NanoCarrier Co, Ltd

NC-6004-004A

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

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Statistical Analysis Plan

Version 2.0

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List of Abbreviations

AE	adverse event
AI	Accumulation Index
ATC	Anatomical Therapeutic Chemical
$AUC_{0-\tau}$	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
CL	clearance
C_{max}	maximum concentration
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DCR	disease control rate
DOR	duration of response
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
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
GCP	Good Clinical Practice
HEENT	head, ears, eyes, nose, throat
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
λ_z	terminal elimination phase rate constant
MDSAI	MD Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
MRT	mean residence time
MTD	Maximum tolerated dose
N-CRM	Bayesian continual reassessment method design per Neuenschwander et al 2008
NCI	National Cancer Institute

NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PK	Pharmacokinetic
PP	per protocol
PPS	per protocol set
PR	partial response
PT	preferred term
Pt	platinum
PVG	Pharmacovigilance
QoL	Quality of Life
QTcB	Corrected QT interval - Bazett's formula
QTcF	Corrected QT interval - Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
$T_{½}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
V_{ss}	volume of distribution at steady-state
V_z	volume of distribution
WHO	World Health Organization

1. Introduction

In general, the purpose of the Statistical Analysis Plan (SAP) is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose: to prospectively (a priori) outline the types of analyses and data presentations that will addresses the study objectives outlined in the protocol, and to explain in detail how the data will be handled and analyzed, adhering to commonly accepted standards and practices of biostatistical analysis in the pharmaceutical industry. This document details the planned statistical methodology for data collected in the study NC-6004-004A based on protocol amendment 4.0.

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 and so on. 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. 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. 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. In 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 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.

2. 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) , maximum tolerated dose (MTD), and Recommended Phase II (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 overall response rate (ORR), disease control rate (DCR=complete response [CR] + partial response [PR] + stable disease [SD]), duration of response (DOR), progression-free survival (PFS), and overall survival (OS)

- To evaluate therapy-related adverse events (AEs)

- The evaluate the safety and tolerability of NC-6004 when combined with Gemcitabine

- To evaluate Quality of Life (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 (MDSAI) and a nausea and vomiting patient diary

2.3. Exploratory Objectives

The exploratory objectives of this study are:

- To assess the Pharmacokinetic (PK) and pharmacodynamic effects of NC-6004

3. Investigational Plan

3.1. Overall Study Design and Plan

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 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.

A Bayesian continual-reassessment method per Neuenschwander et al 2008 (N-CRM) model will be used for dose escalation and determination of MTD. N-CRM classifies the probability of a DLT (p) into four 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: $p \in (0.60, 1.00]$

After each cohort, the posterior distribution of p_i will be summarized for each dose by the four 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 less than a threshold. The 25% target toxicity is chosen.

A two-parameter logistic model is used to model the dose-response relationship.

$$\ln\left(\frac{p_i}{1-p_i}\right) = \ln\alpha + \beta \ln\left(\frac{d_i}{d_r}\right),$$

where p_i is the probability of toxicity at dose level i;

d_i is the dose in mg at level i ;

d_r is the reference dose, which is defined as median dose in this study.

α is the logit of toxicity at the reference dose

β is the parameter to determine the slope of the curve

An uninformative prior is selected. The dose level with the posterior probability of toxicity closest to the target toxicity while controlling the probability of excessive or unacceptable toxicity at 25% will be identified as MTD.

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

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-patient run-in phase at 180 mg/ m^2, the single-patient 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.

Three cohorts of patients are eligible in Part 2 (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. Cohort 3 will stratify patients by creatinine clearance (CrCl) to asses study drug in patients with reduced kidney function (i.e., CrCl of ≥30 to <60 mL/min and/or ECOG PS 2 [unfit] and ≥60 mL/min and ECOG PS 0 to 1 [fit]). Up to 60 patients will be enrolled in Cohort 3 (i.e., 30 unfit and 30 fit bladder cancer patients), so total 160 patients will be enrolled in Part 2. The patients in Cohort 3 of Part 2 will be enrolled in a controlled manner and with the stipulation that enrollment will stop 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 (i.e., 50% reduction from baseline for 2 consecutive assessments, at least 1 week apart).

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.

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 381events.

In Part 1, patients may 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. 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.

After progressive disease (Part 1) or treatment discontinuation due to disease progression (Part 2) is observed, patients will have an End-of-Treatment visit and be contacted for survival every 12 weeks by phone. After 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.

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.

3.2. Treatments

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

3.3. Dose Delay/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.

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 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.

Dose delay and modification for NC-6004 and gemcitabine are discussed in details under protocol section 5.4.1 and 5.4.2 respectively.

4. General Statistical Considerations

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 N-CRM design and DLT incidence. Adverse events (AE) and SAEs (Serious Adverse Event) 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 (Section 4.3) and grade per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Overall survival (OS), progression free survival (PFS), and duration of response (DOR) will be summarized using Kaplan-Meier methods. Ninety-five percent confidence intervals for overall response rate (ORR) and disease control rate (DCR) will be constructed. All safety analyses will be performed on the safety analysis set. All efficacy analyses will be performed on the full analysis set (FAS). All summaries will present data by dose level, for patients with NSCLC dosed at the MTD, and overall.

4.1. Sample Size

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

4.2. Analysis Set

Four analysis sets will be used in this study:

- The DLT-evaluable analysis set consists of all patients in Part 1 who either experiences 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 Per Protocol Set (PPS) consists of all patients treated at RPII dose in Part 1 or Part 2 who receive study product without major protocol deviation that might impact the efficacy results.
- The PK analysis set will consist of all patients in the safety analysis set who have sufficient concentration data for PK analysis.

4.3. Definition of Baseline Values

Unless otherwise specified, for each safety parameter, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration.

4.4. Bayesian Model for Ongoing Data Analyses

Once 10 PFS events have been observed in each cohort, ongoing data analyses will be performed every 6 weeks using Bayesian models on observed PFS events. The hazard rate λ_c in historical control can be derived from median PFS time 5.5 months and therefore

$$\lambda_c = -\ln(0.5)/5.5 = 0.126 \quad \text{(Vermoken JR, et al)}$$

The estimate of the log hazard ratio θ_d of the hazard rate at RPII dose group over that in the historical control arm is assumed to follow a normal distribution with hierarchal model:

$$\theta_d \sim N(\theta_1, \tau^2)$$

and $\theta_1 \sim N(0,1)$

$$\tau^2 \sim IG((1/2, 11/2))$$

The prior mean μ is assumed 0 and prior ν is assumed as 1 as noninformative distribution for the prior distribution of θ_1 and the prior mean τ_μ and prior weight τ_n are assumed as 1 as noninformative distribution for the prior inverse Gama (IG) distribution of variance τ^2 . The posterior probability of the hazard ratio will be evaluated using Markov Chain Monte Carlo (MCMC) with individual parameters updated based on the data available at the time of the update.

These algorithms will be implemented in FACTS with time to event endpoints for interim and final analyses.

At each interim and the final analysis, there are three possible outcomes: Futility, Success and Inconclusive. These outcomes will be determined based on posterior probability of promising HR and phase III success as mentioned above. For Promising HR, the posterior probability of HR < 0.85 will be derived given 10 PFS events observed. For Phase III success, the posterior probability of HR < 0.75 will be derived given 381 PFS events observed.

5. Patient Disposition and Protocol Deviations

Patient disposition will be summarized for all enrolled and will include the number and percentage of patients in the DLT-evaluable, Safety, FAS and PK analysis sets as well as those patients who have completed or discontinued as well as reasons for discontinuation/withdrawal.

A deviation from the protocol is an unintended or unanticipated departure from the procedures or processes approved by the sponsor and the Institutional Review Board (IRB)/ Independent Ethics Committee (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 Food and Drug Administration (FDA)

regulations or International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and will lead to the patient being withdrawn from the study. Protocol violations and deviations will be displayed in a listing for Phase I and II patients and summarized in a table for Phase II patients.

6. Demographics and Baseline Characteristics

6.1. Demographics

Baseline demographics will be summarized for all patients in the safety population. Baseline demographic data to be evaluated will include age, sex, ethnicity, race, height and weight. Age will be calculated as the integer part of (Informed Consent Date - Birth Date + 1)/365.25. Age will also be displayed in categories of 18-65 and > 65 years. Summary statistics will be presented for continuous variables age, height, and weight by cohort and overall. Categorical variables ethnicity, race, age category and gender will be summarized by cohort and overall. No inferential statistics will be generated. All demographic and baseline characteristic data will be listed for each patient in safety population.

6.2. Inclusion/Exclusion Criteria

All inclusion/exclusion information (inclusion and exclusion criteria are detailed in section 4.1.1 and 4.1.2 of the protocol) on enrolled patients (patients who provide signed written informed consent) will be included in a by-patient listing. The listing will include whether all criteria were satisfied. For patients who did not satisfy the criteria, the criteria number will be listed with the deviation, along with whether an exception was obtained. Patient pregnancy test results will be included in a separate by-patient listing.

6.3. Medical History

6.3.1. General Medical History

Medical history will be presented in a data listing for each patient for all Safety population. A summary table of medical history by body system code and preferred term will also be provided for all Safety population in phase II patients with at least one event under each body system code (SOC) and preferred term (PT) using version 18.0 or later of the Medical Dictionary for Regulatory Activities (MedDRA).

6.3.2. Prior Treatments

Prior chemotherapy, prior radiation and prior surgery will be presented in separate listings. Number and percentage of patients with at least one prior chemotherapy, prior radiation, and surgical procedure will be summarized for phase II patients. Number of regimens and prior surgery types will also be summarized in the table.

7. Treatments and Medications

7.1. Prior and Concomitant Medications

If a medication ended before the start of the treatment, this medication is categorized as prior medication; if a medication started between the first dose date and 28 days after the last dosing date, it will be categorized as concomitant medication; if the medication range brackets the treatment start date, it is categorized as both. All medications will be mapped to preferred terms according to the World Health Organization (WHO) drug dictionary, version 01-Jun-2016 or the latest version. The number and percentage of patients in the safety population of phase II patients taking prior and concomitant medications will be tabulated by Anatomical Therapeutic Chemical (ATC) classification system and WHO drug preferred term. At each level of summarization, a patient is counted only once if she/he reported one or more medication. Concomitant medications and procedures will be presented in separate by-patient listings. If the start or end date of concomitant medications is missing, it will be imputed as shown in Appendix D.

7.2. Study Treatments

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. In Part 2, all patients will receive the RPII dose (135 mg/ m^2) of NC-6004 identified in Part 1.

Table for exposure and compliance will be produced separately for NC6004 and gemcitabine. Duration of exposure in days, total number of infusions given, total dose received (mg/m2), relative dose intensity, and number of patients dosed by cycle will be summarized for all patients in the safety analysis set. The number of patients who had dose(s) interrupted or incomplete and their reasons will be summarized. Patient listing of study treatment compliance will be provided as relative dose intensity.

Total actual dose received (mg) is calculated as sum of the actual dose (mg) received for each drug.

Total number of infusions given is defined as sum of number of the actual infusions given for each drug.

Duration of exposure is defined as the total number of days a patient was exposed to the study drug. It will be calculated as (last dose date – first dose date + 1), where the first dose date is assumed to be cycle 1 day 1 for each drug.

The exposure information will be summarized by treatment groups for each drug separately.

Relative dose intensity = actual dose intensity/planned dose intensity where planned dose intensity = planned dose * number of infusions /duration of exposure (days), actual dose intensity = total actual dose received (mg)/duration of exposure (days). The number of infusions will be the planned number of infusion during the exposure period according to the treatment regimen for each drug. The compliance will be categorized into three groups: <80, 80-120 and >120 %. A patient will be classified as compliant if relative dose intensity falls between 80 and 120, and will be classified as not compliant otherwise. A table with compliance, compliance category and compliant or not will be generated by treatment groups for each drug.

8. Efficacy Analysis

Efficacy assessments include disease response assessments, QoL assessments, and symptom changes assessments. OS, PFS, DOR will be summarized using Kaplan-Meier methods in both summary tables and figures. Ninety five percent confidence intervals for ORR and DCR will be constructed and displayed in the summary tables.
The assessment of QoL will be summarized based on FAS by visit, Changes from baseline for QoL will be summarized by dose level, for all phase I MTD patients and phase II patients by cohort.

All efficacy analyses will be performed on the FAS phase II patients by cohort. All summaries will present data by phase II NSCLC, phase II biliary tract carcinoma patients, phase II bladder cancer patients, phase II bladder cancer patients with CrCl ≥60 mL/min and ECOG PS 0-1; fit and phase II bladder cancer patients with CrCl ≥30 to <60 mL/min and/or ECOG PS 2; unfit.

8.1. Primary Efficacy Endpoint

8.1.1. Progression-Free Survival (PFS)

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. Duration of progression-free survival (PFS) in days is defined as the time between the date of first dose of study drug and the date of the first occurrence of one of the following events:

- Radiological disease progression per RECIST 1.1 as assessed by the investigator
- Clinical/Symptomatic disease progression as assessed by the investigator
- Death due to any cause

For patients who do not experience one of these events by the time of data cutoff, PFS will be right censored at the date of last adequate disease assessment. An adequate disease assessment is a scan where the overall assessment as defined by RECIST 1.1 is not missing and not unable to evaluate. For patients who do not experience disease progression and do not have any adequate post-baseline disease assessments, PFS will be right censored at Day 1. Patients who died or progressed after an extended lost-to-follow-up period will be censored at the date of the last adequate disease assessment prior to the extended loss to follow-up. PFS = Date of event/censoring - date of first dose + 1. The full censoring rules for PFS are included in Table 8-1 below.

Table 8-1: Censoring Conventions for PFS

Situation	Date of Progression or Censoring	Outcome
Disease progression documented at or between scheduled visits within 14 weeks of previous adequate assessment or the first dose date	Date of scan or clinical assessment of progression	Event
Disease progression documented from an assessment after extended lost-to-follow-up (greater than 14 weeks from the previous adequate assessment or the first dose date)	Latest of: ➢ Last adequate disease assessment prior to the extended lost-to-follow-up ➢ The first dose date	Censored
Death due to any cause within 14 weeks of the previous adequate assessment or the first dose date	Date of death	Event

Death due to any cause after an extended lost-to-follow-up time (greater than 14 weeks from the previous adequate assessment or the first dose date)	Latest of: ➢ Last adequate disease assessment prior to the extended lost-to-follow-up ➢ The first dose date	Censored
Treatment discontinuation for toxicity or other reasons without disease progression or prior to disease progression	Latest of: ➢ Last adequate disease assessment ➢ The first dose date	Censored
No death and no disease progression after first dose date	Latest of: ➢ Last adequate disease assessment ➢ The first dose date	Censored
Start a new line of anti-cancer treatment	Latest of: ➢ Last adequate disease assessment ➢ The first dose date	Censored

Sensitivity analysis will be performed based on PPS and additional PFS table will be provided separately by cohort based on PPS.

8.1.2. Overall Survival (OS)

Overall survival (OS) 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. Overall Survival = Date of death (or date of last known alive) - Date of first dose + 1.

8.1.3. Duration of Response (DOR)

Duration of Response (DOR) will be defined as the time between the date of the earliest date of confirmed response (CR or PR) and the date of the first occurrence of one of the following events:

- Radiological disease progression per RECIST 1.1 as assessed by the investigator
- Clinical/Symptomatic disease progression as assessed by the investigator
- Death due to any cause

For patients who do not experience one of these events by the time of data cutoff, DOR will be right censored at the date of last adequate disease assessment. An adequate disease assessment is one with a result that is not missing and not unable to evaluate. For patients who do not experience disease progression and do not have any adequate post-baseline disease assessments, DOR will be right censored at Day 1. 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. DOR = Date of event/censoring - date of the earliest response + 1. The full censoring rules for DOR are included in Table 8-2 below.

Table 8-2: Censoring Conventions for DOR

Situation	Date of Progression or Censoring	Outcome
Progression documented at or between scheduled visits (within 14 weeks of previous adequate assessment or from the first confirmed response date if there is no assessment after the response)	Date of scan or clinical assessment of progression	Event
No Progression till last assessment	Date of last adequate assessment	Censored
Treatment discontinuation for toxicity or other reasons before disease progression.	Date of last adequate assessment	Censored
Death within 14 weeks of previous adequate assessment, or of the first confirmed response date if there is no assessment after the response	Date of death	Event
Death or disease progression after an extended lost-to-follow-up time (greater than 14 weeks from previous adequate assessment or from the first confirmed response date if there is no assessment after the response)	Date of last adequate assessment prior to extended lost-to-follow-up	Censored

8.1.4. Disease Control Rate (DCR)

Disease control rate (DCR) 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.

DCR will be summarized by cohort, two-sided 95% CI will be presented by using the Exact (Clopper-Pearson) method.

8.1.5. Overall Response Rate (ORR)

Overall response rate (ORR) 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.

The best overall response is the best overall response recorded from the start of the treatment until the end of study considering any requirement for confirmation. In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Patients who have obtained a response (PR or CR) will have a confirmatory scan at a minimum of 4 weeks following initial scan. When stable disease (SD) is believed to be the best response, it must be at least 7 weeks first documented evidence of SD until disease progression. Otherwise, the patient's best response depends on the subsequent assessment. The best overall response when confirmation of CR and PR is required is presented in table 8-2.

ORR will be summarized by cohort. The two-sided 95% CI will be presented by using the Exact (Clopper-Pearson) method. Best overall response will also be summarized in this table.

Table 8-3: Best overall response when confirmation of CR and PR required

Overall response first time point	Overall response subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met,

		otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

Source: Eisenhauer EA et al.

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.

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

8.2. Secondary Efficacy Endpoint

8.2.1. Quality of Life Analyses

Quality of Life (QoL) 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 for all phase I MTD patients, by cohort of phase II patients, and overall.

The standard scoring procedures as suggested by the EORTC v3.0 will be followed. All of the scales and single item measures range in score from 0 to 100. A high scale score represents a high response level. For all scales, the Raw Score, RS, is the mean of the component items. Then the functional scales will be calculated as:

Score = (1- (RS-1)/range) x100, and

For symptom scales/items and global health status/QoL:

Score = ((RS-1) /range) x 100.

where range is the difference between the maximum possible value of RS and the minimum possible value.

The calculation of scores and methods to deal with missing data will be handled according to the respective questionnaires' standard scoring guidelines. If at least half of the items from the scale have been answered, use all the items that were completed and apply the standard equations given above: ignore any items with missing values when making the calculations. If less than half of the items from the scale have been answered, set scale score to missing. For single-item measures, set score to missing.

8.2.2. Symptoms Assessment Analyses

The MD Anderson Symptom Inventory (MDASI) core 13 symptom items (pain, fatigue, nausea, disturbed sleep, emotional distress, shortness of breath, lack of appetite, drowsiness, dry month, sadness, vomiting, difficulty remembering, and numbness or tingling) and 6 interference items (general activity, mood, walking ability, normal work, relationship with other people, and enjoyment of life) plus the 3 lung cancer-specific symptom items (MDASI-LC: coughing, constipation and sore throat) will be listed by visit, by dose level for all phase I patients and by cohort of phase II patients.

9. Safety Analysis

Safety evaluations will be based on the incidence, severity, type of adverse events (AEs), clinically significant changes or abnormalities in the patient's clinical laboratory results, vital signs, physical examination, electrocardiogram (ECG), and Eastern Cooperative Oncology Group (ECOG). All safety analyses will be conducted on the Safety analysis set.

9.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient enrolled into this study regardless of its causal relationship to study treatment. 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. A serious adverse event (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. AE terms recorded by the clinical site will be mapped to PT using version 18.0 or

later of the MedDRA. Toxicity grade will be defined according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A related AE is an event where the investigator determined that the relationship to study drug was "Possible Related", "Probable Related" or "Definite Related". For summaries by relationship, adverse events with missing relationship are counted as "Possible Related". For summaries by CTCAE grade, adverse events with missing CTCAE grade are counted as CTCAE grade 3 – Severe. If the AE start date is missing, it will be imputed as shown in Appendix D.

The following summaries of AEs by system organ class (SOC) and preferred term (PT) will be provided:

- All TEAEs
- All serious TEAEs
- All treatment-related TEAEs for phase II patients
- All TEAEs resulting in study drug discontinuation
- All TEAEs by NCI CTCAE grade

Data listing will be provided for all AEs. The incidence of deaths and the primary cause of death will be displayed in a listing. The severity of nausea and incidence of vomiting as captured in the diary data will be listed. The DLTs are summarized in a table and listed for DLT-evaluable Analysis Set.

9.2. Clinical Laboratory Evaluations

Clinical hematology and coagulation, biochemistry, and urinalysis data will be displayed at each scheduled assessment. Hematology will include hemoglobin, reticulocytes, red blood cell count, differential white blood cell count, platelets, and International Normalized Ratio. Coagulation will include prothrombin time and international normalized ratio. Biochemistry will include alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, total bilirubin, sodium, potassium, calcium, magnesium, urea, creatinine, creatinine clearance, total protein, albumin, and lactate dehydrogenase. Urinalysis will be performed and will include: leukocyte esterase, nitrite, urobilinogen, protein, pH, blood, specific gravity, ketones, bilirubin, and glucose.

Numeric hematology and coagulation and biochemistry results will be summarized using actual result and change from baseline for Phase II patients. All results will be summarized using shift from baseline. Shifts for all 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 (i.e., no visit windows will be applied). Unscheduled data will be included in "Worst Case Post-baseline" summaries which will capture a worst case across all scheduled and unscheduled visits after the first dose of study treatment.

Numeric clinical hematology and coagulation, biochemistry, and urinalysis results will be summarized using change from baseline for Phase II patients. All results will be summarized using shift from baseline and be displayed in separate data listings.

9.3. Vital Sign Measurements

Vital sign measurements will include arterial blood pressure, heart rate, respiratory rate, and temperature. Vital signs will be measured during the screening period on Day -14 to -1, On Day 1 and day 8 of each Cycle and End-of-Treatment. 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 Cycles 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.

The results of all time points will be displayed in a listing. A summary table of measurement values and changes from baseline by visit for phase II patients will be provided and unscheduled visits will be included in the "Worst Case".

9.4. 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 body surface area (BSA) will be done before each dosing on Day 1 of each cycle. **(***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]). All measurements will be displayed in a listing.

9.5. Electrocardiogram

A 12-lead ECGs 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. Starting in Cycles 2, twelve-lead ECGs will also be performed on Day 1 of each cycle 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.

All measurements including ventricular rate, QT interval, QTcB (Corrected QT interval - Bazett's formula), QTcF (Corrected QT interval - Fridericia's formula), and the overall interpretation will be displayed in a data listing. The QTcB and QTcF are calculated based on the formula below:

$$QTcB = \frac{QT}{\sqrt{Ventricular\ Rate}} \qquad QTcF = \frac{QT}{\sqrt[3]{Ventricular\ \ Rate}}$$

Summary of actual value and change from baseline will be presented in a summary table for phase II patients. Overall interpretation is assessed as normal, abnormal; not clinically significant, clinically significant. A shift table from baseline to current visit will be presented for overall interpretation. The categories of QTcB and QTcF (≤450 msec, >450-480 msec, >480-500 msec, >500 msec) and the categories of change from baseline for QTcB and QTcF (≥30 msec and ≥60 msec) will be summarized by visit and cohort.

9.6. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)

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 PS grades 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, e.g., 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

All measurements will be displayed in a data listing. A shift table from baseline to current ECOG status will be presented.

10. Pharmacokinetic Assessments

10.1 Plasma Concentration

The concentration-versus-time profile of total and free platinum in plasma will be determined in Part 1 and in Part 2.

Part 1 Pharmacokinetic Time Points

- 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

Plasma 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

Actual sampling times, rather than scheduled sampling times, will be used in the computation of PK parameters. However, for ease of presentation, scheduled sampling times will be used to present results in summary tables.

Individual plasma concentration and time deviation data will be presented in a listing. The plasma concentration data will be summarized over time by cohort and cycle using descriptive statistics: n, mean, standard deviation, coefficient of variation (CV), minimum, median, and maximum. All BLQ values will be set to zero for the summary statistics. The individual and mean plasma concentration versus time profiles will be presented in figures on both linear and semi-logarithmic scales. For ease of presentation, individual and mean plasma concentration versus time profiles will be presented with scheduled times.

10.2 Plasma Pharmacokinetic Parameters

Individual plasma concentration versus actual time data will be used to estimate the PK parameters of total and free Pt in plasma by standard noncompartmental methods using WinNonlin (Phoenix) Version 6.4 or higher for each individual. For the calculation of PK parameters all plasma concentrations that are BLQ before the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. The BLQ values occur at the end of the profile (after the last quantifiable concentration) will be set to missing.

The following PK parameters will be derived for total and free Pt in plasma for Part 1 for Cycle 1, Cycle 3, and Cycle 5:

Parameter	Description
$AUC_{0\text{-}t}$	Area under the concentration versus time curve from time 0 to the last quantifiable concentration (C_{last}); calculated using the linear-up/ log-down trapezoidal rule
$AUC_{0\text{-}\tau}$	Area under the plasma concentration-time curve (AUC) from time 0 to the end of the dosing interval, calculated by the linear-up/ log-down trapezoidal rule
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinity, calculated as $AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + C_{last}/ \lambda_z$, where C_{last} is the last quantifiable plasma drug concentration. A %AUC, extrapolated <20% are required in order to retain $AUC_{0\text{-}\infty}$.

Parameter	Description
AI	Accumulation index calculated as $AUC_{0-\tau}$ in Cycle 3 or in Cycle 5 / $AUC_{0-\tau}$ in Cycle 1.
CL	Total body clearance calculated as Dose/AUC_{0-inf}.
C_{max}	Maximum observed plasma concentration.
MRT_{inf}	Mean residence time extrapolated to infinite time calculated as [($AUMC_{0-\infty}$ / $AUC_{0-\infty}$) – TI/2], where TI represents the infusion time (infusion duration).
T_{max}	Time to achieve maximum observed plasma concentration.
λ_z	The first-order terminal elimination rate constant, calculated using linear regression on the terminal portion of the ln-concentration versus time curve. At least 3 time points (excluding T_{max}) and r^2 >0.90 are required to calculate and retain K_{el} and its associated parameters ($t_{1/2}$ and AUC_{0-inf}).
$T_{1/2}$	Plasma terminal elimination half-life, calculated as $t_{1/2}$= ln(2)/ λ_z.
V_{ss}	Steady state volume of distribution calculated as: MRT_{inf} x CL
V_z	Volume of distribution based upon the terminal phase calculated as: Dose / (λ_z × AUC_{0-inf})

The individual PK parameters will be presented in the data listings for the PK analysis set. The PK parameters will be summarized by treatment using descriptive statistics: n, mean, SD, CV, median, minimum and maximum. Descriptive statistics will include geometric means, for AUC, C_{max}, CL, V_{ss} and V_z.

C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ (Y-axis) for total and free Pt in plasma will each be plotted against all available doses (X-axis) for dose proportionality evaluation to assess dose proportionality.

11. Interim Analysis

Once 10 PFS events have been observed in each cohort, interim analyses will be performed every 6 weeks. At each interim and at the final analysis, there are 3 possible outcomes for each cohort (refer to Section 3.1 for details).

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 381events.

12. References

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Appendix D: Imputation Algorithm for Partial and Missing Dates

Adverse Event

- If onset date is completely missing, then onset date is set to date of first dose.
- If (year is present and month and day are missing) or (year and day are present and month is missing):
    - If year = year of first dose, then set onset month and day to month and day of first dose
    - If year < year of first dose, then set onset month and day to December 31st.
    - If year > year of first dose, then set onset month and day to January 1st.
- If month and year are present and day is missing:
    - If year=year of first dose and
        - If month = month of first dose then set day to day of first dose date
        - If month < month of first dose then set day to last day of month
        - If month > month of first dose then set day to 1st day of month
    - If year < year of first dose then set day to last day of month
    - If year > year of first dose then set day to 1st day of month
- For all other cases, set onset date to date of first dose

Concomitant Medications

- If start date is completely missing then start date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing) then set start month and start day to January 1.
- If start year and start month are present and start day is missing then set start day to 1st day of month.
- If end date is completely missing then end date will not be imputed.
- If (year is present and month and day are missing) or (year and day are present and month is missing) then set end month and end day to December 31.
- If end year and end month are present and end day is missing then set end day to last day of the month.