estimated Study Duration***

The study will include a screening period (up to 28 days)~~,~~**;** 4 to 6 treatment cycles**, followed by an additional 4 to 6 cycles (up to a maximum of 10 total cycles) of treatment,** that are 21 days in duration~~,~~**;** tumor assessments for response and disease progression with scans every 6 weeks~~,~~**;** and telephone calls for survival every 12 weeks.

Patients will receive study treatment until any of the following occur:

- Disease progression or completion of 4 to 6 cycles of treatment **(followed by an additional 4 to 6 cycles, up to a maximum of 10 total cycles if they have clinical benefit)**.

***Synopsis – Pharmacokinetic or Pharmacodynamic Assessments***

The concentration-versus-time profile of micellar platinum in ~~whole blood and~~ plasma and of total platinum in plasma~~, whole blood,~~ and plasma ultrafiltrate (ie, free platinum) will be determined in Part 1 and in Part 2.

**Part 1 Pharmacokinetic Time Points**

Pharmacokinetic plasma~~, whole blood,~~ and plasma ultrafiltrate samples will be collected at the following times in Part 1:

…

**Part 2 Pharmacokinetic Time Points**

Pharmacokinetic plasma~~, whole blood,~~ and plasma ultrafiltrate will be collected at the following times in Part 2 for each cycle:

***Synopsis – Safety Assessments***

…

Physical examinations will be performed and vital signs will be measured at Screening, before the start of treatment on Day 1 of each cycle **(or can be completed on Day –1)**, and at the End-of Treatment visit.

…

In Cycles 2 through 6 **(or up to 10)**, vital signs will be measured before before NC-6004 infusion and at the completion of the NC-6004 infusion.

***Synopsis – Definition of DLT***

- Grade 4 neutropenia ~~lasting >~~ **of duration longer than** 7 days **and unresponsive to growth factor support per institutional guidelines or American Society of Oncology guidelines**.

***Synopsis – Study Drug, Dosage, and Route of Administration***

The potential dosage levels of NC-6004 in this study include 60, 75, 90, 105, 120, 135, 150, 165, ~~and~~ 180**, 195, 210, 225, and 240 mg/m$^2$. A full safety review of all AEs for all cycles as well as an optional PK analysis will be conducted by the investigators, the Medical Monitor, and NanoCarrier before increasing the NC-6004 dose beyond 240 mg/m$^2$.**

***Synopsis – Dose Escalation Design***

Sequential doses selected for evaluation are~~:~~ 75, 90, 105, 120, 135, 150, 165, ~~or~~ 180**, 195, 210, 225, and 240 mg/m$^2$.**

…

**If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.**

***Synopsis – Sample Size***

~~The design for Part 2 assumes p0 (the response rate for a poor drug) = 0.05, p1 (the response rate for a good drug) = 0.20, alpha = 0.05, and power = 80%. In the first stage of Part 2, testing will be performed on 10 patients, and if no patients respond at the second disease assessment the trial will be terminated. Any evidence of response, regardless of duration, will be counted as a response. If the trial continues into the second stage, a total of 36 patients will receive study drug. The 36 patients with NSCLC dosed at MTD will provide a 95% chance to detect at least 1 AE of interest with underlying 8% incidence rate.~~

**In order to provide a 95% chance to detect at least 1 AE of interest with underlying 8% incidence rate among patients treated at MTD, additional patients with NSCLC will be enrolled at the MTD in Part 2 of the study. Patients will be enrolled in 2 stages until a total of 36 patients with NSCLC have been dosed at the MTD, including patients with NSCLC receiving the MTD level in Part 1. In the first stage of Part 2, ten patients treated at the MTD will be evaluated for response. If no patients respond, then the patients with NSCLC treated at a lower dose level than the MTD will be considered and a discussion of terminating the trial early will be triggered. Any evidence of response, regardless of duration, will be counted as a response. If at least 1 response is observed, the remaining 26 patients will be treated at the MTD. No formal efficacy analysis will**

**be performed and no inference regarding efficacy will be drawn based on the response rate of the overall study.**

***Section 3.1 – Study Design***

Patients will be treated until disease progression or up to ~~6~~**10** cycles of therapy, whichever occurs first. **After completion of 4 to 6 cycles of treatment, individual patients can continue study drug, subject to sponsor approval, for an additional 4 to 6 cycles of treatment (up to a maximum of 10 total cycles) if they have clinical benefit, with monitoring the same as that in the treatment phase.**

In both Part 1 and Part 2, patients will continue to receive treatment until they experience disease progression or for up to ~~6~~**10** treatment cycles, whichever occurs first. The maximum number of cycles a patient undergoes (~~4 to 6 cycles~~**up to 10 total cycles**) is at the discretion of the investigator and depends on response as described in the ASCO guideline (Appendix 12.4) (Azzoli et al 2011). Patients who complete 4 or more cycles will be considered as having completed the treatment. **Subject to sponsor approval, individual patients could continue study drug for an additional 4 to 6 cycles of treatment (up to a maximum of 10 total cycles) if they have clinical benefit, with monitoring the same as that in the treatment phase**.

***Section 3.1 – Study Design, Table 3-1 Dose Levels of NC-6004***

**Table 3-1 Dose Levels of NC-6004**

| Dose Level Name | NC-6004 Dose Level (mg/m$^2$) |
|---|---|
| 1 | 60 |
| 2 | 75 |
| 3 | 90 |
| 4 | 105 |
| 5 | 120 |
| 6 | 135 |
| 7 | 150 |
| 8 | 165 |
| 9 | 180[a] |
| **10** | **195** |
| **11** | **210** |
| **12** | **225** |
| **13** | **240[b]** |

[a] **If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.**

[b] **A formal review by the safety committee will take place to decide if the dose can be increased beyond 240 mg/m$^2$.**

***Section 3.1 – Study Design***

The N-CRM model will only be updated after all patients in a cohort have either experienced a DLT or completed the first cycle. **If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.**

…

In both Part 1 and Part 2, patients will continue to receive treatment until they experience disease progression or for up to ~~6~~**10** treatment cycles, whichever occurs first. The maximum number of cycles a patient undergoes (~~4 to 6~~**up to 10 total** cycles) is at the discretion of the investigator and depends on response as described in the ASCO guideline (Appendix 12.4) (Azzoli et al 2011). Patients who complete 4 or more cycles will be considered as having

completed the treatment. **Subject to sponsor approval, individual patients can continue study drug for an additional 4 to 6 cycles of treatment (up to a maximum of 10 total cycles) if they have clinical benefit, with monitoring the same as that in the treatment phase.**

After the completion of 4 to 6 cycles of treatment **(or up to 10 cycles)**, patients will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contaced for survival every 12 weeks by phone.

…
*Screening Period (Day -28 to -1)*

The following procedure**s** will be performed during the screening period within 28 days prior to the first study treatment :

- **Signed informed consent can be obtained within 28 days of dosing and prior to performing any study evaluations.**

*Screening Period (Day -14 to -1)*

The following procedures will be performed during the screening period within 14 days prior to the first study treatment:

- ~~Signed informed consent obtained from the patient prior to performing any study evaluations~~

…
*Screening Period (Day -7 to -1)*
…
- **Safety assessments scheduled for Day 1 (physical examination, ECOG performance status, and review of AEs and concomitant medication use) can be completed on Day-1 (not to be conducted in place of screening assessments).**

*Day 1 of Cycle*

…

- Physical examination **(if not performed on Day –1)**

**…**

- ECOG performance status **(if not performed on Day –1)**

**…**

- Adverse events **(if not performed on Day –1)**
- Concomitant medication use **(if not performed on Day –1)**

***Section 3.1.1 – Rationale of Study Design***

…

**At any time, in the absence of an MTD from the N-CRM model, NanoCarrier can recommend a recommended Phase 2 dose less than or equal to the maximum administered dose based on efficacy, full safety, and/or PK data.**

***Section 4.1.2 – Exclusion Criteria***

4. Have unresolved toxicity from prior radiation, chemotherapy, or other targeted treatment, including investigational treatment, with the exception of alopecia and ≤Grade 1 peripheral neuropathy according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 (National Cancer Institute 2010). **Clinical judgment by the investigator is allowed to determine if Grade 1 fatigue at screening is residual toxicity from prior treatment or is a symptom of the patient's general condition or disease. The investigator and Medical Monitor will discuss the eligibility of patients with baseline toxicity.**

…

8. Have uncontrolled diabetes or have hypertension requiring more than ~~2~~ **3** medications for control of hypertension.

…

11. Have ~~a history of~~ **experienced any of the following within the 6-month period prior to screening:** angina pectoris, coronary artery disease or cerebrovascular accident, transient ischemic attack, cardiac failure with known ejection fraction less than 40%, or cardiac arrhythmia requiring medical therapy.

***Section 5.2 – Prophylactic Treatment***

…

- **Pre-hydration will be administered over 1 to 3 hours, as outlined by institutional standards**. A minimum of 1 L of 0.9% sodium chloride solution will be infused intravenously over ~~2~~**1** to 3 hours prior to NC-6004 administration, and a minimum of 500 mL of 0.9% sodium chloride solution will be infused over 2 hours following NC-6004 administration. **The 0.9% sodium chloride is changeable to 0.45% sodium chloride at investigator discretion based on the patient's condition.** When gemcitabine only is infused, hydration is not required.

- **At all cycles, 8 mEq (1 g) of magnesium sulfate will be added to the 1-L 0.9% sodium chloride pre-hydration regimen for all patients. Once a patient's magnesium level drops to <1.8 mg/dL or <lower limit of normal (Grade 1 hypomagnesemia), the investigator may treat as clinically warranted by supplementing with oral and/or intravenous magnesium.**

***Section 5.3 - Treatments Administered***

…

In each part of the study, patients will receive treatment for 4 to 6 cycles as directed in the ASCO guidelines (Appendix 12.4) or until disease progression, whichever occurs first. **After the initial 4 to 6 cycles of treatment, individual patients can continue study drug, subject to sponsor approval, for an additional 4 to 6 cycles of treatment (up to a maximum of 10 total cycles) if they have clinical benefit, with monitoring the same as that in the treatment phase.** Prophylactic antiemetic medications may be administered according to standard treatment center protocols.

The dose level may escalate to 75, 90, 105, 120, 135, 150, 165, ~~or~~ 180, **195, 210, 225, or 240 mg/m$^2$** according to observations of DLTs and the dose-level toxicity relationship (Section 6.3.1.2). **A full safety review of all AEs for all cycles as well as an optional PK analysis will be conducted by the investigators, the Medical Monitor, and NanoCarrier before increasing the NC-6004 dose beyond 240 mg/m$^2$.**

***Section 5.3 - Treatments Administered, Table 5-1 Dose Level Cohorts***

…

| Dose Level | Day 1 of Each Cycle | Day 8 of Each Cycle |
|---|---|---|
| 60 mg/m$^2$ | 60 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 75 mg/m$^2$ | 75 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 90 mg/m$^2$ | 90 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 105 mg/m$^2$ | 105 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 120 mg/m$^2$ | 120 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 135 mg/m$^2$ | 135 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 150 mg/m$^2$ | 150 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 165 mg/m$^2$ | 165 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| 180 mg/m$^2$,[a] | 180 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine | 1250 mg/m$^2$ gemcitabine |
| **195 mg/m$^2$** | **195 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine** | **1250 mg/m$^2$ gemcitabine** |
| **210 mg/m$^2$** | **210 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine** | **1250 mg/m$^2$ gemcitabine** |
| **225 mg/m$^2$** | **225 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine** | **1250 mg/m$^2$ gemcitabine** |
| **240 mg/m$^2$** | **240 mg/m$^2$ NC-6004;<br>1250 mg/m$^2$ gemcitabine** | **1250 mg/m$^2$ gemcitabine** |

[a] **If no DLT is observed in the single-subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.**

***Section 6.2 – Pharmacokinetic and Pharmacodynamic Assessments***

…

Pharmacokinetic samples will be analyzed for concentrations of micellar platinum in ~~whole blood and~~ plasma and total platinum in plasma~~, whole blood,~~ and plasma ultrafiltrate (ie, free platinum). The concentration versus time profile will be determined in Part 1 and in Part 2.

Pharmacokinetic plasma~~, whole blood,~~ and plasma ultrafiltrate samples will be collected at the following times in Part 1:

…

Pharmacokinetic plasma~~, whole blood,~~ and plasma ultrafiltrate samples will be collected at the following times in Part 2 for each cycle:

***Section 6.3.1.1 – Definition of Dose-Limiting Toxicities***

…

- Grade 4 neutropenia ~~lasting >~~ **of duration longer than** 7 days **and unresponsive to growth factor support per institutional guidelines or ASCO guidelines**

***Section 6.3.1.2 – Dose Escalation Scheme***

…

**In the run-in phase, 1 patient will be enrolled sequentially at the following dose levels: 60, 75, 90, 105, 120, 135, 150, 165, and 180 mg/m$^2$ until a DLT is observed or until a patient is treated at 180 mg/m$^2$ for 1 cycle without a DLT.**

**…**

**If no DLT is observed in the single subject run-in phase at 180 mg/m$^2$, the single-subject run-in phase will end and the next cohort will enroll 4 patients at 180 mg/m$^2$.**

***Section 6.3.7 – Physical Examination***

A complete physical examination will be performed during the screening period at Day -14 to -1, before study treatments on Day **–1 or Day** 1 of each cycle, and at the End-of-Treatment visit.

***Section 6.3.8 – Vital Sign Measurements***

…

In Cycles 2 through 6 **(or up to Cycle 10, if there is clinical benefit)**, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion.

***Section 6.3.9 - Eastern Cooperative Oncology Group Performance Status***

The patient's performance status will be assessed during the screening period on Day -14 to -1 and before dosing on Day **–1 or Day** 1 of each cycle using the ECOG performance status grades (Oken et al 1982) below.

***Section 7.2 – Exploratory Endpoints***

The exploratory endpoints of this study include exploratory safety endpoints of the occurrence of AEs and SAEs after 4 to 6 cycles of treatment and the following PK endpoints for micellar platinum in ~~whole blood and~~ plasma and total platinum in plasma~~, whole blood,~~ and plasma ultrafiltrate calculated for all patients using noncompartmental analysis:

***Section 7.3 – Sample Size Calculations***

…

In Part 2 of the study, additional patients with NSCLC will be enrolled at the MTD until a total of 36 patients with NSCLC have been dosed at the MTD, including patients with NSCLC receiving the MTD dose level in Part 1. **In order to provide a 95% chance to detect at least 1 AE of interest with an underlying 8% incidence rate among patients treated at MTD, additional patients with NSCLC will be enrolled at the MTD in Part 2 of the study. Patients will be enrolled in 2 stages until a total of 36 patients with NSCLC have been dosed at the MTD, including patients with NSCLC receiving the MTD level in Part 1. In the first stage of Part 2, ten patients treated at the MTD will be evaluated for response. If no patients respond, then the patients with NSCLC treated at a lower**

**dose level than the MTD will be considered and a discussion of terminating the trial early will be triggered. Any evidence of response, regardless of duration, will be counted as a response. If at least 1 response if observed, the remaining 26 patients will be treated at the MTD. No formal efficacy analysis will be performed and no inference regarding efficacy will be drawn based on the response rate of the overall study.**

~~The design for Part 2 assumes p0 (the response rate for a poor drug) = 0.05, p1 (the response rate for a good drug) = 0.20, alpha = 0.05, and power = 80%. In the first stage of Part 2, testing will be performed on 10 patients. If no patients respond at the second disease assessment the trial will be terminated. Any evidence of response, regardless of duration, will be counted as a response. If the trial continues into the second stage, a total of 36 patients will receive study drug.~~

***Section 7.4 – Analysis Sets***

…

- The Full Analysis Set (FAS) consists of all patients **treated at MTD** in Part 1 or Part 2 who receive study product.

***Section 7.6.3 – Pharmacokinetic and Pharmacodynamic Analyses***

Noncompartmental analysis will be used to calculate the following PK parameters for total platinum in plasma~~, whole blood,~~ and plasma ultrafiltrate:

## *12.1 Appendix: Schedule of Events*

| Procedure | Screening | | | Cycle 1 | | | Cycle 2 | | | Cycles 3-6 | | | Cycles 7-10[a] | | | End-of-Treatment[ab] | Follow-up[bc] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | | |
| Informed consent | **X** | ~~X~~ | | | | | | | | | | | | | | | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | |
| Demography | | X | | | | | | | | | | | | | | | |
| Medical history | | X | | | | | | | | | | | | | | | |
| Pregnancy test (serum or urine) | | | X | X[cd] | | | | | | | | | | | | | |
| Physical examination | | X[e] | | X[e] | | | X | | | X | | | **X** | | | X | |
| Height, weight, and BSA calculation | | X[df] | | X | | | X | | | X | | | **X** | | | | |
| Vital signs | | X | | X[eg] | X | | X | X | | X | X | | **X** | **X** | | X | |
| Performance status (ECOG) | | X[e] | | X[e] | | | X | | | X | | | **X** | | | X | |
| Disease assessment[fh] | X | | | | | | | | | X[h] | | | **X**[h] | | | X | X |
| Audiometry | | X | | X[gi] | | | X[g] | | | X[gi] | | | **X**[i] | | | X[gi] | |
| Hematology | | | X | X[hj] | X | X | X | X | X | X | X | X | **X** | **X** | **X** | X | |
| Biochemistry | | | X | X[hj] | X | X | X | X | X | X | X | X | **X** | **X** | **X** | X | |
| Urinalysis (dipstick) | | X | | | | | | | | | | | | | | X | |
| EORTC QLQ-C30 | | | | X | X | | X | X | | X | X | | **X** | **X** | | X | |
| MDASI or MDASI-LC | | | | X | X | | X | X | | X | X | | **X** | **X** | | X | |
| Nausea and vomiting patient diary[ik] | | | | X | X | X | X | X | X | X | X | X | **X** | **X** | **X** | | |
| Cardiac risk factors | | X | | | | | | | | | | | | | | | |
| 12-lead ECG[jl] | | | X | X | X | | X | | | X | | | **X** | | | X | |
| Pharmacokinetic assessments (Part 1)[k] | | | | X | X | X | X | | | X | X[km] | X[km] | | | | X | |
| Pharmacokinetic assessments (Part 2)[ln] | | | | X | X | | X | X | | X | X | | | | | X | |
| Adverse events | | | | X[e] | X | X | X | X | X | X | X | X | **X** | **X** | **X** | X | X |
| Concomitant medication | | X[e] | | X[e] | X | X | X | X | X | X | X | X | **X** | **X** | **X** | X | X |
| Prophylactic administrations | | | | X | | | X | | | X | | | **X** | | | | |
| NC-6004 administration[a] | | | | X | | | X | | | X | | | **X** | | | | |

| Procedure | Screening | | | Cycle 1 | | | Cycle 2 | | | Cycles 3-6 | | | Cycles 7-10[a] | | | End-of-Treatment[ab] | Follow-up[bc] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | Day 1 | Day 8 | Day 15 | | |
| Gemcitabine administration | | | | X | X | | X | X | | X | X | | **X** | **X** | | | |

Abbreviations: BSA, body surface area; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MDASI, MD Anderson Symptom Inventory; RECIST, Response Evaluation Criteria in Solid Tumors; MDASI-LC, MDASI-lung cancer.

**a** **An optional extension of an additional 4 to 6 cycles of treatment (up to 10 cycles of treatment [including gemcitabine if the patient is tolerating NC-6004]) is allowed, with monitoring the same as that in the treatment phase of the protocol.**

~~a~~b End-of-treatment assessments will be performed within 28 days after treatment discontinuation.

~~b~~c After patient discontinuation or completion of treatment without disease progression, patients will be followed with scans every 9 weeks until disease progression. Patients will be called every 12 (±1) weeks to collect data on patient survival, new treatments, and adverse events.

~~c~~d Not required if screening pregnancy test was performed using serum.

**e** **Safety assessments of physical examination, ECOG, review of AEs, and concomitant medication use can be completed on Day -1 to allow for early morning dosing. These should not be conducted in place of screening assessments.**

~~d~~**f** Height and weight only.

~~e~~**g** On Day 1 of Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the NC-6004 infusion. In Cycles 2 through ~~6~~**10**, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion. Vital signs will be measured before and after gemcitabine infusion on Day 8 of each cycle.

~~f~~**h** Disease assessment will be performed using RECIST version 1.1 and the same imaging method used at screening should be used for all subsequent assessments. Beginning in Cycle 3 and continuing through the remainder of the treatment cycles, disease will be assessed every 6 (±1) weeks (ie, every other cycle) and at the End-of-Treatment visit or until disease progression. Patients who have obtained a partial response or complete response will have a confirmatory scan at a minimum of 4 weeks following the initial scan.

~~g~~**i** To be performed only as clinically indicated.

~~h~~**j** Hematology or biochemistry tests will be repeated prior to dosing on Day 1 of Cycle 1 if they were last performed more than 24 hours before the start of the study drug administration.

~~i~~**k** Diary issued on Day 1 of each cycle. Assessment is performed at the site before dosing on Days 1 and Day 8 as well as Day 15 (no dosing on Day 15) of each cycle. Patient completes diary at home on Days 2 through 8 and returns diary on Day 8.

~~j~~**l** Twelve-lead ECGs will be performed after the patient has rested in the supine position for at least 5 minutes. On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 (Day 2) after the **start** of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the end of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion, and at the End-of-Treatment visit.

~~k~~**m** For Part 1, ~~whole~~ blood samples will be collected at the following times: before the start of the NC-6004 infusion on Day 1 of Cycles 1 through 6, at end of NC-6004 infusion in Cycles 1, 3, and 5, after the **start** of NC-6004 infusion at Hours 3, 6, 12, 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 and prior to gemcitabine infusion (Day 8), and 336 (Day 15) ~~n~~ in Cycles 1, 3, and 5, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed.

~~l~~**n** For Part 2, on the day of NC-6004 infusion for each cycle, ~~whole~~ blood samples will be collected before the start of the NC-6004 infusion, at the end of the NC-6004 infusion, before gemcitabine infusion on Day 8, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed.

## 12.4.2 Protocol Amendment 2–Protocol Version 3.0, Incorporating Amendment 2, Dated 07 July 2015

The following sections detail the changes made to Amendment 1 of the protocol (Version 2.0) dated 31 December 2014. The integrated protocol, Version 3.0, including Amendment 2, was issued on 07 July 2015.

### 12.4.2.1 Assessment of Risk Associated With Amendment 2

The combination of gemcitabine and cisplatin has been used in chemo-naïve patients with bladder, biliary tract cancer, as well as NSCLC, and the toxicity profile was similar overall in the 3 diseases. Nonclinical data suggested that NC-6004 has the potential to be at least as active as cisplatin with less renal toxicity and neurotoxicity compared with cisplatin, and clinical data of the combination of gemcitabine and NC-6004 in recurrent NSCLC showed good activity with a manageable toxicity profile. Thus, the overall risk of this combination in chemo-naïve patients with bladder and biliary tract cancer would be similar to the known risk to NSCLC patients.

### 12.4.2.2 Overview of Changes

The overview of significant changes includes the following:

***Title Page – Title; Protocol Approval – Sponsor Signature – Study Title; Protocol Synopsis – Title***

The title was amended to capture the added indications. The previous title was "... in Patients with Advanced Solid Tumors or Non-Small Cell Lung Cancer" and the amended title is …"in Patients with Advanced Solid Tumors or Squamous Non-Small Cell Lung, Biliary Tract, and Bladder Cancer."

***Title Page – Sponsor Contact; Protocol Approval – Sponsor Signatory – Protocol accepted and approved by***

Sponsor contact name was changed to Kazuhiro Takahashi, and his role and contact information were added as applicable.

***Title Page – Project Manager***

Project manager name and contact information were removed from the protocol.

***Protocol Synopsis – Indication; Section 1 – Introduction; Section 3.1.1 – Rationale of Study Design***

The indication for Part 2 was updated to first-line metastatic squamous NSCLC; first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and first-line metastatic or locally advanced TCC of the urinary tract (bladder cancer).

***Protocol Synopsis – Rationale; Protocol Synopsis – Objectives; Protocol Synopsis – Study Design; Section 1 – Introduction; Section 2.1 – Primary Objectives; Section 3.1 – Study Design; Section 3.1.1 – Rationale of Study Design; Section 5.1 – Method of Assigning Patients to Treatment Groups; Section 5.3 – Treatments Administered; Section 6.3.1.2.1 - Safety Monitoring in Part 2; Section 7.3 – Sample Size Calculation; Section 7.4 – Analysis Sets; Section 7.6.1.6 – Quality of Life Analyses; Section 7.6.1.7 - Symptoms Assessment Analyses; Section 7.6.2.1 – Analyses of Adverse Events***

It was added that a recommended Phase 2 (RPII) dose would be established in the study in addition to the maximum-tolerated dose, which was previously stated. As applicable, the NC-6004 dose used in Phase 2 of the study was changed from the MTD to the RPII dose.

***Protocol Synopsis – Objectives; Section 2.1 – Primary Objectives***

The second primary objective was amended to reflect the updated indications in Part 2 of first-line Stage IV squamous NSCLC, first-line advanced or metastatic biliary tract cancer, and first-line metastatic or locally advanced bladder cancer compared with historical control as measured by local investigator/radiologist-assessed PFS, according to RECIST version 1.1.

***Protocol Synopsis – Objectives; Section 2.2 – Secondary Objectives***

The DCR in the first secondary objective was defined as CR+PR+SD. A third secondary objective of "To evaluate the safety and tolerability of NC-6004 when combined with gemcitabine" was added.

***Protocol Synopsis – Patient Population, Inclusion Criteria; Section 4.1.1 – Inclusion Criteria***

Inclusion criterion 2 was updated to include new definitions for Part 2 cohorts. Cohort 1 will include Stage IV squamous NSCLC patients who did not receive prior chemotherapy for metastatic disease. It was added that patients with known sensitizing mutation in the EGFR gene or ALK fusion oncogene must have received at least 1 and up to 2 targeted therapies prior to enrollment.

It was also clarified that for patients whose tumors are known to harbor an exon 19 deletion or an exon 21 L858R EGFR mutation that they must have had tolerance or have progressed on at least 1 and up to 2 EGFR tyrosine kinase inhibitors.

It was also clarified that for patients whose tumors are known to harbor an ALK translocation that they must have had intolerance or have progressed on at least 1 and up to 2 ALK inhibitors.

For Part 2, Cohort 2, patients had to have a histologically or cytologically confirmed diagnosis of nonresectable, recurrent, or metastatic biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma) and have not received prior systemic anticancer therapy for advanced or metastatic disease.

For Part 2, Cohort 3, patients had to have a histologically or cytologically confirmed diagnosis of metastatic or locally advanced TCC of the urinary tract (bladder, urethra, ureter, renal pelvis) (T3b-T4 N0 M0, Tany N1-N3 M0, or Tany Nany M1) and are not candidates for surgery. Patients must not have received prior treatment with systemic anticancer therapy for metastatic or locally advanced urinary tract cancer. In addition, certain mixed histologies that are predominantly (>50%) TCC are eligible: squamous, adenocarcinoma, and undifferentiated. Mixed undifferentiated histology requires immunohistochemistry consistent with a TCC origin. Predominantly squamous or neuroendocrine tumors are excluded.

***Protocol Synopsis – Patient Population, Exclusion Criteria; Section 4.1.2 – Exclusion Criteria***

Exclusion criterion 1 was amended to exclude prior platinum therapy in the past 3 months for Part 1 of the study and in the past 6 months in the adjuvant or neoadjuvant setting for Part 2 of the study.

***Protocol Synopsis – Study Design; Section 3.1 – Study Design***

Text was added to specify that the study design is adaptive. Dosing in Part 1 was amended such that patients will receive intravenous infusion of NC-6004 at escalating doses on Day 1 in combination with gemcitabine at the fixed dose of 1250 mg/m$^2$ on Days 1 and 8 of a 21-day cycle. The duration of treatment for Part 1 was changed to until progressive disease or until the drug is no longer tolerated (whichever occurs first). The sponsor may agree to supply the drug after discussion of the request with the investigator.

All patients in Part 2 will receive the RPII dose of NC-6004 in combination with gemcitabine 1250 mg/m$^2$ by the same regimen in Part 1. It was added that stage 2 will continue in each cohort after achieving the minimum threshold of clinical responses required and enroll up to 50 patients in each cohort for a total of up to 150 patients in Part 2. The primary endpoint (PFS) will be continuously updated and compared with the historical PFS from Phase 3 pivotal cisplatin and gemcitabine trials within each cohort. The PFS hazard model will be updated as PFS data accrue. A HR for PFS for each cohort versus historical control will be obtained. The historical median durations of PFS and PFS weekly hazard for each cohort were added.

In addition, once 10 PFS events have been observed, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort, which include futility, success, or inconclusive. Each out is defined. Phase 3 success is defined as success in a Phase 3 clinical trail with 381 events – enough to provide 80% power to detect an HR of 0.75. A promising HR is defined as one less than 0.85. Futility can only be declared for a cohort after 10 PFS events have been observed in that cohort. Success can only be declared for a cohort after 25 PFS events have been observed in that cohort. Accrual will stop for any cohort identified as futile or successful at interim. The conclusion of this Phase 2 trial will be that a Phase 3 trial with 381 events should be conducted for each cohort that is a success.

***Protocol Synopsis – Study Design; Protocol Synopsis – Sample Size; Section 3.1 – Study Design; Section 7.3 – Sample Size Calculations***

The Part 2 sample size was added to include up to 150 patients with no more than 50 patients per cohort. The method to determine the sample size was also added.

***Protocol Synopsis – Study Design; Protocol Synopsis – Estimated Study Duration; Section 3.1 – Study Design; Table 12-1 Schedule of Events, footnote "a"***

The number of cycles of treatment in Part 2 was changed to 6 cycles (Cohorts 1 and 3) or 8 cycles of treatment (Cohort 2).

***Protocol Synopsis – Efficacy Assessments; Section 3.1 – Study Design; Section 3.1.1 - Rationale of Study Design; Section 6.1 – Efficacy Assessments; Section 6.1.3 – MD Anderson Symptom Inventory; Table 12-1 Schedule of Events, footnote "l"***

It was clarified that MD Anderson Symptom Inventory-lung cancer (MDASI-LC) was to be conducted in Part 1 only.

***Protocol Synopsis – Pharmacokinetic or Pharmacodynamic Assessments; Section 6.2 – Pharmacokinetic and Pharmacodynamic Assessments; Table 12-1 Schedule of Events, footnote "p"***

For the Part 2 pharmacokinetic time points, it was added that plasma and ultrafiltrate will be collected for up to 6 cycles.

***Protocol Synopsis – Safety Assessments; Section 6.38 – Vital Sign Measurments; Table 12-1 Schedule of Events, footnote "h"***

It was clarified that vital signs will be measured before the NC-6004 infusion and at the completion of the NC-6004 infusion on Day 1 of each cycle starting in Cycle 2.

***Protocol Synopsis – Statistical Methods; Section 7.6 – Statistical Analysis Methodology***

Text was removed that stated that no statistical testing is planned for this study. The statistical methods for Part 2 were added and will include a Bayesian model updated every 6 weeks after 10 PFS have occurred within a cohort.

***Section 6.2 – Pharmacokinetic and Pharmacodynamic Assessments***

It was clarified that the concentration profiles of micellar platinum in plasma and total platinum in plasma and plasma ultrafiltrate will be characterized.

***Section 12.4 – Appendix: American Society of Clinical Oncology Guideline***

This appendix was removed.

***Section 12.4.2.1 – Assessment of Risk Associated With Amendment 2***

A assessment of the risk associated with Amendment 2 was added.

### 12.4.2.3 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in **bold** and deletions are shown in ~~strikethrough~~ text. Minor or obvious editorial and grammatical corrections are not highlighted.

***Title Page – Title***

A Phase 1/b2 Dose Escalation and Expansion Trial of NC-6004 (Nanoparticle Cisplatin) plus Gemcitabine in Patients with Advanced Solid Tumors or **Squamous** Non-Small Cell Lung**, Biliary Tract, and Bladder** Cancer

***Title Page – Sponsor Contact***

~~Atsuhiro Masada~~**Kazuhiro Takahashi**
Director of **International** Clinical Development
NanoCarrier Co, Ltd
Telephone: +81-~~4-7197-7623~~**3-3241-0551**

***Title Page – Project Manager***

~~*Project Manager: Cynthia Nelson*~~
~~*Senior Project Manager, PPD Global Project Management*~~
~~*PPD, Inc.*~~
~~*Telephone: 317-473-1980*~~

***Protocol Approval – Sponsor Signatory***

A Phase 1/b2 Dose Escalation and Expansion Trial of NC-6004 (Nanoparticle Cisplatin) plus Gemcitabine in Patients with Advanced Solid Tumors or **Squamous** Non-Small Cell Lung**, Biliary Tract, and Bladder** Cancer

…

Protocol accepted and approved by:

Director of **International** Clinical Development
~~Atsuhiro Masada~~**Kazuhiro Takahashi**

***Protocol Synopsis – Title***

A Phase 1/b2 Dose Escalation and Expansion Trial of NC-6004 (Nanoparticle Cisplatin) plus Gemcitabine in Patients with Advanced Solid Tumors or **Squamous** Non-Small Cell Lung**, Biliary Tract, and Bladder** Cancer

***Protocol Synopsis – Study Sites***

~~Approximately 6~~ **At least 20** sites in the United States

***Protocol Synopsis – Indication***

…

Part 2: ~~Relapsed non-small cell lung cancer (NSCLC)~~ **First-line metastatic squamous non-small cell lung cancer (NSCLC); first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and first-line metastatic or locally advanced transitional cell carcinoma (TCC) of the urinary tract (bladder cancer)**

***Protocol Synopsis – Rationale***

…

This study will establish a maximum-tolerated dose (MTD) **and recommended Phase 2 (RPII) dose** of NC-6004 in combination with gemcitabine and evaluate the initial activity and tolerability profile.

***Protocol Synopsis – Objectives***

The primary objectives of this study are:

- In the dose-escalation phase of the study (Part 1), to determine the dose-limiting toxicities (DLTs)**,** ~~and~~ MTD, **and RPII dose** of NC-6004 in combination with gemcitabine.
- In the expansion phase of the study (Part 2), to evaluate the activity **of NC-6004 in combination with gemcitabine in patients with first-line Stage IV squamous NSCLC, first-line advanced or metastatic biliary tract cancer, and first-line metastatic or locally advanced bladder cancer compared with historical control as measured by**

**local investigator/radiologist-assessed progression-free survival (PFS), according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.**~~, safety, and tolerability of NC-6004 in combination with gemcitabine in patients with relapsed (second- or third line) squamous and nonsquamous Stage IIIB/IV NSCLC~~.

The secondary objectives of this study are:

- To evaluate overall response rate (ORR), disease control rate (DCR = **complete response + partial response + stable disease**), duration of response (DOR), PFS, overall survival (OS)

…

- **To evaluate the safety and tolerability of NC-6004 when combined with gemcitabine**

***Protocol Synopsis – Patient Population: Inclusion Criteria***

…

(Part 2 only) **Cohort 1**: Have histologically or cytologically confirmed diagnosis of Stage ~~IIIB or~~ IV **squamous** NSCLC and have **not** received ~~1 or 2 lines of~~ prior chemotherapy ~~or targeted therapy for Stage IIIB or IV NSCLC (second- or third-line).~~ **for metastatic disease. Patients with known sensitizing mutation in the epidermal growth factor receptor (EGFR) gene or anaplastic lymphoma kinase (ALK) fusion oncogene must have received at least 1 and up to 2 targeted therapies prior to enrollment**.

…

- Patients whose tumors are known to harbor an exon 19 deletion or exon 21 L858R EGFR mutation must have **had intolerance or have** progressed on ~~or had intolerance to an~~**at least 1 and up to 2** EGFR tyrosine kinase inhibitor**s**.

- Patients whose tumors are known to harbor an ALK translocation must have **had intolerance or have** progressed on ~~or had intolerance to crizotinib~~**at least 1 and up to 2 ALK inhibitors**.

- **(Part 2 only) Cohort 2: Have histologically or cytologically confirmed diagnosis of nonresectable, recurrent, or metastatic biliary tract carcinoma**

**(intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma) and have not received prior systemic anticancer therapy for advanced or metastatic disease.**

- **(Part 2 only) Cohort 3: Have histologically or cytologically confirmed diagnosis of metastatic or locally advanced TCC of the urinary tract (bladder, urethra, ureter, renal pelvis) (T3b-T4 N0 M0, Tany N1-N3 M0, or Tany Nany M1) and are not candidates for surgery.**

- **Patients must not have received prior treatment with systemic anticancer therapy for metastatic or locally advanced urinary tract cancer.**

- **Certain mixed histologies that are predominantly (>50%) TCC are eligible: squamous, adenocarcinoma, and undifferentiated. Mixed undifferentiated histology requires immunohistochemistry consistent with a TCC origin. Predominantly squamous or neuroendocrine tumors are excluded.**

***Protocol Synopsis – Exclusion Criteria***

…

1. Have received prior platinum therapy in the past 3 months **(Part 1) or 6 months in the adjuvant or neoadjuvant setting (Part 2).**

***Protocol Synopsis – Study Design***

This study will consist of 2 parts; Part 1 is a Phase 1b, continual reassessment method dose-escalation trial, and Part 2 is a Phase 2, **adaptive,** two-stage, open-label, expansion trial evaluating activity, safety, and tolerability at the ~~MTD~~**RPII dose** identified in Part 1.

In Part 1, patients will receive **intravenous infusion of** NC-6004 at escalating doses **on Day 1** in combination with gemcitabine **at the fixed dose of 1250 mg/m$^2$ on Days 1 and 8 of a 21-day cycle**. ~~Doses of NC-6004 and gemcitabine will be administered as intravenous infusions in 3-week cycles (ie, 21 days will separate administration of the combined doses of NC-6004 and gemcitabine on Day 1 of each cycle)~~.

…

**In Part 1,** patients will continue to receive treatment until they experience disease progression, experience unacceptable toxicity (UT), **or** withdraw voluntarily~~, or complete a maximum of 10 total cycles of treatment (4 to 6 cycles followed by an additional 4 to 6 cycles, if they have clinical benefit), whichever occurs first~~. **If the investigator and the patient request continuation of NC-6004 administration until progressive disease or until the drug is no longer tolerated (whichever occurs first), the sponsor may agree to supply the drug after discussion of the request with the investigator**.

…

Part 2 of the study (Phase 2 portion) will begin after the ~~MTD~~ **RPII dose** of NC-6004 is identified for use in combination with gemcitabine. **All patients** ~~and will be conducted only in patients with NSCLC. Part 2 will be conducted in two stages. In the first stage, 10 patients with NSCLC~~ will receive NC-6004 at the ~~MTD~~ **RPII dose** in combination with gemcitabine 1250 mg/m$^2$ by the same regimen as in Part 1.

**Three cohorts of patients are eligible (Cohort 1: first-line metastatic squamous NSCLC; Cohort 2: first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and Cohort 3: first-line metastatic or locally advanced TCC of the urinary tract (bladder cancer). Stage 2 will continue in each cohort after achieving the minimum threshold of clinical responses required and enroll up to 50 patients in each cohort for a total of up to 150 patients in Part 2. The primary endpoint (PFS) will be continuously updated and compared with the historical PFS from Phase 3 pivotal cisplatin and gemcitabine trials within each cohort. The PFS hazard model will be updated as PFS data accrue. A hazard ratio (HR) for PFS for each cohort versus historical control will be obtained**.

| **Cohort** | **Biliary** | **Bladder** | **Squamous NSCLC** |
|---|---|---|---|
| **Historical Median Duration of PFS** | **8.8 months** | **7.6 months** | **5 months** |
| **Historical PFS Weekly Hazard** | **0.01795** | **0.020755** | **0.031377** |

**Once 10 PFS events have been observed, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort.**

- **Futility – 10 PFS events have been observed in each cohort and at least 1 of the following conditions is true:**
- **Probability (Promising HR*) <0.4**
- **Probability (Phase 3 Success*) <0.4**
- **Success – 25 PFS events have been observed in each cohort and:**
- **Probability (Phase 3 Success*) >0.8**
- **Inconclusive – neither futility nor success.**

*** Phase 3 success is defined as success in a Phase 3 clinical trial with 381 events - enough to provide 80% power to detect an HR of 0.75. A promising HR is defined as one less than 0.85.**

**Futility can only be declared for a cohort after 10 PFS events have been observed in that cohort. Success can only be declared for a cohort after 25 PFS events have been observed in that cohort. Accrual will stop for any cohort identified as futile or successful at interim. The conclusion of this Phase 2 trial will be that a Phase 3 trial with 381 events should be conducted for each cohort that is a success.**

**If any indication is declared a success, the combination of NC-6004 and gemcitabine advances to a Phase 3 randomized, controlled trial with sample size sufficient to observe 381 events.**

~~If at least one patient in the first stage is a responder (defined as CR or PR per RECIST 1.1 by the week 12 disease assessment) then 26 additional patients with NSCLC will be enrolled in the second stage of Part 2.~~

After completion of ~~4 to~~ 6 cycles of treatment **(Cohorts 1 and 3) or 8 cycles of treatment (Cohort 2)** ~~(or up to 10 cycles)~~, patients will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

…

***Protocol Synopsis – Estimated Study Duration***

~~The~~ **Part 1 of the** study will include a screening period (up to 28 days); **as many cycles until progressive disease or until the drug is no longer tolerated (whichever occurs first); tumor assessments for response and disease progression with scans every 6 weeks; and telephone calls for survival every 12 weeks. The cycles are 21 days in duration.**

**Part 2 of the study will include a screening period (up to 28 days)**; ~~4 to~~ 6 treatment cycles **(Cohorts 1 and 3) or 8 treatment cycles (Cohort 2)**~~, followed by an additional 4 to 6 cycles (up to a maximum of 10 total cycles) of treatment,~~ that are 21 days in duration; tumor assessments for response and disease progression with scans every 6 weeks; and telephone calls for survival every 12 weeks.

Patients will receive study treatment until any of the following occur:

- ~~Disease progression or completion of 4 to 6 cycles of treatment (followed by an additional 4 to 6 cycles, up to a maximum 10 total cycles, if they have clinical benefit)~~ **Progressive disease is observed (Part 1) or completion of 6 cycles of treatment (Part 2; Cohorts 1 and 3) or 8 cycles of treatment (Part 2; Cohort 2)**

…

***Protocol Synopsis – Efficacy Assessments***

…

Symptoms will be assessed before treatment on Day 1 and Day 8 of each cycle and at the End of Treatment visit using the core MD Anderson Symptom Inventory ~~(MDASI)~~ or the MDASI lung cancer **(Part 1 only)** ~~(MDASI-LC)~~.

***Protocol Synopsis – Pharmacokinetic or Pharmacodynamic Assessments***

…

Pharmacokinetic plasma and plasma ultrafiltrate will be collected at the following times in Part 2 for ~~each cycle~~ **up to 6 cycles**:

…

***Protocol Synopsis – Safety Assessments***

…

Additionally, ~~in~~ **on Day 1 of** Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the infusion. ~~In Cycles 2 through 6 (or up to 10)~~ **Starting in Cycle 2**, vital signs will be measured before NC-6004 infusion and at the completion of the NC-6004 infusion **on Day 1 of each cycle**.

…

***Protocol Synopsis – Sample Size***

…

~~Part 2 of the study (Phase 2 portion) will begin after the MTD of NC-6004 is identified for use in combination with gemcitabine and will be conducted only in patients with NSCLC. Part 2 will be conducted in two stages. In the first stage, 10 patients with NSCLC will receive NC-6004 at the MTD in combination with gemcitabine 1250 mg/m$^2$ by the same regimen as in Part 1. If at least one patient in the first stage is a responder (defined as CR or PR per RECIST 1.1 by the week 12 disease assessment) then 26 additional patients with NSCLC will be enrolled in the second stage of Part 2.~~

~~In order to provide a 95% chance to detect at least 1 AE of interest with an underlying 8% incidence rate among patients treated at MTD, additional patients with NSCLC will be enrolled at the MTD in Part 2 of the study. Patients will be enrolled in 2 stages until a total of 36 patients with NSCLC have been dosed at the MTD, including patients with NSCLC receiving the MTD level in Part 1. In the first stage of Part 2, ten patients treated at the MTD will be evaluated for response. If no patients respond, then the patients with NSCLC treated at a lower dose level than the MTD will be considered and a discussion of terminating the trial early will be triggered. Any evidence of response, regardless of duration, will be counted as a response. If at least 1 response is observed, the remaining 26 patients will be treated at the MTD. No formal efficacy analysis will be performed and no inference regarding efficacy will be drawn based on the response rate of the overall study~~.

**Part 2 is a 3-cohort study with an overall sample size of up to 150 patients with no more than 50 patients per cohort. The total sample size will depend on the results of interim**

**futility and superiority analyses. In order to evaluate the overall sample size, simulations were performed assuming scenarios with different HRs for PFS for each cohort compared with historical control and different sample sizes for a subsequent Phase 3 clinical trial. The associated mean sample size for this trial in these scenarios ranged from 136 to 146 patients.**

**Patients who receive study drug will not be replaced.**

***Protocol Synopsis – Statistical Methods***

~~No formal statistical testing is planned for this study~~. Ninety-five percent confidence intervals may be calculated for selected safety and exploratory variables. Dose escalation will be based on the N-CRM model and the incidence of DLTs. Adverse events and serious AEs will be tabulated by system organ class and preferred term. Laboratory test results after the first dose will be summarized with regard to shifts from baseline values and the grade per NCI CTCAE version 4.03. Overall survival, PFS, and DOR will be summarized using Kaplan-Meier methods. The ORR and DCR will be summarized and 95% confidence intervals for both will be created.

**In Part 2, the following posterior probabilities will be derived using a Bayesian model updated every 6 weeks after 10 PFS have occurred within a cohort:**

- **Probability (Promising HR)**
- **Probability (Phase 3 Success)**

**If any cohort at interim or final analyses has a probability (success in a Phase 3 trial with 381 PFS events) >0.8, that indication will be declared a success, and the combination of NC-6004 and gemcitabine advances to a Phase 3 randomized, controlled trial with a sample size sufficient to observe 381 PFS events.**

***Section 1 – Introduction***

…

This study will determine the maximum tolerated dose (MTD) **and recommended Phase 2 (RPII) dose** of NC-6004 in combination with gemcitabine and evaluate the activity, safety, and tolerability of NC-6004 in combination with gemcitabine in patients with advanced solid

tumors and **first-line metastatic squamous NSCLC; first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and first-line metastatic or locally advanced transitional cell carcinoma (TCC) of the urinary tract (bladder cancer)** ~~second- or third-line squamous and nonsquamous Stage IIIB/IV NSCLC~~.

…

***Section 2.1 – Primary Objectives***

The primary objectives of this study are:

- In the dose-escalation phase of the study (Part 1), to determine the dose-limiting toxicities (DLTs) ~~and~~**,** MTD**, and RPII dose** of NC-6004 in combination with gemcitabine;
- In the expansion phase of the study (Part 2), to evaluate the activity~~, safety, and tolerability~~ of NC-6004 in combination with gemcitabine in patients with ~~relapsed (second- or third-line) squamous and nonsquamous Stage IIIB/~~ **first-line Stage IV squamous** NSCLC, **first-line advanced or metastatic biliary tract cancer, and first line metastatic or locally advanced bladder cancer compared with historical control as measured by local investigator/radiologist-assessed progression-free survival (PFS), according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.**

***Section 2.1 – Primary Objectives***

The secondary objectives of this study are:

- To evaluate ORR, DCR **(DCR = complete response [CR] + partial response [PR] + stable disease [SD])**, DOR, PFS, and OS
- To evaluate therapy-related AEs
- **To evaluate the safety and tolerability of NC-6004 when combined with gemcitabine**

…

***Section 3.1 – Study Design***

This study will consist of 2 parts; Part 1 is a Phase 1b, continual reassessment method dose-escalation trial in patients with any advanced solid tumor, and Part 2 is a Phase 2, **adaptive** two-stage, open-label, expansion trial in patients with **squamous** NSCLC**, biliary**

**tract, and bladder cancer** evaluating activity, safety, and tolerability at the ~~MTD~~ **RPII dose** identified in Part 1.

In Part 1, patients will receive **intravenous infusion of** NC-6004 and gemcitabine in 3-week treatment cycles. NC-6004 will be administered on Day 1 of each cycle and gemcitabine 1250 mg/m$^2$ will be administered on Day 1 of each cycle (after the administration of NC-6004) and on Day 8 of each cycle. Patients will be treated until disease progression ~~or up to 10 cycles of therapy, whichever occurs first~~. **If the investigator and the patient request continuation of NC-6004 administration until progressive disease or until the drug is no longer tolerated (whichever occurs first), the sponsor may agree to supply the drug after discussion of the request with the investigator.** ~~After completion of 4 to 6 cycles of treatment, individual patients can continue study drug, subject to sponsor approval, for an additional 4 to 6 cycles of treatment (up to a maximum of 10 total cycles) if they have clinical benefit, with monitoring the same as that in the treatment phase~~**.**

…

Once the MTD **(or RPII dose)** of NC-6004 is identified, dose escalation within Part 1 will cease. Patients in Part 1 who were not assigned to the NC-6004 dose identified as the ~~MTD~~ **RPII dose** will continue treatment cycles at their assigned dose level.

Part 2 of the study (Phase 2 portion) will begin after the ~~MTD~~ **RPII dose** of NC-6004 is identified for use in combination with gemcitabine ~~and will be conducted only in patients with NSCLC~~. ~~Part 2 will be conducted in two stages. In the first stage, 10 patients with NSCLC~~ **All patients** will receive NC-6004 at the ~~MTD~~ **RPII dose** in combination with gemcitabine 1250 mg/m$^2$ by the same regimen as in Part 1.

**Three cohorts of patients are eligible (Cohort 1: first-line metastatic squamous NSCLC; Cohort 2: first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and Cohort 3: first-line metastatic or locally advanced TCC of the urinary tract (bladder cancer). Stage 2 will continue in each cohort after achieving the minimum threshold of clinical responses required and enroll up to 50 patients in each cohort for a total of up to 150 patients in Part 2. The primary endpoint (PFS) will be continuously updated and compared with the historical PFS from Phase 3 pivotal cisplatin and gemcitabine trials within each cohort. The PFS hazard model will be updated as PFS data accrue. A hazard ratio (HR) for PFS for each cohort versus historical control will be obtained.**

| Cohort | Biliary | Bladder | Squamous NSCLC |
|---|---|---|---|
| Historical Median Duration of PFS | 8.8 months | 7.6 months | 5 months |
| Historical PFS Weekly Hazard | 0.01795 | 0.020755 | 0.031377 |

**Once 10 PFS events have been observed, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort.**

- **Futility – 10 PFS events have been observed in each cohort and at least 1 of the following conditions is true:**
- **Probability (Promising HR*) <0.4**
- **Probability (Phase 3 Success*) <0.4**
- **Success – 25 PFS events have been observed in each cohort and:**
- **Probability (Phase 3 Success*) >0.8**
- **Inconclusive – neither futility nor success.**

*** Phase 3 success is defined as success in a Phase 3 clinical trial with 381 events - enough to provide 80% power to detect an HR of 0.75. A promising HR is defined as one less than 0.85.**

***Futility can only be declared for a cohort after 10 PFS events have been observed in that cohort. Success can only be declared for a cohort after 25 PFS events have been observed in that cohort. Accrual will stop for any cohort identified as futile or successful at interim. The conclusion of this Phase 2 trial will be that a Phase 3 trial with 381 events should be conducted for each cohort that is a success.**

**If any indication is declared a success, the combination of NC-6004 and gemcitabine advances to a Phase 3 randomized, controlled trial with sample size sufficient to observe 381 events.**

~~If at least one patient in the first stage is a responder (defined as CR or PR per RECIST 1.1 by the week 12 disease assessment) then 26 additional patients with NSCLC will be enrolled in the second stage of Part 2. Approximately 36 patients with NSCLC will be treated at the MTD, including any patients with NSCLC receiving the MTD in Part 1 and patients receiving the MTD in Part 2. Evaluation will include patients with NSCLC treated at the MTD in either part of the study~~.

In ~~both~~ Part 1 ~~and Part 2~~, patients will continue to receive treatment until they experience disease progression ~~or for up to 10 treatment cycles, whichever occurs first~~. The maximum number of cycles a patient undergoes ~~(up to 10 total cycles)~~ is at the discretion of the investigator and depends on response as described in the **American Society of Clinical Oncology (**ASCO**)** guideline**s** ~~(Appendix 12.4)~~ (Azzoli et al 2011). Patients who complete 4 or more cycles will be considered as having completed the treatment. Subject to sponsor approval, individual patients ~~can continue study drug for an additional 4 to 6 cycles of treatment (up to a maximum of 10 total cycles) if they have clinical benefit, with monitoring the same as that in the treatment phase~~ **will be treated until progressive disease. If the investigator and the patient request continuation of NC-6004 administration until progressive disease or until the drug is no longer tolerated (whichever occurs first), the sponsor may agree to supply the drug after discussion of the request with the investigator. In Part 2, patients will continue to receive treatment for up to 6 cycles (Cohorts 1 and 3) or 8 cycles (Cohort 2).**

After ~~the completion of 4 to 6 cycles of treatment (or up to 10 cycles)~~ **progressive disease is observed (Part 1) or the completion of 6 cycles (Part 2; Cohorts 1 and 3) or 8 cycles (Part 2; Cohort 2),** patients will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

…

***Section 3.1 – Study Design – Day 1 of Cycle***

…

- EORTC QLQ-C30
- Core MDASI or MDASI module specific for lung cancer (MDASI-LC) (Section 6.1.3)

- **MDASI-LC will only be performed by patients with NSCLC in Part 1 and will not be performed in Part 2**

- Nausea and vomiting patient diary completion **(completed in all cycles in Part 1 and only for 2 cycles in Part 2 of the study)**

…

***Section 3.1 – Study Design – Day 8 of Each Cycle***

…

- EORTC QLQ-C30
- Core MDASI or MDASI-LC
    - **MDASI-LC will only be performed by patients with NSCLC in Part 1 and will not be performed in Part 2**
- Nausea and vomiting patient diary completion **(completed in all cycles in Part 1 and only for 2 cycles in Part 2 of the study)**

…

***Section 3.1 – Study Design – Day 15 of Each Cycle (Part 1: required; Part 2: if clinically indicated)***

…

- Biochemistry
- Nausea and vomiting patient diary completion **(completed in all cycles in Part 1 and is not collected at Day 15 in Part 2 of the study)**

…

***Section 3.1 – Study Design – End-of-Treatment Visit***

…

- EORTC QLQ-C30
- Core MDASI or MDASI-LC **(Part 1 only)**

- 12-lead ECG

…

***Section 3.1.1 – Rationale of Study Design***

…

This study will determine the DLTs ~~and~~**,** MTD**, and RPII** of NC-6004 in combination with gemcitabine in patients with advanced solid tumors and ~~relapsed Stage IIIB/~~ **first-line Stage** IV **squamous** NSCLC**, first-line advanced or metastatic biliary tract cancer, and first-line metastatic or locally advanced bladder cancer** for use in future efficacy studies.

…

The MDASI-LC questionnaire is designed specifically for patients with lung cancer and will be used by patients with NSCLC in **Part 1 of** this study.

…

***Section 4.1 – Selection of Study Population***

Approximately **199** ~~85~~ patients (up to 49 patients in Part 1 and up to ~~36~~ **150** patients in Part 2) will be enrolled **in** at a~~pproximately 6~~ **least 20** sites in the United States. Patients will be assigned to a study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

***Section 4.1.1 – Inclusion Criteria***

2. (Part 1 only) Have a histologically or cytologically confirmed diagnosis of advanced solid tumor that has relapsed or is refractory to standard curative or palliative therapy or has a contraindication to standard therapy.

   (Part 2 only) **Cohort 1:** Have histologically or cytologically confirmed diagnosis of Stage ~~IIIB or~~ IV **squamous** NSCLC and have **not** received ~~1 or 2 lines of~~ prior chemotherapy **for metastatic disease. Patients with known sensitizing mutation in the epidermal growth factor receptor (EGFR) gene or anaplastic lymphoma kinase (ALK) fusion oncogene must have received at least 1 and up to 2 targeted therapies**

**prior to enrollment** ~~or targeted therapy for Stage IIIB or IV NSCLC (second- or third-line)~~.

- A patient with stable, treated brain metastases is eligible, provided that there is no evidence of progression after treatment and the patient does not require corticosteroids, or, if the patient requires corticosteroid, has been receiving a stable dose of corticosteroids for at least 14 days prior to assignment to treatment.

- Patients whose tumors are known to harbor an exon 19 deletion or exon 21 L858R ~~epidermal growth factor receptor (~~EGFR~~)~~ mutation must have **had intolerance or have** progressed on ~~or had intolerance to an~~ **at least 1 and up to 2** EGFR tyrosine kinase inhibitor**s**.

- Patients whose tumors are known to harbor an ~~anaplastic lymphoma kinase~~ **ALK** translocation must have **had intolerance or have** progressed on ~~or had intolerance to crizotinib~~ **at least 1 and up to 2 ALK inhibitors**.

**(Part 2 only) Cohort 2: Have histologically or cytologically confirmed diagnosis of nonresectable, recurrent, or metastatic biliary tract carcinoma (intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary carcinoma) and have not received prior systemic anticancer therapy for advanced or metastatic disease.**

**(Part 2 only) Cohort 3: Have histologically or cytologically confirmed diagnosis of metastatic or locally advanced TCC of the urinary tract (bladder, urethra, ureter, renal pelvis) (T3b-T4 N0 M0, Tany N1-N3 M0, or Tany Nany M1) and are not candidates for surgery.**

- **Patients must not have received prior treatment with systemic anticancer therapy for metastatic or locally advanced urinary tract cancer.**

- **Certain mixed histologies that are predominantly (>50%) TCC are eligible: squamous, adenocarcinoma, and undifferentiated. Mixed undifferentiated histology requires immunohistochemistry consistent**

**with a TCC origin. Predominantly squamous or neuroendocrine tumors are excluded.**

***Section 4.1.2 – Exclusion Criteria***

Patients meeting any of the following criteria will be excluded from the study:

1. Have received prior platinum therapy in the past 3 months **(Part 1) or 6 months in the adjuvant or neoadjuvant setting (Part 2).**

…

***Section 5.1 – Method of Assigning Patients to Treatment Groups***

…

In Part 2, all patients will receive the ~~MTD~~ **RPII dose** of NC-6004 identified in Part 1

***Section 5.2 – Prophylactic Treatments***

…

Prophylactic antiemetic medications may be administered according to standard treatment center protocols for cisplatin-based treatments. **The use of prophylactic growth factor support medications is also allowed according to ASCO guidelines (Smith et al 2006) and is encouraged in patients who have experienced myelosuppression on treatment and/or in patients at high risk for experiencing febrile neutropenia**.

***Section 5.3 – Treatments Administered***

…

In ~~each part~~ **Part 1** of the study, patients will receive treatment **until disease progression. In Part 2 of the study, patients will receive treatment** for ~~4 to~~ 6 cycles **(Cohorts 1 and 3) or 8 cycles (Cohort 2)** ~~as directed in the ASCO guidelines (Appendix 12.4) or until disease progression, whichever occurs first. After the initial 4 to 6 cycles of treatment, individual patients can continue study drug, subject to sponsor approval, for an additional 4 to 6 cycles of treatment (up to a maximum of 10 total cycles) if they have clinical benefit, with monitoring the same as that in the treatment phase~~. ~~Prophylactic~~ **Aa**ntiemetic medications

may be administered according to standard treatment center protocols. **The use of growth factor support medications is also allowed according to ASCO guidelines (Smith et al 2006) and is encouraged in patients who have experienced myelosuppression on treatment and/or in patients at high risk for experiencing febrile neutropenia**.

…

In Part 2, on Day 1 of each cycle**,** all patients will receive NC-6004 at the ~~MTD~~ **RPII dose** identified in Part 1 and 1250 mg/m$^2$ gemcitabine. On Day 8 of each cycle**,** all patients in Part 2 of the study will receive 1250 mg/m$^2$ gemcitabine.

***Section 5.10 – Prior, Concomitant, and Subsequent Therapy***

**(Part 2 only) Cohort 1: For patients with Stage IV NSCLC, they may not have received prior chemotherapy for metastatic disease. Patients with known sensitizing mutation in the EGFR gene or ALK fusion oncogene must have received at least 1 and up to 2 targeted therapies prior to enrollment. If a patient with treated, stable brain metastases is otherwise eligible and requires corticosteroids, the patient must have been receiving a stable dose of corticosteroids for at least 14 days prior to assignment to treatment. Patients whose tumors are known to harbor an exon 19 deletion or exon 21 L858R EGFR mutation must have had intolerance or have progressed on at least 1 and up to 2 EGFR tyrosine kinase inhibitors. Patients whose tumors are known to harbor an ALK kinase translocation must have had intolerance or have progressed on at least 1 and up to 2 ALK inhibitors. Patients with eligible biliary tract carcinoma must not have received prior systemic anticancer therapy for advanced or metastatic disease. Patients with eligible TCC of the urinary tract must not have received prior treatment with systemic anticancer therapy for metastatic or locally advanced urinary tract cancer**.

~~Prior chemotherapy or targeted therapy for first- or second-line, Stage IIIB/IV NSCLC is allowed and required for entry in Part 2 of the trial~~. All patients must receive prophylactic treatment at each cycle to reduce the risk of hypersensitivity reactions and nausea and/or vomiting (Section 5.8).

The use of antiemetic medications according to the site's standard of care is allowed. **The use of prophylactic growth factor support medications is also allowed according to ASCO guidelines (Smith et al 2006) and is encouraged in patients who have experienced**

**myelosuppression on treatment and/or in patients at high risk for experiencing febrile neutropenia.**

…

***Section 6.1 – Efficacy Assessments***

…

Symptom changes will be assessed using the core MDASI or MDASI-LC **(only in patients with NSCLC in Part 1)** (Section 6.1.3) on Days 1 and 8 of each cycle and at the End-of-Treatment visit.

…

***Section 6.1.3 – MD Anderson Symptom Inventory***

…

For patients with NSCLC in Part 1 ~~and Part 2~~ **only**, a specific MDASI module designed for patients with lung cancer will be used, MDASI-LC (Appendix 12.3).

…

The core MDASI and the MDASI-LC will be administered as a self-report paper-and-pencil form given to the patient at the site before study treatments on Days 1 and 8 of each cycle **in Part 1 only** (as described in Study Manual).

***Section 6.2 – Pharmacokinetic and Pharmacodynamic Assessments***

…

Pharmacokinetic samples will be analyzed ~~for~~ **according to the bioanalytical laboratory protocol. The** concentration~~s~~ **profiles** of micellar platinum in plasma and total platinum in plasma and plasma ultrafiltrate (ie, free platinum) **will be characterized.**

…

Pharmacokinetic plasma and plasma ultrafiltrate samples will be collected at the following times in Part 2 for **up to 6 cycles**:

…

***Section 6.3.1.2.1 – Safety Monitoring in Part 2***

During Part 2 of the study, patients treated with NC-6004 at the ~~MTD~~ **RPII dose** from Part 1 will be monitored for safety.

…

***Section 6.3.3 – Assessment of Nausea and Vomiting***

…

The investigator will collect the diaries on Day 8, Day 15 **(Part 1 only)**, and Day 22.

…

The patient must return the diary to the site on Day 8, Day 15 **(Part 1 only)**, and Day 22 (Day 1 of the next cycle) of each cycle.

…

***Section 6.3.8 – Vital Sign Measurements***

…

~~In Cycles 2 through 6 (or up to Cycle 10, if there is clinical benefit)~~ **Starting in Cycle 2**, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion **on Day 1 of each cycle**.

…

***Section 7.2 – Exploratory Endpoints***

The exploratory endpoints of this study include exploratory safety endpoints of the occurrence of AEs and SAEs after ~~4 to~~ 6 cycles of treatment and the following PK endpoints for micellar platinum in plasma and total platinum in plasma and plasma ultrafiltrate calculated for all patients using noncompartmental analysis:

…

***Section 7.3 – Sample Size Calculations***

This is a Phase 1b/2 study with an overall sample size of up to ~~85~~ **199** patients (up to 49 patients in Part 1 and up to ~~36~~ **150** patients in Part 2). The total sample size will depend on the number of cohorts required to establish an ~~MTD~~ **RPII dose** and the number of patients with NSCLC enrolled at the ~~MTD~~ **RPII dose** in Part 1.

…

**Part 2 is a 3-cohort study with an overall sample size of up to 150 patients with no more than 50 patients per cohort. The total sample size will depend on the results of interim futility and superiority analyses. In order to evaluate the overall sample size, simulations were performed assuming scenarios with different HRs for PFS for each cohort compared with historical control and different sample sizes for a subsequent Phase 3 clinical trial. The associated mean sample size for this trial in these scenarios ranged from 136 to 146 patients.**

~~In Part 2 of the study, additional patients with NSCLC will be enrolled at the MTD until a total of 36 patients with NSCLC have been dosed at the MTD, including patients with NSCLC receiving the MTD dose level in Part 1. In order to provide a 95% chance to detect at least 1 AE of interest with an underlying 8% incidence rate among patients treated at MTD, additional patients with NSCLC will be enrolled at the MTD in Part 2 of the study. Patients will be enrolled in 2 stages until a total of 36 patients with NSCLC have been dosed at the MTD, including patients with NSCLC receiving the MTD level in Part 1. In the first stage of Part 2, ten patients treated at the MTD will be evaluated for response. If no patients respond, then the patients with NSCLC treated at a lower dose level than the MTD will be considered and a discussion of terminating the trial early will be triggered. Any evidence of response, regardless of duration, will be counted as a response. If at least 1 response if observed, the remaining 26 patients will be treated at the MTD~~. No formal efficacy analysis will be performed and no inference regarding efficacy will be drawn based on the response rate of the overall study.

~~A total of 36 patients with NSCLC will be sufficient to identify toxicities of interest arising from treatment with NC-6004. Toxicities at the MTD with 36 patients enrolled (ie, those with an incidence of at least 8%), will be observed with a probability of at least 95.03% ($1-[1-0.08]^{36}$), and common toxicities (ie, those with an incidence of at least 20%) will be observed with a probability of at least 99.97% ($1-[1-0.2]^{36}$).~~

**Patients who receive study drug will not be replaced.**

~~Patients in Part 1 who discontinue treatment without DLT prior to completing the first cycle will be replaced.~~

***Section 7.4 – Analysis Sets***

...

- The Full Analysis Set (FAS) consists of all patients treated at ~~MTD~~ **RPII dose** in Part 1 or Part 2 who receive study product.

…

***Section 7.6 – Statistical Analysis Methodology***

~~No formal statistical testing is planned for this study~~. Ninety-five percent confidence intervals may be calculated for selected safety and exploratory variables.

…

All summaries will present data by dose level, for patients with NSCLC dosed at the MTD, and overall.

**In Part 2, the following posterior probabilities will be derived using a Bayesian model updated every 6 weeks after 10 PFS have occurred within a cohort:**

- **Probability (Promising HR)**
- **Probability (Phase 3 Success)**

**If any cohort at interim or final analyses has a probability (success in a Phase 3 trial with 381 PFS events) >0.8, that indication will be declared a success, and the combination of NC-6004 and gemcitabine advances to a Phase 3 randomized, controlled trial with a sample size sufficient to observe 381 PFS events.**

***Section 7.6.1.6 – Quality of Life Analyses***

…

Changes from baseline will be summarized by dose level, for all patients ~~with NSCLC~~ dosed at MTD **(or RPII dose)**, and overall

…

***Section 7.6.1.7 – Symptoms Assessment Analyses***

…

Changes from baseline will be summarized by dose level, for all patients ~~with NSCLC~~ dosed at MTD **(or RPII dose)**, and overall

…

***Section 7.6.2.1 – Analyses of Adverse Events***

…

- TEAEs with at least 5% incidence in all patients with NSCLC dosed at the MTD **or RPII dose**
- Treatment-related TEAEs with at least 5% incidence in all patients with NSCLC dosed at the MTD **or RPII dose**

…

***Section 11 – Reference List***

…

**Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol. 2006;24(19):3187-205.**

***Section 12.1 – Appendix: Schedule of Events***

## Table 12-1 Schedule of Events

| Procedure | Screening | | | Cycle 1 | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward ~~Cycles 7-10~~[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | |
| Demography | | X | | | | | | | | | | | | | | | |
| Medical history | | X | | | | | | | | | | | | | | | |
| Pregnancy test (serum or urine) | | | X | X[de] | | | | | | | | | | | | | |
| Physical examination | | X[ef] | | X[ef] | | | X | | | X | | | X | | | X | |
| Height, weight, and BSA calculation | | X[fg] | | X | | | X | | | X | | | X | | | | |
| Vital signs | | X | | X[gh] | X | | X | X | | X | X | | X | X | | X | |
| Performance status (ECOG) | | X[ef] | | X[ef] | | | X | | | X | | | X | | | X | |
| Disease assessment[hi] | X | | | | | | | | | X[hi] | | | X[hi] | | | X | X |
| Audiometry | | X | | X[ij] | | | X[ij] | | | X[ij] | | | X[ij] | | | X[ij] | |
| Hematology | | | X | X[jk] | X | X | X | X | X | X | X | X | X | X | X | X | |
| Biochemistry | | | X | X[jk] | X | X | X | X | X | X | X | X | X | X | X | X | |
| Urinalysis (dipstick) | | X | | | | | | | | | | | | | | X | |
| EORTC QLQ-C30 | | | | X | X | | X | X | | X | X | | X | X | | X | |
| MDASI or MDASI-LC[l] | | | | X | X | | X | X | | X | X | | X | X | | X | |
| Nausea and vomiting patient diary[km] | | | | X | X | X | X | X | X | X | X | X | X | X | X | | |
| **Part 2 Nausea and vomiting patient diary[m]** | | | | **X** | **X** | | **X** | **X** | | | | | | | | | |
| Cardiac risk factors | | X | | | | | | | | | | | | | | | |
| 12-lead ECG[in] | | | X | X | X | | X | | | X | | | | | | X | |

| Procedure | Screening | | | Cycle 1 | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward ~~Cycles 7-10~~[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Pharmacokinetic assessments (Part 1)[ko] | | | | X | X | X | X | | | X | X[mo] | X[mo] | | | | X | |
| Pharmacokinetic assessments (Part 2)[np] | | | | X | X | | X | X | | X | X | | | | | X | |
| Adverse events | | | | X[ef] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication | | X[ef] | | X[ef] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prophylactic administrations | | | | X | | | X | | | X | | | X | | | | |
| NC-6004 administration[a] | | | | X | | | X | | | X | | | X | | | | |
| Gemcitabine administration | | | | X | X | | X | X | | X | X | | X | X | | | |

Abbreviations: BSA, body surface area; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MDASI, MD Anderson Symptom Inventory; RECIST, Response Evaluation Criteria in Solid Tumors; MDASI-LC, MDASI-lung cancer.

a. **In Part 1 of the study, patients will receive treatment until progressive disease. In Part 2 of the study, patients will receive treatment for 6 cycles (Cohorts 1 and 3) or 8 cycles (Cohort 2).** ~~An optional extension of an additional 4 to 6 cycles of treatment (up to 10 cycles of treatment [including gemcitabine if the patient is tolerating NC-6004]) is allowed, with monitoring the same as that in the treatment phase of the protocol.~~

b. End-of-treatment assessments will be performed within 28 days after treatment discontinuation.

c. After patient discontinuation or completion of treatment without disease progression, patients will be followed with scans every 9 weeks until disease progression. Patients will be called every 12 (±1) weeks to collect data on patient survival, new treatments, and adverse events.

**d. Day 15 visit is required in Part 1. In Part 2, Day 15 visit is only necessary if it is clinically indicated.**

~~d~~**e**. Not required if screening pregnancy test was performed using serum.

~~e~~**f**. Safety assessments of physical examination, ECOG, review of AEs, and concomitant medication use can be completed on Day -1 to allow for early morning dosing. These should not be conducted in place of screening assessments.

~~f~~**g**. Height and weight only.

~~g~~**h**. On Day 1 of Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the NC-6004 infusion. **Starting in Cycle 2** ~~In Cycles 2 through 10~~, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion **on Day 1 of each cycle**. Vital signs will be measured before and after gemcitabine infusion on Day 8 of each cycle.

~~h~~**i.** Disease assessment will be performed using RECIST version 1.1 and the same imaging method used at screening should be used for all subsequent assessments. Beginning in Cycle 3 and continuing through the remainder of the treatment cycles, disease will be assessed every 6 (±1) weeks (ie, every other

cycle) and at the End-of-Treatment visit or until disease progression. Patients who have obtained a partial response or complete response will have a confirmatory scan at a minimum of 4 weeks following the initial scan.

~~i~~**j**. To be performed only as clinically indicated.

~~j~~**k**. Hematology or biochemistry tests will be repeated prior to dosing on Day 1 of Cycle 1 if they were last performed more than 24 hours before the start of the study drug administration.

**l. Symptom changes will be assessed using the core MDASI or MDASI-LC (only in patients with NSCLC in Part 1).**

~~k~~**m**. Diary issued on Day 1 of each cycle. Assessment is performed at the site before dosing on Days~~ ~~1 and Day 8 as well as Day 15 (**Day 15 diary collected in Part 1 only; note:** no dosing on Day 15) of each cycle. Patient completes diary at home on Days 2 through 8 and returns diary on Day 8.

l**n**. Twelve-lead ECGs will be performed after the patient has rested in the supine position for at least 5 minutes. On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 (Day 2) after the start of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the end of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion, and at the End-of-Treatment visit.

~~m~~**o**. For Part 1, blood samples will be collected at the following times: before the start of the NC-6004 infusion on Day 1 of Cycles 1 through 6, at end of NC-6004 infusion in Cycles 1, 3, and 5, after the **start** of NC-6004 infusion at Hours 3, 6, 12, 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 and prior to gemcitabine infusion (Day 8), and 336 (Day 15) in Cycles 1, 3, and 5, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed.

~~n~~**p**. For Part 2 **(up to 6 cycles)**, on the day of NC-6004 infusion for each cycle, blood samples will be collected before the start of the NC-6004 infusion, at the end of the NC-6004 infusion, before gemcitabine infusion on Day 8, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed.

***Section 12.4 – Appendix: American Society of Clinical Oncology Guideline***

This appendix was removed.

## 12.4.3 Protocol Amendment 3–Protocol Version 4.0, Incorporating Amendment 3, Dated 31 July 2016

The following sections detail the changes made to Amendment 2 of the protocol (Version 3.0) dated 07 July 2015. The integrated protocol, Version 4.0, including Amendment 3, was issued on 31 July 2016.

### 12.4.3.1 Assessment of Risk Associated With Amendment 3, Version 4.0

No patients treated with NC-6004 in Study NC-6004-004A at the MTD and gemcitabine with normal renal function (≥50 mL/min) experienced a clinically significant decrease in CrCl after initial study drug administration. Creatinine clearance values were stable with no decrease in all patients beyond the first cycle through up to 10 cycles. Therefore, patients with CrCl <60 mL/min are not expected to experience clinically meaningful decreases in renal function after treatment with NC-6004 and gemcitabine. However, increased renal function monitoring and protocol-mandated discontinuation will mitigate this risk.

### 12.4.3.2 Overview of Changes

The overview of significant changes includes the following:

***Protocol Synopsis – Study Sites; Section 4.1 – Selection of Study Population***

The study site details were updated to at least 20 sites in the Unites States and Europe.

***Protocol Synopsis – Inclusion Criteria; Section 4.1.1 – Inclusion Criteria***

The inclusion criterion 5 was updated to the following:

5. Have an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1, with the exception of patients in Part 2 (Cohort 3, unfit bladder cancer patients) who may have an ECOG PS of 2.

***Protocol Synopsis – Inclusion Criteria; Protocol Synopsis – Study Design; Section 3.1 - Study Design; Section 4.1.1 – Inclusion Criteria; Section 5.1 – Method of Assigning Patients to Treatment Groups; Section 6.3.1.2.1 - Safety Monitoring in Part 2***

The inclusion criterion 8 and study design were updated to reflect the following:

8. In Part 1 and in Part 2 in Cohorts 1 and 2: have adequate renal function defined as a CrCl ≥50 mL/minute (calculated according to the formula of Cockcroft and Gault 1976) or serum creatinine <1.5 mg/dL. In Part 2, patients in Cohort 3 (bladder cancer) must have a CrCl of ≥30 mL/min.

- Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 and ≥60 mL/min and ECOG PS 0 to 1. If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.

***Protocol Synopsis – Inclusion Criteria; Section 4.1.1 – Inclusion Criteria***

The inclusion criterion 9 was updated to the following:

9. Have a negative pregnancy test result at screening (for females of childbearing potential; not applicable to patients who are unable to become pregnant, including those with bilateral oophorectomy and/or hysterectomy or postmenopausal [no menses for the previous 12 months]). The test must be performed within 1 week before Day 1 of treatment.

***Protocol Synopsis – Inclusion Criteria; Section 4.1.1 – Inclusion Criteria***

The inclusion criterion 10 was added as follows:

10. Male patients must agree to use a condom during treatment and for 90 days after dosing. Male patients must agree not to donate sperm for 90 days after dosing.

***Protocol Synopsis – Inclusion Criteria; Section 4.1.1 – Inclusion Criteria***

The inclusion criterion 11 was updated to the following:

11. For women of childbearing potential*: are willing to abstain from heterosexual activity or practice physical barrier contraception follow 1 of the following effective methods of birth control from the time of study entry to 6 months after the last day of treatment.:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine devices
- Intrauterine hormone-releasing system
- Vasectomized partner who has received medical assessment of surgical success
- Bilateral tubal occlusion
- True sexual abstinence**

*Patients not of childbearing potential include those who are surgically sterile or postmenopausal (no menses for the previous 12 months). For women not currently taking contraceptive methods at screening, low user dependency contraceptive methods (eg, implantable progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner) are recommended.

**The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

***Protocol Synopsis – Study Design; Section 3.1 – Study Design***

All references to “two-stage” and a minimum threshold of clinical responses in Part 2 were removed.

***Protocol Synopsis – Study Design; Section 3.1 - Study Design; Section 5.1 - Method of Assigning Patients to Treatment Groups; Section 5.3 - Treatments Administered***

The RPII dose of 135 mg/m$^2$ was added to the protocol.

***Protocol Synopsis – Study Design; Section 3.1 - Study Design***

The historical median duration of PFS and PFS weekly hazard were added for the unfit bladder cancer cohort. A successful outcome for unfit and fit bladder cancer patient cohorts with 30 planned patients was updated to 15 PFS events.

***Protocol Synopsis – Study Design; Protocol Synopsis – Sample Size; Section 3.1 - Study Design; Section 4.1 – Selection of Study Population; Section 7.3 - Sample Size Calculations***

The total sample size in Part 2 of the study was changed to 160 patients with no more than 50 patients each in Cohorts 1 and 2 and no more than 60 patients in Cohort 3 (30 unfit and 30 fit bladder cancer patients). The simulated mean sample sizes for this trial were updated to 92.7 to 116.8 patients.

***Protocol Synopsis – Estimated Study Duration; Section 4.2.1 – Reasons for Withdrawal/Discontinuation***

A study treatment discontinuation rule was added as follows:

- For Cohort 3 only, unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart)

***Protocol Synopsis – Definition of a DLT; Section 6.3.1.1 – Definition of Dose-Limiting Toxicities***

It was clarified that DLTs will only be monitored in Part 1 of the study.

***Section 3.1 - Study Design; Section 12.1 - Appendix: Schedule of Events***

A serum or urine pregnancy test was added to Day 1 of each cycle and at the End-of-Treatment visit.

***Section 3.1 - Study Design; Section 12.1 - Appendix: Schedule of Events; Section 6.1.3 - MD Anderson Symptom Inventory***

It was clarified that the MDASI will only be performed in Part 1.

***Section 5.1 - Method of Assigning Patients to Treatment Groups; Section 5.3 - Treatments Administered***

A +10-minute window was added for the 1-hour administration of NC-6004 infusion.

***Section 5.4 - Dose Delays and Modifications; Section 5.4.1 – NC-6004 Dose Delays and Modifications***

Updated "Grade 3 or 4 toxicity" to "Grade 3 or 4 toxicity (recurrence of the same AE)" to more clearly define the recurrence of DLTs that could lead to study drug withdrawn.

***Section 3.1 - Study Design; Section 5.4 - Dose Delays and Modifications; Section 6.3.7 - Physical Examination; Section 11 - Reference List; Section 12.1 - Appendix: Schedule of Events, footnote g***

It was added that the doses of NC-6004 and gemcitabine will be calculated in milligrams per square meter ($mg/m^2$) at screening and will not be changed in subsequent cycles unless the patient's body weight increases or decreases by at least 10% from the patient's screening weight measurement. This threshold should not be confused with a change in the patient's body surface area ($mg/m^2$). Any change in a patient's weight by at least 10% during the study will require a recalculation of the doses of NC-6004 and gemcitabine. Weight will be measured before treatments on Day 1 of each cycle, with a calculation of body surface area before each dosing on Day 1 of each cycle (using the Mosteller formula [Mosteller 1987]).

***Section 5.5.2 - Gemcitabine Drug Product; Section 5.6.1 - Study Drug Packaging and Storage***

The generic gemcitabine was added to the protocol to clarify that it is acceptable for generic gemcitabine to be administered in this study (as per the original intent of the Protocol Author) in place of Gemzar.

***Section 5.6.2 – Test Article Accountability***

It was clarified that the PI should maintain accurate records of receipt of all test articles that are centrally provided.

***Section 6.2 - Pharmacokinetic and Pharmacodynamic Assessments Section 12.1 - Appendix: Schedule of Events***

A 10-minute window after ECG performance was added for the pharmacokinetic blood sampling.

***Section 6.3.2.5 - Assessment of Causality***

"Study drug" was updated to "study drug (NC-6004 and gemcitabine)" to indicate that the assessment of an AE's relatedness was to the combination of NC-6004 and gemcitabine.

***Section 6.3.6 – Electrocardiograms; Section 12.1 - Appendix: Schedule of Events***

A ±10-minute window for performance of 12-lead ECGs was added.

***Section 6.3.6 – Electrocardiograms; Section 6.3.8 - Vital Sign Measurements Section 12.1 - Appendix: Schedule of Events, footnote n***

The text "rest for at least 5 minutes" was updated to "adequately rested" for the patient before ECGs and vital sign measurements.

***Section 10.2.2 - Protocol Violations and Deviations***

Text was updated to clarify that Part 2 of this study will not require sponsor approval prior to each patient being enrolled in the study.

***Section 12.1 - Appendix: Schedule of Events***

A column was added to the Schedule of Events Table (Table 12-1) to clearly show that ECGs will be also performed on Day 2 of Cycle 1. For completeness, PK assessments, AE monitoring, and concomitant medication review were also added to Day 2 of Cycle 1.

### 12.4.3.3 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in **bold** and deletions are shown in ~~strikethrough~~ text. Minor or obvious editorial and grammatical corrections are not highlighted.

***Protocol Synopsis – Study Sites***

Study Sites: At least 20 sites in the United States **and Europe.**

***Protocol Synopsis –Inclusion Criteria***

…

5. Have an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1**, with the exception of patients in Part 2 (Cohort 3, unfit bladder cancer patients) who may have an ECOG PS of 2**.

…

8. **In Part 1 and in Part 2 in Cohorts 1 and 2**: ~~H~~**h**ave adequate renal function defined as a creatinine clearance **(CrCl)** ≥50 mL/minute (calculated according to the formula of Cockcroft and Gault 1976) or serum creatinine <1.5 mg/dL. **In Part 2, patients in Cohort 3 (bladder cancer) must have a CrCl of ≥30 mL/min.**

- **Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 and ≥60 mL/min and ECOG PS 0 to 1. If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.**

9. Have a negative pregnancy test result at screening (for females of childbearing potential; not applicable to patients who are unable to become pregnant, including those with bilateral oophorectomy and/or hysterectomy **or postmenopausal [no menses for the previous 12 months]**). The test must be performed within 1 week before Day 1 of treatment.

10. **Male patients must agree to use a condom during treatment and for 90 days after dosing. Male patients must agree not to donate sperm for 90 days after dosing.**

**11. For women of childbearing potential*:** ~~A~~**a**re willing to ~~abstain from heterosexual activity or practice physical barrier contraception~~**follow 1 of the following effective methods of birth control** from the time of study entry to 6 months after the last day of treatment~~.~~:

- **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)**
- **Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)**
- **Intrauterine devices**
- **Intrauterine hormone-releasing system**
- **Vasectomized partner**
- **Bilateral tubal occlusion**
- **True sexual abstinence****

***Patients not of childbearing potential include those who are surgically sterile or postmenopausal (no menses for the previous 12 months). For women not currently taking contraceptive methods at screening, low user dependency contraceptive methods (eg, implantable progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner) are recommended.**

****The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.**

***Protocol Synopsis – Study Design***

This study will consist of 2 parts; Part 1 is a Phase 1b, continual reassessment method dose-escalation trial, and Part 2 is a Phase 2, adaptive, ~~two-stage~~, open-label, expansion trial evaluating activity, safety, and tolerability at the RPII dose identified in Part 1.

…

Part 2 of the study (Phase 2 portion) will begin after the RPII dose of NC-6004 is identified for use in combination with gemcitabine. All patients will receive NC-6004 at the RPII dose **(135 mg/m$^2$, established in Part 1)** in combination with gemcitabine 1250 mg/m$^2$ by the same regimen as in Part 1.

Three cohorts of patients are eligible (Cohort 1: first-line metastatic squamous NSCLC; Cohort 2: first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and Cohort 3: first-line metastatic or locally advanced TCC of the urinary tract (bladder cancer). **Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 (unfit) and ≥60 mL/min and ECOG PS 0 to 1 (fit). If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.**

~~Stage~~**Part** 2 will ~~continue in each cohort after achieving the minimum threshold of clinical responses required and~~ enroll up to 50 patients **each in Cohorts 1 and 2, and up to 60 patients in Cohort 3,** for a total of up to ~~150~~ **160** patients in Part 2.

…

| **Cohort** | **Biliary** | **Bladder** ***(CrCl: ≥60 mL/min and ECOG PS 0-1; fit)*** | ***Bladder (CrCl: ≥30 to <60 mL/min and/or ECOG PS 2; unfit)*** | **Squamous NSCLC** |
|---|---|---|---|---|
| Historical Median Duration of PFS | 8.8 months | 7.6 months | **5.8 months** | 5 months |
| Historical PFS Weekly Hazard | 0.01795 | 0.020755 | **0.02711** | 0.031377 |

**Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance status.**

Once 10 PFS events have been observed, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort.

- Futility – 10 PFS events have been observed in each cohort and at least 1 of the following conditions is true:
    - Probability (Promising HR*) <0.4
    - Probability (Phase 3 Success*) <0.4
- Success – 25 PFS events have been observed in each **50-patient** cohort **and 15 PFS events in each 30-patient bladder cancer cohort** and:
    - Probability (Phase 3 Success*) >0.8
- Inconclusive – neither futility nor success.

* Phase 3 success is defined as success in a Phase 3 clinical trial with 381 events - enough to provide 80% power to detect an HR of 0.75. A promising HR is defined as one less than 0.85.

*Futility can only be declared for a cohort after 10 PFS events have been observed in that cohort. Success can only be declared for a cohort after 25 **or 15** PFS events have been observed in that **50-patient cohort (Cohort 1 and 2) or 30-patient bladder cancer** cohort **(Cohort 3, fit and unfit), respectively**. Accrual will stop for any cohort identified as futile or successful at interim. The conclusion of this Phase 2 trial will be that a Phase 3 trial with 381 events should be conducted for each cohort that is a success.

***Protocol Synopsis – Estimated Study Duration***

…

Patients will receive study treatment until any of the following occur:
…

- **For Cohort 3 only, unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart)**

***Protocol Synopsis – Definition of DLT***

A DLT **(monitored in Part 1 only)** is defined as the following treatment-related AEs or laboratory abnormalities, graded according to NCI CTCAE version 4.03:

***Protocol Synopsis – Sample Size***

…

Part 2 is a 3-cohort study with an overall sample size of up to ~~150~~**160** patients with no more than 50 patients ~~per cohort~~ **in Cohorts 1 and 2 and no more than 60 patients in Cohort 3 (30 unfit and 30 fit bladder cancer patients)**. The total sample size will depend on the results of interim futility and superiority analyses. In order to evaluate the overall sample size, simulations were performed assuming scenarios with different HRs for PFS for each cohort compared with historical control and different sample sizes for a subsequent Phase 3 clinical trial. The associated mean sample size for this trial in these scenarios ranged from ~~136~~ **92.7** to ~~146~~ **116.8** patients.

***Protocol Synopsis – Study Drug, Dosage, and Route of Administration***

…

In each part of the study, NC-6004 will be administered as a 1 hour **(+10-minute window)** intravenous infusion on Day 1 of each cycle.

***Section 3.1 - Study Design***

This study will consist of 2 parts; Part 1 is a Phase 1b, continual reassessment method dose-escalation trial in patients with any advanced solid tumor, and Part 2 is a Phase 2, adaptive ~~two-stage~~, open-label, expansion trial in patients with squamous NSCLC, biliary tract, and bladder cancer evaluating activity, safety, and tolerability at the RPII dose identified in Part 1.

…

Part 2 of the study (Phase 2 portion) will begin after the RPII dose of NC-6004 is identified for use in combination with gemcitabine. All patients will receive NC-6004 at the RPII dose **(135 mg/m$^2$, established in Part 1)** in combination with gemcitabine 1250 mg/m$^2$ by the same regimen as in Part 1. **Cohort 3 will stratify patients by creatinine clearance (CrCl) to assess study drug in patients with reduced kidney function (ie, CrCl of <60 to**

**≥30 mL/min [unfit] and ≥60 mL/min [fit]) in a controlled manner and with the stipulation that enrollment will stop if 2 of 6 patients in the <30 to ≥60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart).**

Three cohorts of patients are eligible (Cohort 1: first-line metastatic squamous NSCLC; Cohort 2: first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and Cohort 3: first-line metastatic or locally advanced TCC of the urinary tract (bladder cancer). ~~Stage 2 will continue in each cohort after achieving the minimum threshold of clinical responses required and~~ **Part 2 will** enroll up to 50 patients **each in Cohorts 1 and 2, and up to 60 patients in Cohort 3, for a total of up to 160 patients in Part 2.** ~~in each cohort for a total of up to 150 patients in Part 2.~~ The primary endpoint (PFS) will be continuously updated and compared with the historical PFS from Phase 3 pivotal cisplatin and gemcitabine trials within each cohort. The PFS hazard model will be updated as PFS data accrue. A hazard ratio (HR) for PFS for each cohort versus historical control will be obtained.

| **Cohort** | **Biliary** | **Bladder** ***(CrCl: ≥60 mL/min; fit)*** | ***Bladder (CrCl: ≥30 to <60 mL/min; unfit)*** | **Squamous NSCLC** |
|---|---|---|---|---|
| Historical Median Duration of PFS | 8.8 months | 7.6 months | **5.8 months** | 5 months |
| Historical PFS Weekly Hazard | 0.01795 | 0.020755 | **0.02711** | 0.031377 |

**Abbreviations: CrCl: creatinine clearance; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance status.**

Once 10 PFS events have been observed, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort.

- Futility – 10 PFS events have been observed in each cohort and at least 1 of the following conditions is true:
    - Probability (Promising HR*) <0.4
    - Probability (Phase 3 Success*) <0.4
- Success – 25 PFS events have been observed in each **50-patient** cohort **and 15 PFS events in each 30-patient bladder cancer cohort** and:
    - Probability (Phase 3 Success*) >0.8
- Inconclusive – neither futility nor success.

* Phase 3 success is defined as success in a Phase 3 clinical trial with 381 events - enough to provide 80% power to detect an HR of 0.75. A promising HR is defined as one less than 0.85.

*Futility can only be declared for a cohort after 10 PFS events have been observed in that cohort. Success can only be declared for a cohort after 25 **or 15** PFS events have been observed in that **50-patient or 30-patient bladder cancer** cohort**, respectively**. Accrual will stop for any cohort identified as futile or successful at interim. The conclusion of this Phase 2 trial will be that a Phase 3 trial with 381 events should be conducted for each cohort that is a success.

…

**Day 1 of Cycle**

The following procedures will be performed on Day 1 prior to NC-6004 infusion in each treatment cycles unless otherwise specified:

- Pregnancy test **(serum or urine) on Day 1 of each cycle** (at Cycle 1~~only~~, serum or urine; test is not required if pregnancy test at screening was performed using serum)
- Physical examination (if not performed on Day –1)
- Height, weight, and calculation of body surface area **using the Mosteller formula (Mosteller 1987)**

…

- **Part 1 only:** Core MDASI or MDASI module specific for lung cancer (MDASI-LC) (Section 6.1.3)

…

**Day 8 of Each Cycle**

…

- **Part 1 only:** Core MDASI or MDASI-LC

…

**End-of-Treatment Visit**

The following procedures will be performed within 28 days after treatment discontinuation:

- **Pregnancy test (serum or urine)**

…

- **Part 1 only:** Core MDASI or MDASI-LC ~~(Part 1 only)~~

***Section 3.1.1 –Rationale of Study Design***

…

**In Part 1 only, ~~T~~t**he MDASI will be used to evaluate symptoms related to QoL during treatment.

***Section 4.1 –Selection of Study Population***

Approximately **209** ~~199~~ patients (up to 49 patients in Part 1 and up to **160** ~~150~~ patients in Part 2) will be enrolled in at least 20 sites in the United States **and Europe**. Patients will be assigned to a study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

***Section 4.1.1 – Inclusion Criteria***

5. Have an ECOG PS of 0 to 1**, with the exception of patients in Part 2 (Cohort 3, unfit bladder cancer patients) who may have an ECOG PS of 2**.

…

8. **In Part 1 and in Part 2 in Cohorts 1 and 2:** ~~H~~**h**ave adequate renal function defined as a CrCl ≥50 mL/minute (calculated according to the formula of Cockcroft and Gault 1976) or serum creatinine <1.5 mg/dL. **In Part 2, patients in Cohort 3 (bladder cancer) must have a CrCl of ≥30 mL/min.**

- **Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 and ≥60 mL/min and ECOG PS 0 to 1. If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.**

9. Have a negative pregnancy test result at screening (for females of childbearing potential; not applicable to patients who are unable to become pregnant, including those with bilateral oophorectomy and/or hysterectomy **or postmenopausal [no menses for the previous 12 months]**). The test must be performed within 1 week before Day 1 of treatment.

10. **Male patients must agree to use a condom during treatment and for 90 days after dosing. Male patients must agree not to donate sperm for 90 days after dosing.**

**11. For women of childbearing potential*:** ~~A~~**a**re willing to ~~abstain from heterosexual activity or practice physical barrier contraception~~**follow 1 of the following effective methods of birth control** from the time of study entry to 6 months after the last day of treatment~~.~~:

- **Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)**
- **Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)**
- **Intrauterine devices**
- **Intra-uterine hormone-releasing system**
- **Vasectomized partner**

- **Bilateral tubal occlusion**
- **True sexual abstinence**.**

***Patients not of childbearing potential include those who are surgically sterile or postmenopausal (no menses for the previous 12 months). For women not currently taking contraceptive methods at screening, low user dependency contraceptive methods (eg, implantable progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner) are recommended.**

****The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.**

…

Section 4.2.1 – ***Reasons for Withdrawal/Discontinuation***

…

A patient may be withdrawn from the study for any of the following reasons:

…

- **For Cohort 3 only, unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart)**

***Section 5.1 - Method of Assigning Patients to Treatment Groups***

This is an open-label study that will be conducted in 2 parts. In both parts, NC-6004 will be administered as a 1-hour **(+10-minute window)** intravenous infusion on Day 1 of each cycle. Gemcitabine 1250 mg/m$^2$ will be administered as a 30-minute intravenous infusion on Day 1 of each cycle (after the administration of NC-6004) and on Day 8 of each cycle. The duration of each cycle will be 21 days.

**…**

In Part 2, all patients will receive the RPII dose **(135 mg/m$^2$)** of NC-6004 identified in Part 1. **Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min**

**and/or ECOG PS 2 (unfit) and ≥60 mL/min and ECOG PS 0 to 1 (fit) . If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.**

***Section 5.3 - Treatments Administered***

The duration of each treatment cycle will be 21 days in both parts of the study. NC-6004 will be administered on Day 1 of each cycle as a 1-hour **(+10-minute window)** intravenous infusion.

…

In Part 2, on Day 1 of each cycle, all patients will receive NC-6004 at the RPII dose **(135 mg/m$^2$)** identified in Part 1 and 1250 mg/m$^2$ gemcitabine. On Day 8 of each cycle, all patients in Part 2 of the study will receive 1250 mg/m$^2$ gemcitabine.

***Section 5.4 - Dose Delays and Modifications***

**The doses for NC-6004 and gemcitabine will be calculated in milligrams per square meter (mg/m$^2$) at screening, and will not be changed in subsequent cycles unless the patient's body weight has increased or decreased by ≥10% from the patient's weight measurement at screening. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs (*Note:* This threshold should not be confused with a change of a patient's body surface area [BSA] [mg/m$^2$]). Weight will be measured before treatments on Day 1 of each cycle, with calculation of BSA before dosing on Day 1 of each cycle (using the Mosteller formula [Mosteller 1987]).**

Patients experiencing significant toxicities must be immediately and permanently withdrawn from treatment with NC-6004 and gemcitabine as follows:

- Any patient who experiences a Grade 3 or 4 hypersensitivity reaction during any cycle of treatment
- Any patient who experiences 2 protocol-defined DLTs during treatment
- Any patient who experiences a recurrent Grade 3 or 4 toxicity **(recurrence of the same AE)** after a dose reduction

***Section 5.4.1 – NC-6004 Dose Delays and Modifications***

…

Following recovery to Grade 1 or lower, treatment may resume at the investigator's discretion. Patients who resume treatment following a dose delay will have the dose of study drug reduced by 50% for the remainder of study treatment. If toxicities persist or recur to Grade 3 or 4 **(recurrence of the same AE)** after the dose reduction, study treatment will be terminated.

***Section 5.5.2 - Gemcitabine Drug Product***

Gemzar® (gemcitabine for injection, USP), is available in sterile single-use vials individually packaged in a carton containing: 200 mg white to off-white, lyophilized powder in a 10-mL size sterile single-use vial or 1 g white to off-white, lyophilized powder in a 50-mL size sterile single-use vial. Vials of **gemcitabine**~~Gemzar~~ contain either 200 mg or 1 g of gemcitabine hydrochloride (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

***Section 5.6.1 - Study Drug Packaging and Storage***

All study drugs must be stored in a secure area (eg, a locked cabinet). NC-6004 should be protected from light and stored refrigerated (2° to 8°C). Unopened vials of ~~Gemzar~~ ~~(~~gemcitabine~~)~~ are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C that allows for excursions between 15° and 30°C.

Section 5.6.2 **–** ***Test Article Accountability***

The investigator will maintain accurate records of receipt of all test articles **that are centrally provided**, including dates of receipt.

***Section 6.1 – Efficacy Assessments***

…

Symptom changes will be assessed using the core MDASI **(Part 1 only)** or MDASI-LC (only in patients with NSCLC in Part 1) (Section 6.1.3) on Days 1 and 8 of each cycle and at the End-of-Treatment visit.

…

***Section 6.2 - Pharmacokinetic and Pharmacodynamic Assessments***

…

Pharmacokinetics blood sampling should occur within 10% of nominal time for Days 1 and 2 and ±4 hours of nominal time for all other time points, **and should occur within 10 minutes after the 12-lead ECGs performance at time-matched visits (Section 6.3.6).** All PK samples will be evaluable as long as the actual collection times are recorded.

***Section 6.3.1.1 – Definition of Dose-Limiting Toxicities***

A DLT **(monitored in Part 1 only)** is defined as the following treatment-related AEs or laboratory abnormalities, graded according to the NCI CTCAE version 4.03:

***Section 6.3.1.2.1 - Safety Monitoring in Part 2***

During Part 2 of the study, patients treated with NC-6004 at the RPII dose from Part 1 will be monitored for safety. Dose delay and modification rules for both NC-6004 and gemcitabine apply in Part 2 as in Part 1.

**In Part 2 (Cohort 3) if 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort. In addition, in Part 2 (Cohort 3), if an unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening**

**of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart) he or she may be withdrawn from the study (Section 4.2.1).**

***Section 6.3.2.5 - Assessment of Causality***

The investigator's assessment of an AE's relationship to study drug **(combination of NC-6004 and gemcitabine)** is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

***Section 6.3.6 – Electrocardiograms***

All 12-lead ECGs will be performed after the patient has **adequately** rested in the supine position ~~for at least 5 minutes~~.

On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 hours (Day 2) after **start** of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the completion of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will also be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion and at the End-of-Treatment visit. **All 12-lead ECGs should be performed within a ±10-minute window.**

***Section 6.3.7 - Physical Examination***

A complete physical examination will be performed during the screening period at Day -14 to -1, before study treatments on Day –1 or Day 1 of each cycle, and at the End-of-Treatment visit. Height and weight will also be assessed at the time of the screening period physical examination and before treatments on Day 1 of each cycle**.** ~~with~~ **Calculation of BSA will be done before each dosing on Day 1 of each cycle (using the Mosteller formula [Mosteller 1987]. (*Note:* Dose will only be recalculated if there is a ≥10% increase or decrease in the patient's weight from the patient's weight measurement at screening. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs. This threshold should not be confused with a change of a patient's BSA [mg/m$^2$]).**

***Section 6.3.8 - Vital Sign Measurements***

Vital sign measurements will include arterial blood pressure, heart rate, respiratory rate, and temperature. Vital signs will be measured after the patient has **adequately** rested in the supine position ~~for at least 5 minutes~~.

***Section 7.3 - Sample Size Calculations***

This is a Phase 1b/2 study with an overall sample size of up to ~~199~~ **209** patients (up to 49 patients in Part 1 and up to ~~150~~**160** patients in Part 2). The total sample size will depend on the number of cohorts required to establish an RPII dose and the number of patients with NSCLC enrolled at the RPII dose in Part 1.

…

Part 2 is a 3-cohort study with an overall sample size of up to ~~150~~ **160** patients with no more than 50 patients ~~per cohort~~ **in Cohorts 1 and 2 and no more than 60 patients in Cohort 3**. The total sample size will depend on the results of interim futility and superiority analyses. In order to evaluate the overall sample size, simulations were performed assuming scenarios with different HRs for PFS for each cohort compared with historical control and different sample sizes for a subsequent Phase 3 clinical trial. The associated mean sample size for this trial in these scenarios ranged from **92.7**~~136~~ to **116.8** ~~146~~ patients.

***Section 10.2.2 - Protocol Violations and Deviations***

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria, ~~enrollment of the patient without prior sponsor approval,~~ or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

***Section 11 - Reference List***

…

**Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987;317(17):1098.**

## *Section 12.1 - Appendix: Schedule of Events*

**Table 12-1 Schedule of Events**

| Procedure | Screening | | | Cycle 1 | | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | **Day 2** | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Informed consent | X | | | | | | | | | | | | | | | | | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | | |
| Demography | | X | | | | | | | | | | | | | | | | |
| Medical history | | X | | | | | | | | | | | | | | | | |
| Pregnancy test (serum or urine) | | | X | X[e] | | | | **X** | | | **X** | | | **X** | | | **X** | |
| Physical examination | | X[f] | | X[f] | | | | X | | | X | | | X | | | X | |
| Height, weight, and BSA calculation[g] | | X[g] | | X | | | | X | | | X | | | X | | | | |
| Vital signs[h] | | X | | X[h] | | X | | X | X | | X | X | | X | X | | X | |
| Performance status (ECOG) | | X[f] | | X[f] | | | | X | | | X | | | X | | | X | |
| Disease assessment[i] | X | | | | | | | | | | X[i] | | | X[i] | | | X | X |
| Audiometry | | X | | X[j] | | | | X[j] | | | X[j] | | | X[j] | | | X[j] | |
| Hematology | | | X | X[k] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Biochemistry | | | X | X[k] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Urinalysis (dipstick) | | X | | | | | | | | | | | | | | | X | |
| EORTC QLQ-C30 | | | | X | | X | | X | X | | X | X | | X | X | | X | |
| MDASI or MDASI-LC[l] | | | | X | | X | | X | X | | X | X | | X | X | | X | |
| Nausea and vomiting patient diary[m] | | | | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| Part 2 Nausea and vomiting patient diary[m] | | | | X | | X | | X | X | | | | | | | | | |
| Cardiac risk factors | | X | | | | | | | | | | | | | | | | |
| 12-lead ECG[n] | | | X | X | **X** | X | | X | | | X | | | | | | X | |
| Pharmacokinetic assessments (Part 1)[o] | | | | X | **X** | X | X | X | | | X | X[o] | X[o] | | | | X | |
| Pharmacokinetic assessments (Part 2)[p] | | | | X | | X | | X | X | | X | X | | | | | X | |

| Procedure | Screening | | | Cycle 1 | | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | **Day 2** | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Adverse events | | | | X[f] | **X** | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication | | X[f] | | X[f] | **X** | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prophylactic administrations | | | | X | | | | X | | | X | | | X | | | | |
| NC-6004 administration[a] | | | | X | | | | X | | | X | | | X | | | | |
| Gemcitabine administration | | | | X | | X | | X | X | | X | X | | X | X | | | |

Abbreviations: BSA, body surface area; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MDASI, MD Anderson Symptom Inventory; RECIST, Response Evaluation Criteria in Solid Tumors; MDASI-LC, MDASI-lung cancer.

a. In Part 1 of the study, patients will receive treatment until progressive disease. In Part 2 of the study, patients will receive treatment for 6 cycles (Cohorts 1 and 3) or 8 cycles (Cohort 2).
b. End-of-treatment assessments will be performed within 28 days after treatment discontinuation.
c. After patient discontinuation or completion of treatment without disease progression, patients will be followed with scans every 9 weeks until disease progression. Patients will be called every 12 (±1) weeks to collect data on patient survival, new treatments, and adverse events.
d. Day 15 visit is required in Part 1. In Part 2, Day 15 visit is only necessary if it is clinically indicated.
e. Not required if screening pregnancy test was performed using serum.
f. Safety assessments of physical examination, ECOG, review of AEs, and concomitant medication use can be completed on Day -1 to allow for early morning dosing. These should not be conducted in place of screening assessments.
**g.** ~~Height and weight only.~~ **From Day -14 to -1 at screening, only height and weight will be measured, On Day 1 of Cycle 1 through 7, weight will be measured before treatments and BSA will be calculated before each dose using the Mosteller formula (Mosteller 1987). (*Note:* Dose will only be recalculated if there is a ≥10% increase or decrease in the patient's weight from the patient's screening weight measurement. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs. This threshold should not be confused with a change of a patient's BSA [mg/m$^2$]).**
h. On Day 1 of Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the NC-6004 infusion. Starting in Cycle 2, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion on Day 1 of each cycle. Vital signs will be measured before and after gemcitabine infusion on Day 8 of each cycle.

i. Disease assessment will be performed using RECIST version 1.1 and the same imaging method used at screening should be used for all subsequent assessments. Beginning in Cycle 3 and continuing through the remainder of the treatment cycles, disease will be assessed every 6 (±1) weeks (ie, every other cycle) and at the End-of-Treatment visit or until disease progression. Patients who have obtained a partial response or complete response will have a confirmatory scan at a minimum of 4 weeks following the initial scan.
j. To be performed only as clinically indicated.
k. Hematology or biochemistry tests will be repeated prior to dosing on Day 1 of Cycle 1 if they were last performed more than 24 hours before the start of the study drug administration.
l. Symptom changes will be assessed using the core MDASI **(Part 1 only)** or MDASI-LC (only in patients with NSCLC in Part 1).
m. Diary issued on Day 1 of each cycle. Assessment is performed at the site before dosing on Day 1 and Day 8 as well as Day 15 (Day 15 diary collected in Part 1 only; note: no dosing on Day 15) of each cycle. Patient completes diary at home on Days 2 through 8 and returns diary on Day 8.
**n.** Twelve-lead ECGs will be performed after the patient has **adequately** rested in the supine position ~~for at least 5 minutes~~. On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 (Day 2) after the **start** of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the end of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion, and at the End-of-Treatment visit. **All 12-lead ECGs can be performed within a ±10-minute window.**
**o.** For Part 1, blood samples will be collected at the following times: before the start of the NC-6004 infusion on Day 1 of Cycles 1 through 6, at end of NC-6004 infusion in Cycles 1, 3, and 5, after the **start** of NC-6004 infusion at Hours 3, 6, 12, 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 and prior to gemcitabine infusion (Day 8), and 336 (Day 15) in Cycles 1, 3, and 5, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed. **Blood samples will be collected within 10 minutes after the 12-lead ECGs performance.**
**p.** For Part 2 (up to 6 cycles), on the day of NC-6004 infusion for each cycle, blood samples will be collected before the start of the NC-6004 infusion, at the end of the NC-6004 infusion, before gemcitabine infusion on Day 8, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed. **Blood samples will be collected within 10 minutes after the 12-lead ECGs performance.**

## 12.4.4 Protocol Amendment 3–Protocol Version 4.1, Incorporating Amendment 3, Dated 31 August 2016

The following sections detail the changes made to Amendment 2 of the protocol (Version 3.0) dated 07 July 2015. The integrated protocol, Version 4.1, including Amendment 3, was issued on 31 August 2016.

### 12.4.4.1 Overview of Changes

The overview of significant changes includes the following:

Inclusion criteria numbers 9, 10, 11 (Synopsis and Section 4.1.1) and the Schedule of Events (Table 12-1, Section 12.1) were amended per the recommendation by the Voluntary Harmonisation Procedure (VHP) on 25 July 2016. These changes were made to account for the toxic reproductive characteristics of cisplatin and gemcitabine, and to adequately define contraceptive measures that comply with the "Recommendations related to contraception and pregnancy testing in clinical trials" per the Clinical Trials Facilitation Group (CTFG).

Inclusion criterion #9 added that a negative pregnancy test is not applicable for female patients who are postmenopausal (defined as no menses for the previous 12 months).

Inclusion criterion #10 added the requirement that male patients must agree to use a condom during treatment and for 90 days after dosing. Male patients must agree not to donate sperm for 90 days after dosing.

Inclusion criterion #11 added that women of childbearing potential should be willing to follow 1 of the following effective methods of birth control from the time of study entry to 6 months after the last day of treatment:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine devices
- Intrauterine hormone-releasing system
- Vasectomized partner who has received medical assessment of surgical success
- Bilateral tubal occlusion

- True sexual abstinence

In the Schedule of Events, pregnancy testing was added for Day 1 of Cycle 2, Cycles 3 through 6, and Cycle 7 Onward, and at the End of Treatment.

### 12.4.4.2 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in **bold** and deletions are shown in strikethrough text. Minor or obvious editorial and grammatical corrections are not highlighted.

***Synopsis – Inclusion Criteria***

…

9. Have a negative pregnancy test result at screening (for females of childbearing potential; not applicable to patients who are unable to become pregnant, including those with bilateral oophorectomy and/or hysterectomy~~).~~ **or postmenopausal [no menses for the previous 12 months]).** The test must be performed within 1 week before Day 1 of treatment.

10. **Male patients must agree to use a condom during treatment and for 90 days after dosing. Male patients must agree not to donate sperm for 90 days after dosing.**

11. **For women of childbearing potential*: are** willing to ~~abstain from heterosexual activity or practice physical barrier contraception~~ **follow 1 of the following effective methods of birth control** from the time of study entry to 6 months after the last day of treatment**:**

    - **Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)**
    - **Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)**
    - **Intrauterine devices**

- **Intrauterine hormone-releasing system**
- **Vasectomized partner who has received medical assessment of surgical success**
- **Bilateral tubal occlusion**
- **True sexual abstinence****

***Patients not of childbearing potential include those who are surgically sterile or postmenopausal (no menses for the previous 12 months). For women not currently taking contraceptive methods at screening, low user-dependency contraceptive methods (eg, implantable progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner) are recommended.**

****The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.**

***Section 4.1.1 – Inclusion Criteria***

…

9. Have a negative pregnancy test result at screening (for females of childbearing potential; not applicable to patients who are unable to become pregnant, including those with bilateral oophorectomy and/or hysterectomy~~).~~ **or postmenopausal [no menses for the previous 12 months]).** The test must be performed within 1 week before Day 1 of treatment.

10. **Male patients must agree to use a condom during treatment and for 90 days after dosing. Male patients must agree not to donate sperm for 90 days after dosing.**

11. **For women of childbearing potential*: are** willing to ~~abstain from heterosexual activity or practice physical barrier contraception~~ **follow 1 of the following effective methods of birth control from the time of study entry to 6 months after the last day of treatment:**

- **Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)**
- **Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)**
- **Intrauterine devices**
- **Intrauterine hormone-releasing system**
- **Vasectomized partner who has received medical assessment of surgical success**
- **Bilateral tubal occlusion**
- **True sexual abstinence****

***Patients not of childbearing potential include those who are surgically sterile or postmenopausal (no menses for the previous 12 months). For women not currently taking contraceptive methods at screening, low user-dependency contraceptive methods (eg, implantable progestogen-only hormonal contraception, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomized partner) are recommended.**

****The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.**

***Table 12-1, Section 12.1 – Schedule of Events***

## Table 12-1 Schedule of Events

| Procedure | Screening | | | Cycle 1 | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Informed consent | X | | | | | | | | | | | | | | | | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | |
| Demography | | X | | | | | | | | | | | | | | | |
| Medical history | | X | | | | | | | | | | | | | | | |
| Pregnancy test (serum or urine) | | | X | X[e] | | | **X** | | | **X** | | | **X** | | | **X** | |
| Physical examination | | X[f] | | X[f] | | | X | | | X | | | X | | | X | |
| Height, weight, and BSA calculation | | X[g] | | X | | | X | | | X | | | X | | | | |
| Vital signs | | X | | X[h] | X | | X | X | | X | X | | X | X | | X | |
| Performance status (ECOG) | | X[f] | | X[f] | | | X | | | X | | | X | | | X | |
| Disease assessment[i] | X | | | | | | | | | X[i] | | | X[i] | | | X | X |
| Audiometry | | X | | X[j] | | | X[j] | | | X[j] | | | X[j] | | | X[j] | |
| Hematology | | | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | |
| Biochemistry | | | X | X[k] | X | X | X | X | X | X | X | X | X | X | X | X | |
| Urinalysis (dipstick) | | X | | | | | | | | | | | | | | X | |
| EORTC QLQ-C30 | | | | X | X | | X | X | | X | X | | X | X | | X | |
| MDASI or MDASI-LC[l] | | | | X | X | | X | X | | X | X | | X | X | | X | |
| Nausea and vomiting patient diary[m] | | | | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Part 2 Nausea and vomiting patient diary[m] | | | | X | X | | X | X | | | | | | | | | |
| Cardiac risk factors | | X | | | | | | | | | | | | | | | |
| 12-lead ECG[n] | | | X | X | X | | X | | | X | | | | | | X | |
| Pharmacokinetic assessments (Part 1)[o] | | | | X | X | X | X | | | X | X[o] | X[o] | | | | X | |
| Pharmacokinetic assessments (Part 2)[p] | | | | X | X | | X | X | | X | X | | | | | X | |
| Adverse events | | | | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X |

| Procedure | Screening | | | Cycle 1 | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Concomitant medication | | X[f] | | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Prophylactic administrations | | | | X | | | X | | | X | | | X | | | | |
| NC-6004 administration[a] | | | | X | | | X | | | X | | | X | | | | |
| Gemcitabine administration | | | | X | X | | X | X | | X | X | | X | X | | | |

Abbreviations: BSA, body surface area; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MDASI, MD Anderson Symptom Inventory; RECIST, Response Evaluation Criteria in Solid Tumors; MDASI-LC, MDASI-lung cancer.

a. In Part 1 of the study, patients will receive treatment until progressive disease. In Part 2 of the study, patients will receive treatment for 6 cycles (Cohorts 1 and 3) or 8 cycles (Cohort 2).
b. End-of-treatment assessments will be performed within 28 days after treatment discontinuation.
c. After patient discontinuation or completion of treatment without disease progression, patients will be followed with scans every 9 weeks until disease progression. Patients will be called every 12 (±1) weeks to collect data on patient survival, new treatments, and adverse events.
d. Day 15 visit is required in Part 1. In Part 2, Day 15 visit is only necessary if it is clinically indicated.
e. Not required if screening pregnancy test was performed using serum.
f. Safety assessments of physical examination, ECOG, review of AEs, and concomitant medication use can be completed on Day -1 to allow for early morning dosing. These should not be conducted in place of screening assessments.
g. Height and weight only.
h. On Day 1 of Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the NC-6004 infusion. Starting in Cycle 2, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion on Day 1 of each cycle. Vital signs will be measured before and after gemcitabine infusion on Day 8 of each cycle.
i. Disease assessment will be performed using RECIST version 1.1 and the same imaging method used at screening should be used for all subsequent assessments. Beginning in Cycle 3 and continuing through the remainder of the treatment cycles, disease will be assessed every 6 (±1) weeks (ie, every other cycle) and at the End-of-Treatment visit or until disease progression. Patients who have obtained a partial response or complete response will have a confirmatory scan at a minimum of 4 weeks following the initial scan.
j. To be performed only as clinically indicated.
k. Hematology or biochemistry tests will be repeated prior to dosing on Day 1 of Cycle 1 if they were last performed more than 24 hours before the start of the study drug administration.
l. Symptom changes will be assessed using the core MDASI or MDASI-LC (only in patients with NSCLC in Part 1).
m. Diary issued on Day 1 of each cycle. Assessment is performed at the site before dosing on Day 1 and Day 8 as well as Day 15 (Day 15 diary collected in Part 1 only; note: no dosing on Day 15) of each cycle. Patient completes diary at home on Days 2 through 8 and returns diary on Day 8.

n. Twelve-lead ECGs will be performed after the patient has rested in the supine position for at least 5 minutes. On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 (Day 2) after the **start** of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the end of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion, and at the End-of-Treatment visit.
o. For Part 1, blood samples will be collected at the following times: before the start of the NC-6004 infusion on Day 1 of Cycles 1 through 6, at end of NC-6004 infusion in Cycles 1, 3, and 5, after the **start** of NC-6004 infusion at Hours 3, 6, 12, 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 and prior to gemcitabine infusion (Day 8), and 336 (Day 15) in Cycles 1, 3, and 5, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed.
p. For Part 2 (up to 6 cycles), on the day of NC-6004 infusion for each cycle, blood samples will be collected before the start of the NC-6004 infusion, at the end of the NC-6004 infusion, before gemcitabine infusion on Day 8, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed.

## 12.4.5 Protocol Amendment 3-Protocol Version 4.2, Incorporating Amendment 3-Version 4.0 (US only, dated 31 July 2016)

The following sections detail the changes made to Protocol Amendment 3-Version 4.0 (US only, dated 31 July 2016). Version 4.0 was submitted to the FDA and not subsequently modified.

Version 4.0 included European Medicines Agency (EMA) VHP-requested changes in addition to other changes not specifically requested by the VHP. Following submission of Version 4.0 to the VHP, the VHP requested a version of the protocol that only included the VHP-requested changes; therefore, Protocol Amendment 3-Version 4.1 (dated 31 August 2016) was submitted to the VHP (EU only) to meet this request.

Protocol Amendment 3-Version 4.2 (US and EU) harmonizes Versions 4.0 and 4.1 and was finalized on 12 December 2016. A separate summary of the changes made to Version 4.1 is included in Section 12.4.6.

### 12.4.5.1 Risk Assessment for Amendment 3, Version 4.2

No anticipated increased patient risk has been introduced with the updates made during this protocol amendment. Based on new safety information received from an ongoing non-US, non-IND, Japanese trial with NC-6004 (Study NC-6004-007), additional exclusion criteria have been added to mitigate risk of liver toxicity in patients predisposed to liver injury. In addition, sites and investigators have been instructed to closely monitor ongoing NC-6004 patients who are known to have pre-existing alcoholic liver injury and/or concurrent heavy alcohol consumption for newly emerging liver injury.

### 12.4.5.2 Overview of Changes

The overview of significant changes includes the following:

***Title Page – Current Version and Date of Protocol; Title Page – Previous Dates and Versions***

The current and previous protocol amendment versions and applicable regions were updated to provide complete transparency and increased clarity.

***Declaration of Investigator***

A declaration of investigator page, which includes a principal investigator signature line was added.

***Protocol Synopsis – Exclusion Criteria; Section 4.1.2 – Exclusion Criteria***

The exclusion criteria 11 and 12 were added to reflect the following:

11. Have pre-existing alcoholic liver injury or significant liver disease.

12. Are regularly consuming alcohol within 6 months of Screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 8 g of alcohol: a half-pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.

***Protocol Synopsis – Study Design***

A +10-minute window was added to the 1-hour infusion of NC-6004 infusion.

***Protocol Synopsis – Study Design; Section 3.1 – Study Design***

It was clarified that all patients who discontinue treatment and have not progressed will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

***Protocol Synopsis – Safety Assessments; Section 6.3.5 – Clinical Laboratory Analyses***

It was specified that only abnormal laboratory results deemed to be clinically significant will be recorded as AEs or SAEs.

***Protocol Synopsis – Safety Assessments***

For internal consistency, it was added that audiometry will also be performed as clinically indicated at the End-of-Treatment visit.

***Section 3.1 - Study Design***

A cross-reference to the amendment-specified imaging methods was added.

At the Follow-up visit, text was updated to specify that new treatments would be collected (Previous text stated medication history would be collected).

***Section 3.1 - Study Design***

Text was added to specify that pregnancy testing at Cycle 1, serum or urine; test is not required on Day 1 of Cycle 1 if pregnancy test at screening was performed using serum.

***Section 5.2 – Prophylactic Treatments; Section 5.8 – Prophylaxis and Management of Hypersensitivity Reactions***

It was added that 20 mg famotidine can be given intravenously as an option in place of 50 mg of ranitidine given intravenously.

***Section 5.8 – Prophylaxis and Management of Hypersensitivity Reactions***

If a Grade 1 or Grade 2 hypersensitivity occurs in a patient, it was added that 40 mg famotidine can be given orally once per day as an option in place of ranitidine 150 mg orally given 2 times per day.

***Section 6.1.1 – Disease Response Definitions***

Guidelines for imaging, including the timing, anatomic coverage, imaging method, and slice thickness were added.

***Section 6.1.3 – MD Anderson Symptom Inventory***

Reference to the Study Manual was removed from the protocol.

***Section 6.3.2.3 – Reporting Adverse Events***

Text was added to clarifying the process for capturing events in the EDC system, and European SAE hotline and fax line numbers were added.

***Section 6.3.3 – Assessment of Nausea and Vomiting; Section 12.1 - Appendix: Schedule of Events, footnote m***

Text was added to specify the process for administering and capturing data in the nausea and vomiting patient diary.

***Section 6.3.5.3 – Urinalysis; Section 12.1 - Appendix: Schedule of Events***

Reference to a dipstick urinalysis was removed to allow flexibility in the type of urinalysis testing.

***Section 6.3.6 – Electrocardiograms; Section 6.3.8 - Vital Sign Measurements; Section 12.1 - Appendix: Schedule of Events, footnote h and n***

Text was also added to specify that ECGs will be performed during the screening period at Day –7 to –1 and that vital signs will also be measured at the End-of-Treatment visit. The ECG performance window was updated to a ±30-minute window.

***Section 12.1 - Appendix: Schedule of Events, footnote g***

Text was updated to specify that weight will be measured on Day 1 of each cycle.

### 12.4.5.3 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in **bold** and deletions are shown in ~~strikethrough~~ text. Minor or obvious editorial and grammatical corrections are not highlighted.

***Protocol Synopsis – Exclusion Criteria***

…

**11. Have pre-existing alcoholic liver injury or significant liver disease.**

**12. Are regularly consuming alcohol within 6 months of Screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 8 g of alcohol: a half-pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.**

***Protocol Synopsis – Study Design***

…

On Day 1 of each cycle, patients will receive NC-6004 over 1 hour **(+10-minute window)** followed by an infusion of gemcitabine 1250 mg/m$^2$ over 30 minutes.

***Protocol Synopsis – Study Design***

…

Patients who discontinue treatment ~~due to an AE~~ and have not progressed will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

***Protocol Synopsis – Safety Assessments***

Adverse events will be evaluated at each visit during every cycle and graded according to NCI CTCAE version 4.03 dated June 14, 2010 **(only abnormal laboratory results deemed to be clinically significant will be recorded as AEs or SAES)** ~~(NCI CTCAE version 4.03)~~.

…

Audiometry will be performed at screening and only as clinically indicated before treatment on Day 1 of each cycle **and as clinically indicated at the End-of-Treatment visit**.

***Section 3.1 - Study Design***

…

Patients who discontinue treatment ~~due to an AE~~ and have not progressed will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

…

The following procedures will be performed during the screening period within 28 days prior to the first study treatment:

- Signed informed consent can be obtained within 28 days of dosing and prior to performing any study evaluations.
- Disease assessment will be evaluated with a baseline ~~computed tomography~~ scan **(see Section 6.1.1 for imaging methods)** and should be performed within the 28 days before the start of study treatment.

…

The following procedures will be performed on Day 1 prior to NC-6004 infusion in each treatment cycles unless otherwise specified:

- Pregnancy test (serum or urine) on Day 1 of each cycle (at Cycle 1, serum or urine; test is not required **on Day 1 of Cycle 1** if pregnancy test at screening was performed using serum)

Follow-Up

Patients who complete treatment **or discontinue treatment** without disease progression will continue to be followed until disease progression with scans every 9 weeks. Following disease progression, patients will be contacted by telephone every 12 (±1) weeks to collect the following data:

- Survival
- Adverse events (All AEs will be followed until resolution, Section 6.3.2.6)
- ~~Medication history~~**New treatments** (targeted therapy or chemotherapy used after study disease progression and treatment completion)

***Section 4.1.2 – Exclusion Criteria***

…

**11. Have pre-existing alcoholic liver injury or significant liver disease.**

**12. Are regularly consuming alcohol within 6 months of Screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 8 g of alcohol: a half-pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.**

***Section 5.2 – Prophylactic Treatments***

All patients will receive the following medications before administration of NC-6004 on Day 1 of each cycle:

…

- Patients will be given 50 mg of ranitidine intravenously **or 20 mg famotidine intravenously** 30 minutes before the start of NC-6004 infusion on Day 1 of each cycle.

***Section 5.8 – Prophylaxis and Management of Hypersensitivity Reactions***

All patients must receive the following prophylactic treatment at each cycle to reduce the risk of hypersensitivity reactions:

…

- Diphenhydramine hydrochloride 50 mg and **either** ranitidine 50 mg **or 20 mg famotidine** will be administered intravenously 30 minutes before the infusion of NC-6004.

**…**

If a Grade 1 or Grade 2 hypersensitivity occurs in a patient, the following medications should be administered for 48 hours after NC-6004 infusion:

- Ranitidine 150 mg orally given 2 times per day **or 40 mg famotidine orally given once per day**

***Section 6.1.1 – Disease Response Definitions***

…

The rate of confirmed response and tumor growth control will be determined according to RECIST version 1.1 in solid tumor patients for patients evaluable for response **using the following imaging methods:**

**Timing**

**Disease assessment will occur at Screening and every 6 weeks (±1 week) until disease progression. Patients who have obtained a response (PR or CR) will have a confirmatory scan at a minimum of 4 weeks following the initial scan.**

**Anatomic Coverage**

**Imaging should include a computed tomography scan of the chest, abdomen, and pelvis. In addition, areas of known predisposition for metastases (eg, the brain for NSCLC) and any areas identified by the clinician as probable sites of metastasis based on clinical evaluation should be included in imaging if clinically indicated. Other imaging may be performed at the investigator's discretion as standard of care.**

**Imaging Method**

**The preferred method for imaging is computed tomography with IV contrast. If the patient is allergic to contrast media or has another medical contraindication, magnetic resonance imaging with contrast can be used at the clinician's discretion.** ***It is critical that the same method of imaging is used throughout the study for a given patient.***

**Slice Thickness**

**The preferred slice thickness is 5 mm. If a larger slice thickness is used (eg, 7 mm), the smallest tumor measurement that can be reported is twice the thickness of the slice.**

~~The ORR, DCR, and DOR will be determined immediately prior to the initiation of maintenance therapy. The OS and PFS will be determined at the end of the study for evaluable patients without censoring at the initiation of maintenance therapy. Patients who have obtained a response (PR or CR) will have a confirmatory scan at a minimum of 4 weeks following the initial scan.~~

***Section 6.1.3 – MD Anderson Symptom Inventory***

…

The core MDASI and the MDASI-LC will be administered as a self-report paper-and-pencil form given to the patient at the site before study treatments on Days 1 and 8 of each cycle in Part 1 only ~~(as described in Study Manual)~~.

***Section 6.3.2.3 – Reporting Adverse Events***

…

Any AE that meets SAE criteria (Section 6.3.2.1) must be reported to PPD immediately (ie, within 24 hours after the time site personnel first learn about the event). ~~The following contact information is to be used for SAE reporting~~**The event is reported via the electronic data capture (EDC) system where site personnel complete as much of the respective AE page (eCRF) as they are able.**

**If the EDC system is unavailable, the AE information must be recorded on the manual SAE report form and immediately (ie, within 24 hours of awareness) sent to PPD by one of the following methods (refer to the "SAE Guidelines" document for WorldReach toll-free access numbers if necessary):**

Pharmacovigilance Department

**United States** SAE Hotline: **+1** 800-201-8725

**United States** SAE Fax line: **+1** 888-488-9697

**Europe SAE Hotline:** **+44 1223 374 240 (to be used for questions concerning SAEs)**

**Europe SAE Fax line:** **+44 1223 374 102 (to be used for reporting SAEs)**

**Once the EDC system becomes available again, the site needs to transfer all data to the respective eCRF page of the patient.**

***Section 6.3.3 - Assessment of Nausea and Vomiting***

…

**For Parts 1 and 2, e**~~E~~ach patient will be given a nausea and vomiting patient diary to take home. This diary will be used to record the severity of nausea and incidence of emetic episodes over the previous 24 hours daily on Days 2 through 21. **The first 7 days of the diary will be recorded verbatim in the eCRF. The patient will be given the diary and instructed on how and when to complete the diary before discharge from the site on Day 1 of each cycle.**

**Part 1:** The investigator will collect the **nausea and vomiting patient diary from each patient** ~~diaries~~ on Day 8 **and** Day 15 **for Cycle 1. For all subsequent cycles, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle), Day 8, and Day 15** ~~(Part 1 only), and Day 22. The first 7 days of the diary will be recorded verbatim in the eCRF.~~ The investigator will record the worst severity of the patient's nausea and the total number of emetic episodes occurring over the previous 7 days in the eCRF for Day 8 , Day 15, and Day 21. ~~The patient will be given the diary and instructed on how and when to complete the diary before discharge from the site on Day 1 of each cycle. The patient must return the diary to the site on Day 8, Day 15 (Part 1 only), and Day 22 (Day 1 of the next cycle) of each cycle.~~

**Part 2: The investigator will collect the nausea and vomiting patient diary from each patient at the site on Day 8 for Cycle 1. For Cycle 2, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle) and Day 8. Note that nausea and vomiting patient diaries will not be collected past Cycle 2. The investigator will record the worst severity of the patient's nausea and the total number of emetic episodes occurring over the previous 7 days in the eCRF for Day 8 and Day 21.**

***Section 6.3.5 – Clinical Laboratory Analyses***

…

~~Any~~ **Only** abnormal laboratory test results (hematology, biochemistry, or urinalysis) **that are deemed clinically significant by the PI will** ~~are to~~ be recorded as AEs or SAEs per the NCI CTCAE version 4.03.

***Section 6.3.5.3 – Urinalysis***

Urinalysis will be performed ~~using a dipstick test~~ and will include: leukocyte esterase, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose.

***Section 6.3.6 – Electrocardiograms***

…

**A 12-lead ECG will be performed during the screening period at Day -7 to -1.** On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 hours (Day 2) after start of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the completion of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will also be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion and at the End-of-Treatment visit. All 12-lead ECGs should be performed within a ±**3**~~1~~0-minute window.

***Section 6.3.8 - Vital Sign Measurements***

…

**Vital signs will also be measured at the End-of-Treatment visit.**

***Section 7.3 - Sample Size Calculations***

…

Part 2 is a 3-cohort study with an overall sample size of up to ~~150~~ **160** patients with no more than 50 patients in Cohorts 1 and 2 and no more than 60 patients in Cohort 3 **(30 unfit and 30 fit bladder cancer patients)**.

***Section 12.1 - Appendix: Schedule of Events***

**Table 12-1 Schedule of Events**

| Procedure | Screening | | | Cycle 1 | | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 2 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Informed consent | X | | | | | | | | | | | | | | | | | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | | |
| Demography | | X | | | | | | | | | | | | | | | | |
| Medical history | | X | | | | | | | | | | | | | | | | |
| Pregnancy test (serum or urine) | | | X | X[e] | | | | X | | | X | | | X | | | X | |
| Physical examination | | X[f] | | X[f] | | | | X | | | X | | | X | | | X | |
| Height, weight, and BSA calculation[g] | | X[g] | | X | | | | X | | | X | | | X | | | | |
| Vital signs[h] | | X | | X[h] | | X | | X | X | | X | X | | X | X | | X | |
| Performance status (ECOG) | | X[f] | | X[f] | | | | X | | | X | | | X | | | X | |
| Disease assessment[i] | X | | | | | | | | | | X[i] | | | X[i] | | | X | X |
| Audiometry | | X | | X[j] | | | | X[j] | | | X[j] | | | X[j] | | | X[j] | |
| Hematology | | | X | X[k] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Biochemistry | | | X | X[k] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Urinalysis ~~(dipstick)~~ | | X | | | | | | | | | | | | | | | X | |
| EORTC QLQ-C30 | | | | X | | X | | X | X | | X | X | | X | X | | X | |
| MDASI or MDASI-LC[l] | | | | X | | X | | X | X | | X | X | | X | X | | X | |
| **Part 1:** Nausea and vomiting patient diary[m] | | | | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| Part 2 Nausea and vomiting patient diary[m] | | | | X | | X | | X | X | | | | | | | | | |
| Cardiac risk factors | | X | | | | | | | | | | | | | | | | |
| 12-lead ECG[n] | | | X | X | **X** | X | | X | | | X | | | | | | X | |
| Pharmacokinetic assessments (Part 1)[o] | | | | X | **X** | X | X | X | | | X | X[o] | X[o] | | | | X | |
| Pharmacokinetic assessments (Part 2)[p] | | | | X | | X | | X | X | | X | X | | | | | X | |

| Procedure | Screening | | | Cycle 1 | | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 2 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Adverse events | | | | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication | | X[f] | | X[f] | X | X | X | X | X | X | X | X | X | X | X | X | X | X[e] |
| Prophylactic administrations | | | | X | | | | X | | | X | | | X | | | | |
| NC-6004 administration[a] | | | | X | | | | X | | | X | | | X | | | | |
| Gemcitabine administration | | | | X | | X | | X | X | | X | X | | X | X | | | |

Abbreviations: BSA, body surface area; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MDASI, MD Anderson Symptom Inventory; RECIST, Response Evaluation Criteria in Solid Tumors; MDASI-LC, MDASI-lung cancer.

a. In Part 1 of the study, patients will receive treatment until progressive disease. In Part 2 of the study, patients will receive treatment for 6 cycles (Cohorts 1 and 3) or 8 cycles (Cohort 2).
b. End-of-treatment assessments will be performed within 28 days after treatment discontinuation.
c. After patient discontinuation or completion of treatment without disease progression, patients will be followed with scans every 9 weeks until disease progression. Patients will be called every 12 (±1) weeks to collect data on patient survival, new treatments, and adverse events.
d. Day 15 visit is required in Part 1. In Part 2, Day 15 visit is only necessary if it is clinically indicated.
e. Not required if screening pregnancy test was performed using serum.
f. Safety assessments of physical examination, ECOG, review of adverse events, and concomitant medication use can be completed on Day -1 to allow for early morning dosing. These should not be conducted in place of screening assessments.
g. From Day -14 to -1 at screening, only height and weight will be measured. On Day 1 of ~~Cycle 1 through 7~~ **each cycle**, weight will be measured before treatments and BSA will be calculated before each dose using the Mosteller formula (Mosteller 1987). (Note: Dose will only be recalculated if there is a ≥10% increase or decrease in the patient's weight from the patient's screening weight measurement. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs. This threshold should not be confused with a change in the patient's BSA [$m^2$]).
h. On Day 1 of Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the NC-6004 infusion. Starting in Cycle 2, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion on Day 1 of each cycle. Vital signs will be measured before and after gemcitabine infusion on Day 8 of each cycle. **Vital signs will also be measured at the End-of-Treatment visit.**
i. Disease assessment will be performed using RECIST version 1.1 and the same imaging method used at screening should be used for all subsequent assessments. Beginning in Cycle 3 and continuing through the remainder of the treatment cycles, disease will be assessed every 6 (±1) weeks (ie, every other cycle) and at the End of Treatment visit or until disease progression. Patients who have obtained a partial response or complete response will have a confirmatory scan at a minimum of 4 weeks following the initial scan.
j. To be performed only as clinically indicated.
k. Hematology ~~or~~and biochemistry tests will be repeated prior to dosing on Day 1 of Cycle 1 if they were last performed more than 24 hours before the start of the study drug administration.
l. Symptom changes will be assessed using the core MDASI (Part 1 only) or MDASI-LC (only in patients with NSCLC in Part 1).

m. **Part 1: The investigator will collect the nausea and vomiting patient diary from each patient on Day 8 and Day 15 for Cycle 1. For all subsequent cycles, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle), Day 8, and Day 15. Part 2: The investigator will collect the nausea and vomiting patient diary from each patient at the site on Day 8 for Cycle 1. For Cycle 2, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle) and Day 8. Note that nausea and vomiting patient diaries will not be collected past Cycle 2. For additional details, see Section 6.3.3.** ~~Diary issued on Day 1 of each cycle. Assessment is performed at the site before dosing on Day 1 and Day 8 as well as Day 15 (Day 15 diary collected in Part 1 only; note: no dosing on Day 15) of each cycle. Patient completes diary at home on Days 2 through 8 and returns diary on Day 8.~~

n. Twelve-lead ECGs will be performed after the patient has adequately rested in the supine position. **A 12-lead ECG will be performed during the screening period at Day –7 to –1.** On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 (Day 2) after the start of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the end of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion, and at the End-of-Treatment visit. All 12-lead ECGs should be performed within a ±**3**0~~1~~-minute window.

o. For Part 1, blood samples will be collected at the following times: before the start of the NC-6004 infusion on Day 1 of Cycles 1 through 6, at end of NC-6004 infusion in Cycles 1, 3, and 5, after the start of NC-6004 infusion at Hours 3, 6, 12, 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 ~~and~~ **(Day 8,** prior to gemcitabine infusion ~~(Day 8)~~, and 336 (Day 15) in Cycles 1, 3, and 5, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed. Blood samples will be collected within 10 minutes after the 12-lead ECGs performance.

p. For Part 2 (up to 6 cycles), on the day of NC-6004 infusion for each cycle, blood samples will be collected before the start of the NC-6004 infusion, at the end of the NC-6004 infusion, before gemcitabine infusion on Day 8, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed. Blood samples will be collected within 10 minutes after the 12-lead ECGs performance.

## 12.4.6 Protocol Amendment 3-Protocol Version 4.2, Incorporating Amendment 3-Version 4.1 (EU only, dated 31 August 2016)

The following sections detail the changes made to Protocol Amendment 3-Version 4.1 (EU only, dated 31 August 2016).

Protocol Amendment 3-Version 4.0 (US only, dated 31 July 2016) included EMA VHP-requested changes in addition to other changes not specifically requested by the VHP. Following submission of Version 4.0 to the VHP, the VHP requested a version of the protocol that only included the VHP-requested changes; therefore, Version 4.1 was submitted to the VHP to meet this request. Version 4.0 was submitted to the FDA and not subsequently modified.

Protocol Amendment 3-Version 4.2 (US and EU) harmonizes Versions 4.0 and 4.1 and was finalized on 12 December 2016. A separate summary of the changes made to Version 4.0 is included in Section 12.4.5.

### 12.4.6.1 Risk Assessment for Amendment 3, Version 4.2

Because the following sections detail the changes made to Protocol Amendment 3-Version 4.1 (EU only, dated 31 August 2016), the risk associated with this amendment comprises both the risk described in Section 12.4.3.1 and the risk assessed in the following text and repeated in Section 12.4.5.1.

No anticipated increased patient risk has been introduced with the updates made during this protocol amendment. Based on new safety information received from an ongoing non-US, non-IND, Japanese trial with NC-6004 (Study NC-6004-007), additional exclusion criteria have been added to mitigate risk of liver toxicity in patients predisposed to liver injury. In addition, sites and investigators have been instructed to closely monitor ongoing NC-6004 patients who are known to have pre-existing alcoholic liver injury and/or concurrent heavy alcohol consumption, for newly emerging liver injury.

### 12.4.6.2 Overview of Changes

The overview of significant changes includes the following:

***Title Page – Current Version and Date of Protocol; Title Page – Previous Dates and Versions***

The current and previous protocol amendment versions and applicable regions were updated to provide complete transparency and increased clarity.

***Declaration of Investigator***

A declaration of investigator page, which includes a principal investigator signature line was added.

***Protocol Synopsis – Study Sites; Section 4.1 – Selection of Study Population***

The study site details were updated to at least 20 sites in the Unites States and Europe.

***Protocol Synopsis – Inclusion Criteria; Section 4.1.1 – Inclusion Criteria***

The inclusion criterion 5 was updated to the following:

5. Have an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1, with the exception of patients in Part 2 (Cohort 3, unfit bladder cancer patients) who may have an ECOG PS of 2.

***Protocol Synopsis – Inclusion Criteria; Protocol Synopsis – Study Design; Section 3.1 - Study Design; Section 4.1.1 – Inclusion Criteria; Section 5.1 – Method of Assigning Patients to Treatment Groups; Section 6.3.1.2.1 - Safety Monitoring in Part 2***

The inclusion criterion 8 and study design were updated to reflect the following:

8. In Part 1 and in Part 2 in Cohorts 1 and 2: have adequate renal function defined as a creatinine clearance (CrCl) ≥50 mL/minute (calculated according to the formula of Cockcroft and Gault 1976) or serum creatinine <1.5 mg/dL. In Part 2, patients in Cohort 3 (bladder cancer) must have a CrCl of ≥30 mL/min.

- Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 and ≥60 mL/min and ECOG PS 0 to 1. If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for

2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.

***Protocol Synopsis – Exclusion Criteria; Section 4.1.2 – Exclusion Criteria***

The exclusion criteria 11 and 12 were added to reflect the following:

11. Have pre-existing alcoholic liver injury or significant liver disease.

12. Are regularly consuming alcohol within 6 months of Screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 8 g of alcohol: a half-pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.

***Protocol Synopsis – Study Design; Section 3.1 – Study Design***

All references to "two-stage" and a minimum threshold of clinical responses in Part 2 were removed.

***Protocol Synopsis – Study Design; Protocol Synopsis – Study Drug, Dosage, and Route of Administration; Section 5.1 - Method of Assigning Patients to Treatment Groups; Section 5.3 - Treatments Administered***

A +10-minute window was added to the 1-hour infusion of NC-6004.

***Protocol Synopsis – Study Design; Section 3.1 - Study Design; Section 5.1 - Method of Assigning Patients to Treatment Groups; Section 5.3 - Treatments Administered***

The RPII dose of 135 mg/m$^2$ was added to the protocol.

***Protocol Synopsis – Study Design; Section 3.1 - Study Design***

The historical median duration of PFS and PFS weekly hazard were added for the unfit bladder cancer cohort. A successful outcome for unfit and fit bladder cancer patient cohorts with 30 planned patients was updated to 15 PFS events.

***Protocol Synopsis – Study Design; Protocol Synopsis – Sample Size; Section 3.1 - Study Design; Section 4.1 – Selection of Study Population; Section 7.3 - Sample Size Calculations***

The total sample size in Part 2 of the study was changed to 160 patients with no more than 50 patients each in Cohorts 1 and 2 and no more than 60 patients in Cohort 3 (30 unfit and 30 fit bladder cancer patients). The simulated mean sample sizes for this trial were updated to 92.7 to 116.8 patients.

***Protocol Synopsis – Study Design; Section 3.1 – Study Design***

It was clarified that all patients who discontinue treatment and have not progressed will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

***Protocol Synopsis – Estimated Study Duration; Section 4.2.1 – Reasons for Withdrawal/Discontinuation***

A study treatment discontinuation rule was added as follows:

- For Cohort 3 only, unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart)

***Protocol Synopsis – Safety Assessments; Section 6.3.5 – Clinical Laboratory Analyses***

It was specified that only abnormal laboratory results deemed to be clinically significant will be recorded as AEs or SAEs.

***Protocol Synopsis – Safety Assessments***

For internal consistency, it was added that audiometry will also be performed as clinically indicated at the End-of-Treatment visit.

***Protocol Synopsis – Definition of a DLT; Section 6.3.1.1 – Definition of Dose-Limiting Toxicities***

It was clarified that DLTs will only be monitored in Part 1 of the study.

***Section 3.1 - Study Design; Section 3.1.1 – Rationale of Study Design; Section 6.1 - Efficacy Assessments; Section 12.1 - Appendix: Schedule of Events;***

It was clarified that the MDASI will only be performed in Part 1.

***Section 3.1 - Study Design***

A cross-reference to the amendment-specified imaging methods was added.

At the Follow-up visit, text was updated to specify that new treatments would be collected (Previous text stated medication history would be collected).

***Section 3.1 - Study Design***

Text was added to specify that at Cycle 1, either serum or urine; test is not required on Day 1 of Cycle 1 if pregnancy test at screening was performed using serum.

***Section 5.2 – Prophylactic Treatments; Section 5.8 – Prophylaxis and Management of Hypersensitivity Reactions***

It was added that 20 mg famotidine can be given intravenously as an option in place of 50 mg of ranitidine given intravenously.

***Section 5.8 – Prophylaxis and Management of Hypersensitivity Reactions***

If a Grade 1 or Grade 2 hypersensitivity occurs in a patient, it was added that 40 mg famotidine can be given orally once per day as an option in place of ranitidine 150 mg orally given 2 times per day.

***Section 3.1 - Study Design; Section 5.4 - Dose Delays and Modifications; Section 6.3.7 - Physical Examination; Section 11 - Reference List; Section 12.1 - Appendix: Schedule of Events, footnote g***

It was added that the doses of NC-6004 and gemcitabine will be calculated in milligrams per square meter ($mg/m^2$) at screening and will not be changed in subsequent cycles unless the patient's body weight increases or decreases by at least 10% from the patient's screening weight measurement. This threshold should not be confused with a change in the patient's body surface area ($m^2$). Any change in a patient's weight by at least 10% during the study will require a recalculation of the doses of NC-6004 and gemcitabine. Weight will be

measured before treatments on Day 1 of each cycle, with a calculation of body surface area before each dosing on Day 1 of each cycle (using the Mosteller formula [Mosteller 1987]).

***Section 5.4 - Dose Delays and Modifications; Section 5.4.1 – NC-6004 Dose Delays and Modifications***

Updated "Grade 3 or 4 toxicity" to "Grade 3 or 4 toxicity (recurrence of the same AE)" to more clearly define the recurrence of events that could lead to study drug withdrawal.

***Section 5.5.2 - Gemcitabine Drug Product; Section 5.6.1 - Study Drug Packaging and Storage***

The generic gemcitabine was added to the protocol to clarify that it is acceptable for generic gemcitabine to be administered in this study (as per the original intent of the protocol) in place of Gemzar.

***Section 5.6.2 – Test Article Accountability***

It was clarified that the PI should maintain accurate records of receipt of all test articles that are centrally provided.

***Section 6.1.1 – Disease Response Definitions***

Guidelines for imaging, including the timing, anatomic coverage, imaging method, and slice thickness were added.

***Section 6.1.3 – MD Anderson Symptom Inventory***

Reference to the Study Manual was removed from the protocol.

***Section 6.2 - Pharmacokinetic and Pharmacodynamic Assessments;***
***Section 12.1 - Appendix: Schedule of Events, footnotes o and p***

A 10-minute window after ECG performance was added for the PK blood sampling.

***Section 6.3.2.3 – Reporting Adverse Events***

Text was added to clarifying the process for capturing events in the EDC system, and European SAE hotline and fax line numbers were added.

***Section 6.3.2.5 - Assessment of Causality***

"Study drug" was updated to "study drug (NC-6004 and gemcitabine)" to indicate that the assessment of an AE's relatedness was to the combination of NC-6004 and gemcitabine.

***Section 6.3.3 – Assessment of Nausea and Vomiting; Section 12.1 - Appendix: Schedule of Events, footnote m***

Text was added to specify the process for administering and capturing data in the nausea and vomiting patient diary.

***Section 6.3.5.3 – Urinalysis; Section 12.1 - Appendix: Schedule of Events***

Reference to a dipstick urinalysis was removed to allow flexibility in the type of urinalysis testing.

***Section 6.3.6 – Electrocardiograms; Section 6.3.8 - Vital Sign Measurements; Section 12.1 - Appendix: Schedule of Events, footnotes n and h***

The text "rest for at least 5 minutes" was updated to "adequately rested" for the patient before ECGs and vital sign measurements. Text was also added to specify that ECGs will be performed during the screening period at Day –7 to –1 and that vital signs will also be measured at the End-of-Treatment visit.

***Section 6.3.6 – Electrocardiograms; Section 12.1 - Appendix: Schedule of Events, footnote n***

A ±30-minute window for collection of 12-lead ECGs was added.

***Section 10.2.2 - Protocol Violations and Deviations***

Text was updated to clarify that Part 2 of this study will not require sponsor approval prior to each patient being enrolled in the study.

***Section 12.1 - Appendix: Schedule of Events***

A column was added to the Schedule of Events Table (Table 12-1) to clearly show that ECGs will be also performed on Day 2 of Cycle 1. For completeness, PK assessments, AE monitoring, and concomitant medication review were also added to Day 2 of Cycle 1.

## 12.4.6.3 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in **bold** and deletions are shown in ~~strikethrough~~ text. Minor or obvious editorial and grammatical corrections are not highlighted.

***Protocol Synopsis – Study Sites***

Study Sites: At least 20 sites in the United States **and Europe.**

***Protocol Synopsis – Inclusion Criteria***

…

5. Have an Eastern Cooperative Oncology Group (ECOG) PS of 0 to 1**, with the exception of patients in Part 2 (Cohort 3, unfit bladder cancer patients) who may have an ECOG PS of 2**.

…

8. **In Part 1 and in Part 2 in Cohorts 1 and 2**: ~~H~~**h**ave adequate renal function defined as a creatinine clearance **(CrCl)** ≥50 mL/minute (calculated according to the formula of Cockcroft and Gault 1976) or serum creatinine <1.5 mg/dL. **In Part 2, patients in Cohort 3 (bladder cancer) must have a CrCl of ≥30 mL/min.**

- **Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 and ≥60 mL/min and ECOG PS 0 to 1. If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.**

***Protocol Synopsis – Exclusion Criteria***

…

**11. Have pre-existing alcoholic liver injury or significant liver disease.**

**12. Are regularly consuming alcohol within 6 months of Screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 8 g of alcohol: a half-pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.**

***Protocol Synopsis – Study Design***

This study will consist of 2 parts; Part 1 is a Phase 1b, continual reassessment method dose-escalation trial, and Part 2 is a Phase 2, adaptive, ~~two-stage,~~ open-label, expansion trial evaluating activity, safety, and tolerability at the RPII dose identified in Part 1.

…

On Day 1 of each cycle, patients will receive NC-6004 over 1 hour **(+10-minute window)** followed by an infusion of gemcitabine 1250 mg/m$^2$ over 30 minutes.

…

Part 2 of the study (Phase 2 portion) will begin after the RPII dose of NC-6004 is identified for use in combination with gemcitabine. All patients will receive NC-6004 at the RPII dose **(135 mg/m$^2$, established in Part 1)** in combination with gemcitabine 1250 mg/m$^2$ by the same regimen as in Part 1.

Three cohorts of patients are eligible (Cohort 1: first-line metastatic squamous NSCLC; Cohort 2: first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer (biliary tract cancer); and Cohort 3: first-line metastatic or locally advanced TCC of the urinary tract (bladder cancer). **Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 (unfit) and ≥60 mL/min and ECOG PS 0 to 1 (fit). If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.**

~~Stage~~**Part** 2 will ~~continue in each cohort after achieving the minimum threshold of clinical responses required and~~ enroll up to 50 patients **each in Cohorts 1 and 2, and up to 60 patients in Cohort 3,** for a total of up to ~~150~~ **160** patients in Part 2.

…

| Cohort | Biliary | Bladder (CrCl: ≥60 mL/min and ECOG PS 0-1; fit) | Bladder (CrCl: ≥30 to <60 mL/min and/or ECOG PS 2; unfit) | Squamous NSCLC |
|---|---|---|---|---|
| Historical Median Duration of PFS | 8.8 months | 7.6 months | **5.8 months** | 5 months |
| Historical PFS Weekly Hazard | 0.01795 | 0.020755 | **0.02711** | 0.031377 |

**Abbreviations: CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance status.**

Once 10 PFS events have been observed, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort.

- Futility – 10 PFS events have been observed in each cohort and at least 1 of the following conditions is true:
    - Probability (Promising HR*) <0.4
    - Probability (Phase 3 Success*) <0.4
- Success – 25 PFS events have been observed in each **50-patient cohort and 15 PFS events in each 30-patient bladder cancer** cohort and:
    - Probability (Phase 3 Success*) >0.8
- Inconclusive – neither futility nor success.

*Phase 3 success is defined as success in a Phase 3 clinical trial with 381 events - enough to provide 80% power to detect an HR of 0.75. A promising HR is defined as one less than 0.85.

*****Futility can only be declared for a cohort after 10 PFS events have been observed in that cohort. Success can only be declared for a cohort after 25 **or 15** PFS events have been observed in that **50-patient cohort (Cohort 1 and 2) or 30-patient bladder cancer** cohort **(Cohort 3, fit and unfit), respectively**. Accrual will stop for any cohort identified as futile or

successful at interim. The conclusion of this Phase 2 trial will be that a Phase 3 trial with 381 events should be conducted for each cohort that is a success.

…

Patients who discontinue treatment ~~due to an AE~~ and have not progressed will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

***Protocol Synopsis – Estimated Study Duration***

…

Patients will receive study treatment until any of the following occur:
…

- **For Cohort 3 only, unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart)**

***Protocol Synopsis – Safety Assessments***

Adverse events will be evaluated at each visit during every cycle and graded according to NCI CTCAE version 4.03 dated June 14, 2010 **(only abnormal laboratory results deemed to be clinically significant will be recorded as AEs or SAES)** ~~(NCI CTCAE version 4.03)~~.

…

Audiometry will be performed at screening and only as clinically indicated before treatment on Day 1 of each cycle **and as clinically indicated at the End-of-Treatment visit**.

***Protocol Synopsis – Definition of DLT***

A DLT **(monitored in Part 1 only)** is defined as the following treatment-related AEs or laboratory abnormalities, graded according to NCI CTCAE version 4.03:

***Protocol Synopsis – Study Drug, Dosage, and Route of Administration***

In each part of the study, NC-6004 will be administered as a 1-hour **(+10-minute window)** intravenous infusion on Day 1 of each cycle.

***Protocol Synopsis – Sample Size***

…

Part 2 is a 3-cohort study with an overall sample size of up to ~~150~~**160** patients with no more than 50 patients ~~per cohort~~ **in Cohorts 1 and 2 and no more than 60 patients in Cohort 3 (30 unfit and 30 fit bladder cancer patients)**. The total sample size will depend on the results of interim futility and superiority analyses. In order to evaluate the overall sample size, simulations were performed assuming scenarios with different HRs for PFS for each cohort compared with historical control and different sample sizes for a subsequent Phase 3 clinical trial. The associated mean sample size for this trial in these scenarios ranged from ~~136~~ **92.7** to ~~146~~ **116.8** patients.

***Section 3.1 - Study Design***

This study will consist of 2 parts; Part 1 is a Phase 1b, continual reassessment method dose-escalation trial in patients with any advanced solid tumor, and Part 2 is a Phase 2, adaptive ~~two-stage~~, open-label, expansion trial in patients with squamous NSCLC, biliary

tract, and bladder cancer evaluating activity, safety, and tolerability at the RPII dose identified in Part 1.

…

Part 2 of the study (Phase 2 portion) will begin after the RPII dose of NC-6004 is identified for use in combination with gemcitabine. All patients will receive NC-6004 at the RPII dose **(135 mg/m$^2$, established in Part 1)** in combination with gemcitabine 1250 mg/m$^2$ by the same regimen as in Part 1. **Cohort 3 will stratify patients by creatinine clearance (CrCl) to assess study drug in patients with reduced kidney function (ie, CrCl of <60 to ≥30 mL/min [unfit] and ≥60 mL/min [fit]) in a controlled manner and with the stipulation that enrollment will stop if 2 of 6 patients in the <30 to ≥60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart).**

Three cohorts of patients are eligible (Cohort 1: first-line metastatic squamous NSCLC; Cohort 2: first-line metastatic or locally advanced cholangiocarcinoma, gallbladder cancer, or ampullary cancer **[**~~(~~biliary tract cancer~~)~~**]**; and Cohort 3: first-line metastatic or locally advanced TCC of the urinary tract **[**~~(~~bladder cancer**]**). ~~Stage 2 will continue in each cohort after achieving the minimum threshold of clinical responses required and~~ **Part 2 will** enroll up to 50 patients **each in Cohorts 1 and 2, and up to 60 patients in Cohort 3, for a total of up to 160 patients in Part 2.** ~~in each cohort for a total of up to 150 patients in Part 2.~~ The primary endpoint (PFS) will be continuously updated and compared with the historical PFS from Phase 3 pivotal cisplatin and gemcitabine trials within each cohort. The PFS hazard model will be updated as PFS data accrue. A hazard ratio (HR) for PFS for each cohort versus historical control will be obtained.

| Cohort | Biliary | Bladder (CrCl: ≥60 mL/min; fit) | Bladder (CrCl: ≥30 to <60 mL/min; unfit) | Squamous NSCLC |
|---|---|---|---|---|
| Historical Median Duration of PFS | 8.8 months | 7.6 months | **5.8 months** | 5 months |
| Historical PFS Weekly Hazard | 0.01795 | 0.020755 | **0.02711** | 0.031377 |

**Abbreviations: CrCl: creatinine clearance; ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PS, performance status.**

Once 10 PFS events have been observed, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort.

- Futility – 10 PFS events have been observed in each cohort and at least 1 of the following conditions is true:
    - Probability (Promising HR*) <0.4
    - Probability (Phase 3 Success*) <0.4
- Success – 25 PFS events have been observed in each **50-patient** cohort **and 15 PFS events in each 30-patient bladder cancer cohort** and:
    - Probability (Phase 3 Success*) >0.8
- Inconclusive – neither futility nor success.

* Phase 3 success is defined as success in a Phase 3 clinical trial with 381 events - enough to provide 80% power to detect an HR of 0.75. A promising HR is defined as one less than 0.85.

*Futility can only be declared for a cohort after 10 PFS events have been observed in that cohort. Success can only be declared for a cohort after 25 **or 15** PFS events have been observed in that **50-patient (Cohort 1 and 2) or 30-patient bladder cancer cohort (Cohort 3, fit and unfit), respectively**. Accrual will stop for any cohort identified as futile or

successful at interim. The conclusion of this Phase 2 trial will be that a Phase 3 trial with 381 events should be conducted for each cohort that is a success.

…

Patients who discontinue treatment ~~due to an AE~~ and have not progressed will have an End-of-Treatment visit, will be followed with scans every 9 weeks until disease progression, and will be contacted for survival every 12 weeks by telephone.

…

The following procedures will be performed during the screening period within 28 days prior to the first study treatment:

- Signed informed consent can be obtained within 28 days of dosing and prior to performing any study evaluations.
- Disease assessment will be evaluated with a baseline ~~computed tomography~~ scan **(see Section 6.1.1 for imaging methods)** and should be performed within the 28 days before the start of study treatment.

…

The following procedures will be performed on Day 1 prior to NC-6004 infusion in each treatment cycles unless otherwise specified:

- Pregnancy test (serum or urine) on Day 1 of each cycle (at Cycle 1, serum or urine; test is not required **on Day 1 of Cycle 1** if pregnancy test at screening was performed using serum)

…

- Height, weight, and calculation of body surface area **using the Mosteller formula (Mosteller 1987)**

…

  - **Part 1 only:** Core MDASI or MDASI module specific for lung cancer (MDASI-LC) (Section 6.1.3)

…

Day 8 of Each Cycle

…

- **Part 1 only:** Core MDASI or MDASI-LC

…

Follow-Up

Patients who complete treatment **or discontinue treatment** without disease progression will continue to be followed until disease progression with scans every 9 weeks. Following disease progression, patients will be contacted by telephone every 12 (±1) weeks to collect the following data:

- Survival
- Adverse events (All AEs will be followed until resolution, Section 6.3.2.6)
- ~~Medication history~~**New treatments** (targeted therapy or chemotherapy used after study disease progression and treatment completion)
- ***Section 3.1.1 –Rationale of Study Design***
- …
- **In Part 1 only,** ~~T~~**t**he MDASI will be used to evaluate symptoms related to QoL during treatment.

***Section 4.1 –Selection of Study Population***

Approximately **209** ~~199~~ patients (up to 49 patients in Part 1 and up to **160** ~~150~~ patients in Part 2) will be enrolled in at least 20 sites in the United States **and Europe**. Patients will be assigned to a study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

***Section 4.1.1 – Inclusion Criteria***

5. Have an ECOG PS of 0 to 1**, with the exception of patients in Part 2 (Cohort 3, unfit bladder cancer patients) who may have an ECOG PS of 2**.

…

8. **In Part 1 and in Part 2 in Cohorts 1 and 2:** ~~H~~**h**ave adequate renal function defined as a CrCl ≥50 mL/minute (calculated according to the formula of Cockcroft and Gault 1976) or

serum creatinine <1.5 mg/dL. **In Part 2, patients in Cohort 3 (bladder cancer) must have a CrCl of ≥30 mL/min.**

- **Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 and ≥60 mL/min and ECOG PS 0 to 1. If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.**

***Section 4.1.2 – Exclusion Criteria***

…

**11. Have pre-existing alcoholic liver injury or significant liver disease.**

**12. Are regularly consuming alcohol within 6 months of Screening defined as an average weekly intake of >21 units (or an average daily intake of >3 units) for males or >14 units (or an average daily intake >2 units) for females. One unit is equivalent to 8 g of alcohol: a half-pint (approximately 240 mL) of beer, 1 glass (125 mL) of wine, or 1 measure (25 mL) of spirits.**

***Section 4.2.1 – Reasons for Withdrawal/Discontinuation***

…

A patient may be withdrawn from the study for any of the following reasons:

…

- **For Cohort 3 only, unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart)**

***Section 5.1 - Method of Assigning Patients to Treatment Groups***

This is an open-label study that will be conducted in 2 parts. In both parts, NC-6004 will be administered as a 1-hour **(+10-minute window)** intravenous infusion on Day 1 of each cycle. Gemcitabine 1250 mg/m$^2$ will be administered as a 30-minute intravenous infusion on Day 1

of each cycle (after the administration of NC-6004) and on Day 8 of each cycle. The duration of each cycle will be 21 days.

**…**

In Part 2, all patients will receive the RPII dose **(135 mg/m$^2$)** of NC-6004 identified in Part 1. **Bladder cancer patients in Cohort 3 of Part 2 will be stratified by ≥30 to <60 mL/min and/or ECOG PS 2 (unfit) and ≥60 mL/min and ECOG PS 0 to 1 (fit). If 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort.**

***Section 5.2 – Prophylactic Treatments***

All patients will receive the following medications before administration of NC-6004 on Day 1 of each cycle:

…

- Patients will be given 50 mg of ranitidine intravenously **or 20 mg famotidine intravenously** 30 minutes before the start of NC-6004 infusion on Day 1 of each cycle.

***Section 5.3 - Treatments Administered***

The duration of each treatment cycle will be 21 days in both parts of the study. NC-6004 will be administered on Day 1 of each cycle as a 1-hour **(+10-minute window)** intravenous infusion.

…

In Part 2, on Day 1 of each cycle, all patients will receive NC-6004 at the RPII dose **(135 mg/m$^2$)** identified in Part 1 and 1250 mg/m$^2$ gemcitabine. On Day 8 of each cycle, all patients in Part 2 of the study will receive 1250 mg/m$^2$ gemcitabine.

***Section 5.4 - Dose Delays and Modifications***

**The doses for NC-6004 and gemcitabine will be calculated in milligrams per square meter (mg/m$^2$) at screening, and will not be changed in subsequent cycles unless the**

**patient's body weight has increased or decreased by ≥10% from the patient's weight measurement at screening. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs (*Note:* This threshold should not be confused with a change of a patient's body surface area [BSA] [$m^2$]). Weight will be measured before treatments on Day 1 of each cycle, with calculation of BSA before dosing on Day 1 of each cycle (using the Mosteller formula [Mosteller 1987]).**

Patients experiencing significant toxicities must be immediately and permanently withdrawn from treatment with NC-6004 and gemcitabine as follows:

- Any patient who experiences a Grade 3 or 4 hypersensitivity reaction during any cycle of treatment
- Any patient who experiences 2 protocol-defined DLTs during treatment
- Any patient who experiences a recurrent Grade 3 or 4 toxicity **(recurrence of the same AE)** after a dose reduction

***Section 5.4.1 – NC-6004 Dose Delays and Modifications***

…

Following recovery to Grade 1 or lower, treatment may resume at the investigator's discretion. Patients who resume treatment following a dose delay will have the dose of study drug reduced by 50% for the remainder of study treatment. If toxicities persist or recur to Grade 3 or 4 **(recurrence of the same AE)** after the dose reduction, study treatment will be terminated.

***Section 5.5.2 - Gemcitabine Drug Product***

Gemzar® (gemcitabine for injection, USP), is available in sterile single-use vials individually packaged in a carton containing: 200 mg white to off-white, lyophilized powder in a 10-mL size sterile single-use vial or 1 g white to off-white, lyophilized powder in a 50-mL size sterile single-use vial. Vials of **gemcitabine**~~Gemzar~~ contain either 200 mg or 1 g of gemcitabine hydrochloride (expressed as free base) formulated with mannitol (200 mg or 1 g, respectively) and sodium acetate (12.5 mg or 62.5 mg, respectively) as a sterile lyophilized powder. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

***Section 5.6.1 - Study Drug Packaging and Storage***

All study drugs must be stored in a secure area (eg, a locked cabinet). NC-6004 should be protected from light and stored refrigerated (2° to 8°C). Unopened vials of ~~Gemzar~~ ~~(~~gemcitabine~~)~~ are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C that allows for excursions between 15° and 30°C.

***Section 5.6.2 – Test Article Accountability***

The investigator will maintain accurate records of receipt of all test articles **that are centrally provided**, including dates of receipt.

***Section 5.8 – Prophylaxis and Management of Hypersensitivity Reactions***

All patients must receive the following prophylactic treatment at each cycle to reduce the risk of hypersensitivity reactions:

…

- Diphenhydramine hydrochloride 50 mg and **either** ranitidine 50 mg **or 20 mg famotidine** will be administered intravenously 30 minutes before the infusion of NC-6004.

**…**

If a Grade 1 or Grade 2 hypersensitivity occurs in a patient, the following medications should be administered for 48 hours after NC-6004 infusion:

- Ranitidine 150 mg orally given 2 times per day **or 20 mg famotidine given intravenously once per day**

***Section 6.1 – Efficacy Assessments***

…

Symptom changes will be assessed using the core MDASI **(Part 1 only)** or MDASI-LC (only in patients with NSCLC in Part 1) (Section 6.1.3) on Days 1 and 8 of each cycle and at the End-of-Treatment visit.

***Section 6.1.1 – Disease Response Definitions***

…

The rate of confirmed response and tumor growth control will be determined according to RECIST version 1.1 in solid tumor patients for patients evaluable for response **using the following imaging methods:**

**Timing**

**Disease assessment will occur at Screening and every 6 weeks (±1 week) until disease progression. Patients who have obtained a response (PR or CR) will have a confirmatory scan at a minimum of 4 weeks following the initial scan.**

**Anatomic Coverage**

**Imaging should include a computed tomography scan of the chest, abdomen, and pelvis. In addition, areas of known predisposition for metastases (eg, the brain for NSCLC) and any areas identified by the clinician as probable sites of metastasis based on clinical evaluation should be included in imaging if clinically indicated. Other imaging may be performed at the investigator's discretion as standard of care.**

**Imaging Method**

**The preferred method for imaging is computed tomography with IV contrast. If the patient is allergic to contrast media or has another medical contraindication, magnetic resonance imaging with contrast can be used at the clinician's discretion.** ***It is critical that the same method of imaging is used throughout the study for a given patient.***

**Slice Thickness**

**The preferred slice thickness is 5 mm. If a larger slice thickness is used (eg, 7 mm), the smallest tumor measurement that can be reported is twice the thickness of the slice.**

~~The ORR, DCR, and DOR will be determined immediately prior to the initiation of maintenance therapy. The OS and PFS will be determined at the end of the study for evaluable patients without censoring at the initiation of maintenance therapy. Patients who have obtained a response (PR or CR) will have a confirmatory scan at a minimum of 4 weeks following the initial scan.~~

***Section 6.1.3 – MD Anderson Symptom Inventory***

…

The core MDASI and the MDASI-LC will be administered as a self-report paper-and-pencil form given to the patient at the site before study treatments on Days 1 and 8 of each cycle in Part 1 only ~~(as described in Study Manual)~~.

***Section 6.2 - Pharmacokinetic and Pharmacodynamic Assessments***

…

Pharmacokinetics blood sampling should occur within 10% of nominal time for Days 1 and 2, ~~and~~ ±4 hours of nominal time for all other time points, **and should occur within 10 minutes after the 12-lead ECGs performance at time-matched visits (Section 6.3.6).** All PK samples will be evaluable as long as the actual collection times are recorded.

***Section 6.3.1.1 – Definition of Dose-Limiting Toxicities***

A DLT **(monitored in Part 1 only)** is defined as the following treatment-related AEs or laboratory abnormalities, graded according to the NCI CTCAE version 4.03:

***Section 6.3.1.2.1 - Safety Monitoring in Part 2***

During Part 2 of the study, patients treated with NC-6004 at the RPII dose from Part 1 will be monitored for safety. Dose delay and modification rules for both NC-6004 and gemcitabine apply in Part 2 as in Part 1.

**In Part 2 (Cohort 3), if 2 of 6 patients (or ≥33% at any point during the study) in the ≥30 to <60 mL/min group have a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart), then enrollment of patients with CrCl <60 mL/min will stop in the bladder cancer cohort. In addition, in Part 2 (Cohort 3), if an unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart) he or she may be withdrawn from the study (Section 4.2.1).**

***Section 6.3.2.3 – Reporting Adverse Events***

…

Any AE that meets SAE criteria (Section 6.3.2.1) must be reported to PPD immediately (ie, within 24 hours after the time site personnel first learn about the event).~~The following contact information is to be used for SAE reporting;~~ **The event is reported via the electronic data capture (EDC) system where site personnel complete as much of the respective AE page (eCRF) as they are able.**

**If the EDC system is unavailable, the AE information must be recorded on the manual SAE report form and immediately (ie, within 24 hours of awareness) sent to PPD by one of the following methods (refer to the "SAE Guidelines" document for WorldReach toll-free access numbers if necessary):**

Pharmacovigilance Department

**United States** SAE Hotline: **+1** 800-201-8725

**United States** SAE Fax line: **+1** 888-488-9697

**Europe SAE Hotline:** **+44 1223 374 240 (to be used for questions concerning SAEs)**

**Europe SAE Fax line:** **+44 1223 374 102 (to be used for reporting SAEs)**

**Once the EDC system becomes available again, the site needs to transfer all data to the respective eCRF page of the patient.**

***Section 6.3.2.5 - Assessment of Causality***

The investigator's assessment of an AE's relationship to study drug **(combination of NC-6004 and gemcitabine)** is part of the documentation process, but it is not a factor in determining what is or is not reported in the study. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

***Section 6.3.3 - Assessment of Nausea and Vomiting***

…

**For Parts 1 and 2, e**~~E~~ach patient will be given a nausea and vomiting patient diary to take home. This diary will be used to record the severity of nausea and incidence of emetic episodes over the previous 24 hours daily on Days 2 through 21. **The first 7 days of the diary will be recorded verbatim in the eCRF. The patient will be given the diary and instructed on how and when to complete the diary before discharge from the site on Day 1 of each cycle.**

**Part 1:** The investigator will collect the **nausea and vomiting patient diary from each patient** ~~diaries~~ on Day 8 **and** Day 15 **for Cycle 1. For all subsequent cycles, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle), Day 8, and Day 15** ~~(Part 1 only), and Day 22. The first 7 days of the diary will be recorded verbatim in the eCRF.~~ The investigator will record the worst severity of the patient's nausea and the total number of emetic episodes occurring over the previous 7 days in the eCRF for Day 8 , Day 15, and Day 21. ~~The patient will be given the diary and instructed on how and when to complete the diary before discharge from the site on Day 1 of each cycle. The patient must return the diary to the site on Day 8, Day 15 (Part 1 only), and Day 22 (Day 1 of the next cycle) of each cycle.~~

**Part 2: The investigator will collect the nausea and vomiting patient diary from each patient at the site on Day 8 for Cycle 1. For Cycle 2, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle) and Day 8. Note that nausea and vomiting patient diaries will not be collected past Cycle 2. The investigator will record the worst severity of the patient's nausea and the total number of emetic episodes occurring over the previous 7 days in the eCRF for Day 8 and Day 21.**

***Section 6.3.5 – Clinical Laboratory Analyses***

…

~~Any~~ **Only** abnormal laboratory test results (hematology, biochemistry, or urinalysis) **that are deemed clinically significant by the PI will** ~~are to~~ be recorded as AEs or SAEs per the NCI CTCAE version 4.03.

***Section 6.3.5.3 – Urinalysis***

Urinalysis will be performed ~~using a dipstick test~~ and will include: leukocyte esterase, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose.

***Section 6.3.6 – Electrocardiograms***

All 12-lead ECGs will be performed after the patient has **adequately** rested in the supine position ~~for at least 5 minutes~~.

**A 12-lead ECG will be performed during the screening period at Day -7 to -1.** On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 hours (Day 2) after start of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the completion of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will also be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion and at the End-of-Treatment visit. **All 12-lead ECGs should be performed within a ±30-minute window.**

***Section 6.3.7 - Physical Examination***

A complete physical examination will be performed during the screening period at Day -14 to -1, before study treatments on Day –1 or Day 1 of each cycle, and at the End-of-Treatment visit. Height and weight will also be assessed at the time of the screening period physical examination and before treatments on Day 1 of each cycle**.** ~~with~~ **Calculation of BSA will be done before each dosing on Day 1 of each cycle (using the Mosteller formula [Mosteller 1987]. (*Note:* Dose will only be recalculated if there is a ≥10% increase or decrease in the patient's weight from the patient's weight measurement at screening. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs. This threshold should not be confused with a change of a patient's BSA [$m^2$]).**

***Section 6.3.8 - Vital Sign Measurements***

Vital sign measurements will include arterial blood pressure, heart rate, respiratory rate, and temperature. Vital signs will be measured after the patient has **adequately** rested in the supine position ~~for at least 5 minutes~~.

…

**Vital signs will also be measured at the End-of-Treatment visit.**

***Section 7.3 - Sample Size Calculations***

This is a Phase 1b/2 study with an overall sample size of up to ~~199~~ **209** patients (up to 49 patients in Part 1 and up to ~~150~~**160** patients in Part 2). The total sample size will depend on the number of cohorts required to establish an RPII dose and the number of patients with NSCLC enrolled at the RPII dose in Part 1.

…

Part 2 is a 3-cohort study with an overall sample size of up to ~~150~~ **160** patients with no more than 50 patients ~~per cohort~~ **each** **in Cohorts 1 and 2 and no more than 60 patients in Cohort 3 (30 unfit and 30 fit bladder cancer patients)**. The total sample size will depend on the results of interim futility and superiority analyses. In order to evaluate the overall sample size, simulations were performed assuming scenarios with different HRs for PFS for each cohort compared with historical control and different sample sizes for a subsequent Phase 3 clinical trial. The associated mean sample size for this trial in these scenarios ranged from **92.7**~~136~~ to **116.8** ~~146~~ patients.

***Section 10.2.2 - Protocol Violations and Deviations***

…

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the IRB/IEC and agreed to by the investigator. A significant deviation occurs when there is nonadherence to the protocol by the patient or investigator that results in a significant, additional risk to the patient. Significant deviations can include nonadherence to inclusion or exclusion criteria, ~~enrollment of the~~

~~patient without prior sponsor approval,~~ or nonadherence to FDA regulations or ICH GCP guidelines, and will lead to the patient being withdrawn from the study (Section 4.2).

***Section 11 - Reference List***

…

**Mosteller RD. Simplified calculation of body-surface area. N Engl J Med. 1987;317(17):1098.**

***Section 12.1 - Appendix: Schedule of Events***

**Table 12-1 Schedule of Events**

| Procedure | Screening | | | Cycle 1 | | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | **Day 2** | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Informed consent | X | | | | | | | | | | | | | | | | | |
| Eligibility criteria | | X | | | | | | | | | | | | | | | | |
| Demography | | X | | | | | | | | | | | | | | | | |
| Medical history | | X | | | | | | | | | | | | | | | | |
| Pregnancy test (serum or urine) | | | X | X[e] | | | | **X** | | | **X** | | | **X** | | | **X** | |
| Physical examination | | X[f] | | X[f] | | | | X | | | X | | | X | | | X | |
| Height, weight, and BSA calculation[g] | | X[g] | | X | | | | X | | | X | | | X | | | | |
| Vital signs[h] | | X | | X[h] | | X | | X | X | | X | X | | X | X | | X | |
| Performance status (ECOG) | | X[f] | | X[f] | | | | X | | | X | | | X | | | X | |
| Disease assessment[i] | X | | | | | | | | | | X[i] | | | X[i] | | | X | X |
| Audiometry | | X | | X[j] | | | | X[j] | | | X[j] | | | X[j] | | | X[j] | |
| Hematology | | | X | X[k] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Biochemistry | | | X | X[k] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| Urinalysis ~~(dipstick)~~ | | X | | | | | | | | | | | | | | | X | |
| EORTC QLQ-C30 | | | | X | | X | | X | X | | X | X | | X | X | | X | |
| MDASI or MDASI-LC[l] | | | | X | | X | | X | X | | X | X | | X | X | | X | |
| **Part 1:** Nausea and vomiting patient diary[m] | | | | X | | X | X | X | X | X | X | X | X | X | X | X | | |
| Part 2 Nausea and vomiting patient diary[m] | | | | X | | X | | X | X | | | | | | | | | |
| Cardiac risk factors | | X | | | | | | | | | | | | | | | | |
| 12-lead ECG[n] | | | X | X | **X** | X | | X | | | X | | | | | | X | |
| Pharmacokinetic assessments (Part 1)[o] | | | | X | **X** | X | X | X | | | X | X[o] | X[o] | | | | X | |
| Pharmacokinetic assessments (Part 2)[p] | | | | X | | X | | X | X | | X | X | | | | | X | |
| Adverse events | | | | X[f] | **X** | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Concomitant medication | | X[f] | | X[f] | **X** | X | X | X | X | X | X | X | X | X | X | X | X | X[c] |

| Procedure | Screening | | | Cycle 1 | | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | **Day 2** | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| Prophylactic administrations | | | | X | | | | X | | | X | | | X | | | | |
| NC-6004 administration[a] | | | | X | | | | X | | | X | | | X | | | | |
| Gemcitabine administration | | | | X | | X | | X | X | | X | X | | X | X | | | |

Abbreviations: BSA, body surface area; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; MDASI, MD Anderson Symptom Inventory; RECIST, Response Evaluation Criteria in Solid Tumors; MDASI-LC, MDASI-lung cancer.

a. In Part 1 of the study, patients will receive treatment until progressive disease. In Part 2 of the study, patients will receive treatment for 6 cycles (Cohorts 1 and 3) or 8 cycles (Cohort 2).

b. End-of-treatment assessments will be performed within 28 days after treatment discontinuation.

c. After patient discontinuation or completion of treatment without disease progression, patients will be followed with scans every 9 weeks until disease progression. Patients will be called every 12 (±1) weeks to collect data on patient survival, new treatments, and adverse events.

d. Day 15 visit is required in Part 1. In Part 2, Day 15 visit is only necessary if it is clinically indicated.

e. Not required if screening pregnancy test was performed using serum.

f. Safety assessments of physical examination, ECOG, review of adverse events, and concomitant medication use can be completed on Day -1 to allow for early morning dosing. These should not be conducted in place of screening assessments.

**g. From Day -14 to -1 at screening, only height and weight will be measured. On Day 1 of each cycle, weight will be measured before treatments and BSA will be calculated before each dose using the Mosteller formula (Mosteller 1987). (Note: Dose will only be recalculated if there is a ≥10% increase or decrease in the patient's weight from the patient's screening weight measurement. Any change in a patient's weight by ≥10% during the study will require a recalculation of the doses of all study drugs. This threshold should not be confused with a change in the patient's BSA [$m^2$]).**

~~g. Height and weight only.~~

~~h.~~ Vital signs will be measured after the patient has **adequately** rested in the supine position ~~for at least 5 minutes~~. On Day 1 of Cycle 1, vital signs will be measured before the start of the NC-6004 infusion, every 20 minutes during the infusion, at the completion of the infusion, and 1 hour after the completion of the NC-6004 infusion. Starting in Cycle 2, vital signs will be measured before the start of the NC-6004 infusion and at the completion of the NC-6004 infusion on Day 1 of each cycle. Vital signs will be measured before and after gemcitabine infusion on Day 8 of each cycle. **Vital signs will also be measured at the End-of-Treatment visit.**

~~i.~~ Disease assessment will be performed using RECIST version 1.1 and the same imaging method used at screening should be used for all subsequent assessments. Beginning in Cycle 3 and continuing through the remainder of the treatment cycles, disease will be assessed every 6 (±1) weeks (ie, every other cycle) and at the End of Treatment visit or until disease progression. Patients who have obtained a partial response or complete response will have a confirmatory scan at a minimum of 4 weeks following the initial scan.

~~j.~~ To be performed only as clinically indicated.

~~k.~~ Hematology and biochemistry tests will be repeated prior to dosing on Day 1 of Cycle 1 if they were last performed more than 24 hours before the start of the study drug administration.

~~l.~~ Symptom changes will be assessed using the core MDASI **(Part 1 only)** or MDASI-LC (only in patients with NSCLC in Part 1).

~~m.~~ **Part 1: The investigator will collect the nausea and vomiting patient diary from each patient on Day 8 and Day 15 for Cycle 1. For all subsequent cycles, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle), Day 8, and Day 15. Part 2: The investigator will collect the nausea and vomiting patient diary from each patient at the site on Day 8 for Cycle 1. For Cycle 2, the investigator will collect diaries on Day 1 (prior to dosing to capture the last 7 days of the previous cycle) and Day 8. Note that nausea and vomiting patient diaries will not be collected past Cycle 2. For additional details, see Section 6.3.3.** ~~Diary issued on Day 1 of each cycle. Assessment is performed at the site before dosing on Day 1 and Day 8 as well as Day 15 (Day 15 diary collected in Part 1 only; note: no dosing on Day 15) of each cycle. Patient completes diary at home on Days 2 through 8 and returns diary on Day 8.~~

~~n.~~ Twelve-lead ECGs will be performed after the patient has **adequately** rested in the supine position ~~for at least 5 minutes~~. **A 12-lead ECG will be performed during the screening period at Day –7 to –1.** On Day 1 of Cycle 1, 12-lead ECGs will be performed before the start of the NC-6004 infusion, at completion of infusion (~1 hour after start of infusion), and at Hours 3 and 24 (Day 2) after the start of infusion. On Day 8 of Cycle 1, 12-lead ECGs will be performed before the start of gemcitabine infusion, at the end of gemcitabine infusion, and at 1 hour after completion of gemcitabine infusion. Twelve-lead ECGs will be performed on Day 1 of Cycles 2 through 6 before the start of the NC-6004 infusion, and at the End-of Treatment visit. **All 12-lead ECGs should be performed within a ±30-minute window.**

~~n.~~**o.** For Part 1, blood samples will be collected at the following times: before the start of the NC-6004 infusion on Day 1 of Cycles 1 through 6, at end of NC-6004 infusion in Cycles 1, 3, and 5, after the **start** of NC-6004 infusion at Hours 3, 6, 12, 24 (Day 2), 48 (Day 3), 96 (Day 5), 168 ~~and~~ **(Day 8,** prior to gemcitabine infusion ~~(Day 8)~~, and 336 (Day 15) in Cycles 1, 3, and 5, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed. **Blood samples will be collected within 10 minutes after the 12-lead ECGs performance.**

~~o.~~**p.** For Part 2 (up to 6 cycles), on the day of NC-6004 infusion for each cycle, blood samples will be collected before the start of the NC-6004 infusion, at the end of the NC-6004 infusion, before gemcitabine infusion on Day 8, and at the End-of-Treatment visit. Additional pharmacokinetic blood sample collections may be performed, at the discretion of the investigator, during any visit where toxicity is observed. **Blood samples will be collected within 10 minutes after the 12-lead ECGs performance.**

### 12.4.7 Protocol Amendment 4-Protocol Version 5.0, Incorporating Amendment 3-Version 4.2 (dated 12 December 2016)

The following sections detail the changes made to Protocol Amendment 3-Version 4.2 (dated 12 December 2016). The integrated protocol, Version 5.0, including Amendment 4, was issued on 13 March 2017.

#### 12.4.7.1 Risk Assessment for Amendment 4, Version 5.0

No anticipated increased patient risk has been introduced with the updates made during this protocol amendment. Detailed management guidelines for NC-6004-related liver dysfunction have been added in Section 6.3.2.7.

#### 12.4.7.2 Overview of Changes

The overview of significant changes includes the following. (Note that minor word changes and copyedits are not identified). Global changes for Protocol Amendment 4, Version 5.0 include the following changes resulting from FDA feedback on IND 118108:

- Revised the entry criteria to require baseline alanine transaminase and aspartate transaminase <2.0 × ULN or, in patients with documented hepatic metastasis <5.0 × ULN and also serum albumin ≥3.5 g/dL, and prothrombin time within normal limits.

- Revised the entry criteria (Part 2 only) Cohort 1 to require that patients histologically or cytologically confirmed diagnosis of Stage IV squamous NSCLC and have not received prior chemotherapy or immunotherapy for metastatic disease and are not known to be PD-L1 positive (known high PD-L1 expression defined as Tumor Proportion Score [TPS] greater than or equal to 50%).

- Added a criterion to exclude patients with known active hepatitis B (defined as a known positive HBsAg result) or hepatitis C (defined by a known positive hepatitis C antibody result and known quantitative HCV RNA results greater than the lower limits of detection of the assay).

- Revised Section 5.4.1 NC-6004 Dose Delay and Modification to hold NC-6004 in the event of a Grade 3 liver enzyme elevation until return to Grade ≤1. NC-6004 to be immediately and permanently discontinued for Grade 4 liver enzyme elevation.

- Revised the protocol to include a section with detailed management guidelines for NC-6004-related liver dysfunction.

### 12.4.7.3 Changes to the Protocol Text

In this section, all affected protocol sections are detailed; the sequence of the sections follows the structure of the original protocol. Additions to the protocol text are shown in bold and deletions are shown in strikethrough text. Minor or obvious editorial and grammatical corrections are not described.

***Protocol Synopsis – Inclusion Criteria***

Inclusion Criterion 2 (Cohort 1) was revised:

2. (Part 2 only) Cohort 1: Have histologically or cytologically confirmed diagnosis of Stage IV squamous NSCLC and have not received prior chemotherapy **or immunotherapy** for metastatic disease **and are not known to be PD-L1 positive (known high PD-L1 expression defined as Tumor Proportion Score [TPS] greater than or equal to 50%).** Patients with known sensitizing mutation in the epidermal growth factor receptor (EGFR) gene or anaplastic lymphoma kinase (ALK) fusion oncogene must have received at least 1 and up to 2 targeted therapies prior to enrollment.

Inclusion Criterion 7 was revised:

7. Have adequate liver function defined as:

   - Total serum bilirubin <1.5 × upper limit of normal (ULN) and

   - **Baseline** ~~A~~alanine transaminase, **and** aspartate transaminase <2.~~5~~0 × ULN or, in patients with documented hepatic metastasis ≤ **<**5.0 × ULN and

   - **Serum albumin ≥3.5 g/dL**

Inclusion criterion 8 was added:

8. **Prothrombin time within normal limits**

***Protocol Synopsis – Exclusion Criteria***

**…**

Exclusion Criterion 9 was added:

9. **Have known active hepatitis B (defined as a known positive hepatitis B surface antigen [HBsAg] result) or hepatitis C (defined by a known positive hepatitis C antibody result and known quantitative HCV RNA results greater than the lower limits of detection of the assay).**

***Protocol Synopsis – Estimated Study Duration***

…

Part 2 of the study will include a screening period (up to 28 days); 6 treatment cycles (Cohorts 1 and 3) or 8 treatment cycles (Cohort 2) that are 21 days in duration; tumor assessments for response and disease progression with scans every 6 weeks; and telephone calls for survival every 12 weeks.

Patients will receive study treatment until any of the following occur:

…

- **Grade 4 liver enzyme elevation**

***Protocol Synopsis – Safety Assessments***

…

Hematology **and coagulation** and biochemistry tests will be performed at screening and on Days 1, 8, and 15 of each cycle (before any study drug infusions), and at the End of Treatment visit. Urinalyses will be performed at screening and at the End of Treatment visit.

***Section 3.1 – Study Design***

…

**Screening Period (Day -7 to -1)**

The following procedures will be performed during the screening period within 7 days prior to the first study treatment:

**…**

- Hematology **and coagulation**

…

**Day 1 of Cycle**

The following procedures will be performed on Day 1 prior to NC-6004 infusion in each treatment cycles unless otherwise specified:

…

- Hematology **and coagulation**

**Day 8 of Each Cycle**

The following procedures will be performed on Day 8 prior to gemcitabine infusion in each treatment cycle:

…

- Hematology **and coagulation**

…

**Day 15 of Each Cycle (Part 1: required; Part 2: if clinically indicated)**

The following procedures will be performed on Day 15 in each treatment cycle:

- Hematology **and coagulation**

…

**End-of-Treatment Visit**

The following procedures will be performed within 28 days after treatment discontinuation:

…

- Hematology **and coagulation**

***Section 4.1.1 – Inclusion Criteria***

Inclusion Criterion 2 (Cohort 1) was revised:

2. (Part 2 only) Cohort 1: Have histologically or cytologically confirmed diagnosis of Stage IV squamous NSCLC and have not received prior chemotherapy **or immunotherapy** for metastatic disease **and are not known to be PD-L1 positive (known high PD-L1 expression defined as Tumor Proportion Score [TPS] greater than or equal to 50%).** Patients with known sensitizing mutation in the epidermal growth factor receptor (EGFR) gene or anaplastic lymphoma kinase (ALK) fusion oncogene must have received at least 1 and up to 2 targeted therapies prior to enrollment.

Inclusion Criterion 7 was revised:

7. Have adequate liver function defined as:

   - Total serum bilirubin <1.5 × upper limit of normal (ULN) and
   - **Baseline** ~~A~~alanine transaminase, **and** aspartate transaminase <2.~~5~~0 × ULN or, in patients with documented hepatic metastasis ≤ **<**5.0 × ULN and
   - **Serum albumin ≥3.5 g/dL**

Inclusion criterion 8 was added:

9. **Prothrombin time within normal limits**

***Section 4.1.2 – Exclusion Criteria***

**…**

Exclusion Criterion 9 was added:

**9. Have known active hepatitis B (defined as a known positive hepatitis B surface antigen [HBsAg] result) or hepatitis C (defined by a known positive hepatitis C antibody result and known quantitative HCV RNA results greater than the lower limits of detection of the assay).**

***Section 4.2.1 – Reasons for Withdrawal/Discontinuation***

**…**

A patient may be withdrawn from the study for any of the following reasons:

- Disease progression
- Unacceptable toxicity experienced
- **Grade 4 liver enzyme elevation**
- Withdrawal of consent
- Major protocol violation
- Required treatment delay >14 days (except in case of potential patient benefit, which must be approved by the sponsor)
- Symptoms or an intercurrent illness not consistent with the protocol requirements or that justifies withdrawal
- For Cohort 3 only, unfit bladder cancer patient (≥30 to <60 mL/min CrCl at screening) has a worsening of CrCl (ie, 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart)
- Lost to follow-up
- Other (eg, pregnancy, development of contraindications of use of the study drug)

- The investigator or sponsor determines it is in the best interest of the patient to discontinue the patient's participation in the study.

***Section 5.4 - Dose Delays and Modifications***

**…**

- Any patient who experiences a Grade 3 or 4 hypersensitivity reaction during any cycle of treatment.

- Any patient who experiences 2 protocol-defined DLTs during treatment.

- Any patient who experiences a recurrent Grade 3 or 4 toxicity (recurrence of the same AE) after a dose reduction.

- Any patient who requires a dosing delay >14 days at any time during treatment (except in case of potential patient benefit, which must be approved by the sponsor).

- **Any patient who experiences a Grade 4 liver enzyme elevation.**

***Section 5.4.1 – NC-6004 Dose Delay and Modification***

During any treatment cycle, investigators should suspend further dosing with NC-6004 for up to 14 days after the scheduled dose in the event of a protocol-defined DLT or any Grade 4 hematologic toxicity or Grade 3 or 4 nonhematologic toxicity that is possibly, probably, or definitely related to NC-6004 (excluding alopecia and Grade 3 nausea, vomiting, diarrhea, and electrolyte imbalances lasting less than 48 hours or with suboptimal prophylactic and suboptimal curative treatment). **Any patient experiencing a Grade 3 liver enzyme elevation should have their next dose of NC-6004 suspended until improvement to Grade 1 or lower.** At the discretion of the investigator, the dose may also be delayed for up to 14 days for any toxicity possibly or probably related to NC-6004 that does not meet DLT criteria. A delay of more than 14 days will require the patient to be removed from the study (except in case of potential patient benefit, which must be approved by the sponsor). The toxicity for which the dose was suspended must have improved to Grade 1 or lower prior to NC-6004 infusion.

***Section 5.10 – Prior, Concomitant, and Subsequent Therapy***

(Part 2 only) Cohort 1: For patients with Stage IV NSCLC, they may not have received prior chemotherapy **or immunotherapy** for metastatic disease.

***Section 6.3 – Safety and Tolerability Assessments***

Safety will be assessed using frequent collection of AE reports (Section 6.3.2) and clinical hematology **and coagulation**, biochemistry, and urinalysis test results (Section 6.3.5).

***Section 6.3.2.7 – Management Guidelines for NC 6004-Related Liver Dysfunction***

**At the onset of Grade 4 liver enzyme elevation, NC-6004 must be immediately and permanently discontinued. Patients should be referred promptly to a hepatologist/gastroenterologist/specialist to be further evaluated. Patients with Grade 4 liver enzyme elevation should have a physical examination performed and should be assessed for signs of fever, rash and jaundice. Liver function tests including serum transaminases, alkaline phosphatase, γ-glutamyl transpeptidase, and total bilirubin (including direct and indirect), albumin choline esterase, total cholesterol, as well as hematological tests including prothrombin time (PT), PT/international normalized ratio (INR) and eosinophil count should be performed. Other testing including a serological test may be performed at the hepatologist/gastroenterologist/specialist's discretion. Patients should then be monitored on a bi-weekly basis (or more frequent if indicated by the hepatologist/gastroenterologist/specialist) until improvement to Grade 2 or below and clinical stability. Section 5.4.1 provides details for management of Grade 3 liver enzyme elevation.**

**Section 6.3.5 –** ***Clinical Laboratory Analyses***

Samples for hematology **and coagulation**, biochemistry, and urinalysis will be collected at the time points specified in Appendix 12.1, Schedule of Events.

…

Only abnormal laboratory test results (hematology **and coagulation**, biochemistry, or urinalysis) that are deemed clinically significant by the PI will be recorded as AEs or SAEs per the NCI CTCAE version 4.03.

***Section 6.3.5.1 – Hematology and Coagulation***

Hematology will include hemoglobin, reticulocytes, red blood cell count, differential white blood cell count, **and** platelets~~, and~~**. Coagulation will include prothrombin time and** international normalized ratio. Hematology **and coagulation** tests will be performed during the screening period on Day -7 to -1, prior to dosing on Day 1 of Cycle 1 (if they were last performed more than 24 hours before the start of the study drug administration), weekly at each study visit prior to any treatments, and at the End-of-Treatment visit.

***Section 7.6.2.3 – Clinical Laboratory Results***

Clinical hematology **and coagulation**, biochemistry, and urinalysis data will be summarized at each scheduled assessment. Numeric hematology **and coagulation** and biochemistry results will be summarized using change from baseline.

…

Numeric clinical hematology **and coagulation**, biochemistry, and urinalysis results will be summarized using change from baseline.

## *Table 12-1 – Schedule of Events*

| Procedure | Screening | | | Cycle 1 | | | | Cycle 2 | | | Cycles 3-6 | | | Cycle 7 Onward[a] | | | End-of-Treatment[b] | Follow-up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Day -28 to -1 | Day -14 to -1 | Day -7 to -1 | Day 1 | Day 2 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | Day 1 | Day 8 | Day 15[d] | | |
| … | | | | | | | | | | | | | | | | | | |
| Hematology **and coagulation** | | | X | X[k] | | X | X | X | X | X | X | X | X | X | X | X | X | |
| … | | | | | | | | | | | | | | | | | | |

…

k. Hematology **and coagulation** and biochemistry tests will be repeated prior to dosing on Day 1 of Cycle 1 if they were last performed more than 24 hours before the start of the study drug administration.