

Phase Ib/II Trial of NC-6004 (Nanoparticle Cisplatin) Plus Gemcitabine in Patients with Advanced Solid Tumors

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Abstract

Purpose: NC-6004, a novel cisplatin nanoparticle developed using micellar technology exhibits sustained release of cisplatin and selective distribution to tumors. Preclinical data demonstrated a favorable tolerability profile and preserved or improved antitumor activity compared with cisplatin across animal models. We evaluated the safety and tolerability of NC-6004 and gemcitabine using a Bayesian continual reassessment model (N-CRM) to determine the optimal dose.

Experimental Design: Patients with advanced solid tumors received NC-6004 at 60 to 180 mg/m² on day 1 and gemcitabine at 1,250 mg/m² on days 1 and 8 every 3 weeks. Dose escalation of NC-6004 began with a single patient run-in until a dose-limiting toxicity occurred at 180 mg/m². Cohorts of four patients were enrolled at doses predicted by the N-CRM. The maximum tolerated dose (MTD) was defined as having the greatest probability of

target toxicity <25%. Quality of life was assessed using EORTC-QLQ-C30.

Results: Among 22 patients, the most common grade III/IV hematologic adverse events were leukopenia (68%) and thrombocytopenia (59%). Of 20 pretreated patients evaluable for response, half were previously exposed to a platinum agent. The MTD was 135 mg/m². Nine patients were treated at the MTD with median treatment duration of 15 weeks (range, 3–50). Tumor shrinkage occurred in 11 (55%), partial responses in 3 (15%), and stable disease in 14 (70%). Most patients reported stable or improved EORTC QLQ-C30 scores.

Conclusions: Greater cisplatin equivalent doses were achieved with no clinically significant neuro-, oto-, or nephrotoxicity. These data demonstrate tolerability and promising activity of NC-6004 in combination with gemcitabine. *Clin Cancer Res*; 24(1); 43–51. ©2017 AACR.

Introduction

Many potent chemotherapies are limited in their use due to significant toxicities from continuous administration and development of resistance over time. Cisplatin is highly active and widely used for the treatment of a variety of cancers; however, its use in practice is limited due to cumulative dose-limiting toxicities (DLT) and lack of improvement in efficacy despite longer treatment (1–4). Although highly effective, the use of cisplatin is associated with irreversible ototoxicity and nephrotoxicity (5).

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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doi: 10.1158/1078-0432.CCR-17-1114

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Renal toxicity necessitates the use of prehydration and can preclude patients with deteriorating renal or cardiac function from receiving cisplatin. Continuous use of cisplatin is associated with neurotoxicity, myelotoxicity, and gastrointestinal toxicity including nausea and vomiting (5, 6). Carboplatin exhibits less nephrotoxicity and no ototoxicity and is often used as an alternative for cisplatin (7). Cisplatin has demonstrated superior activity over carboplatin in several studies of patients with squamous cell carcinoma of the head and neck (SCCHN) and bladder cancer (8–12). A meta-analysis of randomized trials comparing cisplatin versus carboplatin-based therapy in patients with bladder cancer demonstrated that cisplatin-based therapy significantly improved complete response and overall response compared with carboplatin (13). In addition, a meta-analysis of patients with SCCHN treated with cisplatin-based chemotherapy achieved greater overall survival compared with carboplatin (14). In addition, a cisplatin nanoparticle (NC-6004) was chosen over carboplatin because it is believed that a nanoparticle cisplatin can overcome the classic cisplatin DLTs while maintaining or increasing the activity of cisplatin due to its pharmacokinetic characteristics.

NC-6004 is a novel cisplatin nanoparticle developed using micellar technology. The nanoparticle is approximately 30 nm in diameter and consists of a hydrophilic outer shell composed of polyethylene glycol which extends circulation time in the bloodstream by preventing the micelles from being captured by the

Translational Relevance

Although cisplatin is a highly effective anticancer agent and standard of care in many cancer types, it is associated with dose-limiting nephrotoxicity, neurotoxicity, and nausea and vomiting. Carboplatin is another widely available platinum agent with less nonhematologic toxicity compared with cisplatin, however is less active than cisplatin in several tumor types including squamous cell carcinoma of the head and neck, bladder cancer, testicular cancer, and some patients with lung cancer where a rapid and more significant response is needed. In addition, it is still considered a reference regime in many curative settings. NC-6004 is a cisplatin nanoparticle developed using micellar technology and exhibiting sustained release of cisplatin and selective distribution to tumors. The sustained release allows NC-6004 to achieve a higher area under the curve (AUC) and a lower maximum concentration (C_{max}), resulting in a longer period of systemic cisplatin exposure. These pharmacokinetic characteristics potentially lead to an improved activity (higher AUC) and tolerability profile (lower C_{max}) compared with cisplatin. Preclinical data demonstrate that NC-6004 has a favorable tolerability profile (nephrotoxicity and neurotoxicity) and preserved or improved antitumor activity compared to cisplatin across a variety of animal models. These data demonstrate tolerability and promising activity of NC-6004 and gemcitabine warranting further investigation. In this phase Ib trial of NC-6004 plus gemcitabine, the MTD was 135 mg/m², nearly double commonly used cisplatin dose with no clinically significant neuro-, oto-, or nephrotoxicity. This was achieved by using an adaptive, Bayesian N-CRM dose-escalation design which led to an expedited and higher MTD determination compared with a traditional modified Fibonacci 3+3 dose escalation trial design.

reticuloendothelial system and enhancing tumor-specific accumulation (15). The small size of NC-6004 micelles provide an advantage over other formulations of doxorubicin or paclitaxel using albumin or liposomal-based nanovehicles which are 90 and 130 nm, respectively, and enables greater accumulation and penetration of poorly permeable organs such as the pancreas (16). The micelles progressively break down in the presence of chloride to provide a sustained release of cisplatin and the polymer. Each micellar nanoparticle contains an average of 720 cisplatin residues. NC-6004 has a narrow polydispersity index of 0.070 and has a high cisplatin content of 39%. Cisplatin is nearly uniformly distributed throughout the micelle (17) The sustained release allows NC-6004 to achieve a lower maximum concentration (C_{max}) and a higher area under the curve (AUC), resulting in a longer period of systemic cisplatin exposure while exhibiting a similar toxicity profile to cisplatin. In preclinical studies, NC-6004 exhibited preferential distribution to tumors, significantly lowered toxicity compared with cisplatin at equivalent doses, and increased antitumor activity (18). Biodistribution studies in tumor-bearing mice were performed demonstrating the highest tissue distribution of released cisplatin (in rank order) in the kidney, liver, spleen, and muscle. The NC-6004 accumulation and AUC ratios (tumor to normal tissues) were 2.0 and 0.97 for

tumor/kidney, 1.6 and 1.3 for tumor/liver, and 1.3 and 1.5 for tumor/spleen, respectively. Ratios >1 illustrate high tumor selectivity for the nanoparticle. For released cisplatin, higher selectivity to the kidney and liver were observed (17). Stability studies in normal saline at 37°C were performed demonstrating greater than 50% release of cisplatin from the nanoparticle at 120 hours illustrating the breakdown in the presence of chloride and the reason NC-6004 is reconstituted in 5% dextrose in water (17). *In vitro* studies were conducted in eight human, solid tumor cell lines with fixed concentrations of NC-6004 and increasing concentrations of gemcitabine. The combination of NC-6004 and gemcitabine demonstrated synergistic effects in cisplatin-refractory lung, breast, colon, and pancreatic adenocarcinomas. The *in vivo* antitumor activity of NC-6004 in combination with gemcitabine was compared to single agent NC-6004, cisplatin, gemcitabine, and cisplatin in combination with gemcitabine in human breast, prostate, and lung tumor xenograft models. Significant change in mean tumor size was observed in the NC-6004 and gemcitabine combination compared to NC-6004 alone or cisplatin alone. Preclinical data also demonstrate that NC-6004 has a favorable tolerability profile (nephrotoxicity and neurotoxicity) and preserved or improved antitumor activity compared with cisplatin (19). In a previous NC-6004 clinical trial completed in the United Kingdom, the ultrafiltrate cisplatin [free, protein unbound (active)] exposure following NC-6004 administration in patients with advanced solid tumors was prolonged with a significantly longer half-life (230-fold increase) and greater AUC (8.5-fold increase) compared to equivalent cisplatin dose levels. At 90 mg/m², the mean half-lives of intact micelles and released (protein-unbound) cisplatin were 83.5 and 123 hours, respectively. Circulating levels of the therapeutically active form of cisplatin (released, protein unbound) were regularly quantifiable out to 500 hours. These characteristics suggest that at the maximum-tolerated dose (MTD) of NC-6004, antitumor activity may be greater than that of cisplatin. In addition, the ultrafiltrate platinum C_{max} of NC-6004 was 34-fold lower than ultrafiltrate levels of cisplatin at therapeutic doses (20). The lower C_{max} is potentially a clinically significant characteristic, particularly in patients with poor renal function as high ultrafiltrate platinum C_{max} levels (≥ 400 mg/mL) are associated with nephrotoxicity and a decline in creatinine clearance (21). A nanoparticle cisplatin (NC-6004) with these characteristics has the potential to improve activity over cisplatin and allow for cisplatin use in subjects who may otherwise not tolerate cisplatin.

The results from the previous phase I trial of single agent NC-6004 in patients with solid tumors suggested acceptable tolerability and dose-proportional activity in the treatment of advanced solid tumors and defined a recommended dose of 90 mg/m² (20). Following this trial, a phase I/II trial in Asia was started in patients with metastatic pancreatic cancer evaluating escalating doses of NC-6004 in combination with gemcitabine using a traditional 3+3 modified Fibonacci dose escalation design. This trial determined a MTD of 120 mg/m² and a RP2D of 90 mg/m² for the combination. Overall, the combination of NC-6004 and gemcitabine was tolerable and demonstrated activity with several responders.

We conducted an open-label, nonrandomized, phase Ib/II dose escalation and expansion trial using a Bayesian Continual Reassessment Model (N-CRM) assuming the dose-response relationship could be modeled by a Bayesian two-parameter logistic model with an uninformative prior (clinicaltrials.gov

NCT02043288). The Bayesian CRM model originated from Neuenschwander and was simulated, designed, and implemented using Fixed and Adaptive Clinical Trial Simulator (FACTS) software version 5.6 (22). The goals of the phase Ib portion of the trial were to determine the MTD and RP2D of NC-6004 in combination with gemcitabine and evaluate the initial activity and tolerability profile of the combination. The pharmacokinetics of NC-6004 was also evaluated. The NC-6004 doses are reported as the cisplatin-equivalent to facilitate dose comparisons with cisplatin. The study was approved by the institutional review boards from all investigative sites and was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practice, and all applicable regulations.

Materials and Methods

Patient population

Patients 18 years or older with advanced solid tumors that relapsed or were refractory to standard curative or palliative therapy or had a contraindication to therapy were eligible for enrollment. In addition, patients were required to have measurable disease per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST), performance status [Eastern Cooperative Oncology Group (ECOG) 0–1], adequate bone marrow reserve (absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 100 \times 10^9/L$, and hemoglobin ≥ 10 g/dL), and met organ function criteria [total serum bilirubin $< 1.5 \times$ upper limit of normal (ULN), alanine transaminase, aspartate transaminase $< 2.5 \times$ ULN or in patients with documented hepatic metastases $\leq 5.0 \times$ ULN, serum creatinine < 1.5 mg/dL]. Patients were excluded from enrolling in the trial if they received platinum therapy 3 months prior to screening, cisplatin and gemcitabine concomitantly 6 months prior or were unable to receive platinum-based therapy due to previous toxicity. Those with uncontrolled comorbidities (diabetes, hypertension, and liver disease) and cardiovascular related events within the 6-month period prior to screening were also excluded.

Trial design

This is an ongoing, open-label, phase Ib/II, dose escalation, and expansion trial of NC-6004 (nanoparticle cisplatin) plus gemcitabine conducted in the United States and Europe. Here we present the results of the phase Ib dose escalation portion of the trial. NC-6004 was administered as a 1-hour intravenous infusion on day 1 of each 21-day cycle. All patients were administered a hydration regimen preinfusion (minimum of 1 L over 1–3 hours) and post-infusion (minimum of 500 mL over 2 hours) of NC-6004 with 0.9% sodium chloride (0.45% sodium chloride was allowed based on investigator discretion). The protocol was amended to orally or intravenously supplement 8 mEq (1 g) of magnesium sulfate during the pre-hydration regimen and as needed if magnesium levels decreased to < 1.8 mg/dL or the lower limit of normal (grade 1 hypomagnesemia). This amendment was made following the observation of grade 1 to 2 hypomagnesemia in the first seven patients during the first cycle. To reduce the risk of hypersensitivity reactions, all patients received: an antihistamine (diphenhydramine 50 mg, ranitidine 50 mg, or 20 mg famotidine) intravenously 30 minutes prior to administration of NC-6004 and dexamethasone 20 mg orally 12 and 6 hours prior to NC-6004 and 4 mg twice daily for 2 days after the end of infusion.

The use of antiemetic agents was allowed based on the standard treatment center protocols for cisplatin-based regimens but were not required. Gemcitabine $1,250$ mg/m² was administered following NC-6004 as a 30-minute intravenous infusion on day 1 and on day 8 of each cycle. Patients were enrolled sequentially in single patient cohorts from 60 to 180 mg/m² in 15 mg/m² increments until a DLT was observed or a patient was treated at 180 mg/m² for one cycle without a DLT. Patients were not enrolled at higher dose levels until the patient at the lower dose level finished one full cycle. A Bayesian continual-reassessment method was used to determine the dose for the remainder of the dose escalation when the single patient cohorts ended and incorporated the single patient run-in data (21). Four patients were then enrolled at each dose level predicted by the N-CRM until the MTD was determined. The N-CRM dose levels were based on a probability of $< 25\%$ for the occurrence of a DLT. All patients were treated until disease progression, unacceptable toxicity, or withdrawal from trial, whichever occurred first. Patients who discontinued treatment for reasons other than experiencing a DLT prior to completing the first cycle were replaced. The primary objectives of the trial were to determine the MTD, RP2D, and tolerability of NC-6004 when combined with gemcitabine in patients with advanced solid tumors. The secondary objectives were to evaluate the safety, quality of life, pharmacokinetics, and antitumor activity of NC-6004 when combined with gemcitabine. Treatment-emergent adverse events were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE). Quality of life was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). Pharmacokinetic samples were collected and plasma concentrations of micellar platinum, total platinum, and free platinum were measured and key pharmacokinetic parameters were determined using noncompartmental analysis.

Dose-limiting toxicity

A DLT was defined as any of the following conditions manifesting in the first cycle of treatment, graded according to the NCI CTCAE: grade 3 or 4 nonhematologic toxicity (excluding alopecia and grade 3 nausea and vomiting, diarrhea and electrolyte imbalances lasting less than 48 hours or hypersensitivity reactions), grade 4 hematologic toxicity, grade 4 decreased neutrophil counts ($< 500/mm^3$) lasting for seven or more days unresponsive to growth factor support and grade 3 decreased neutrophil counts ($< 1,000$ to $500/mm^3$) with a fever of $38^\circ C$ or greater. During any treatment cycle, dosing of NC-6004 was suspended for up to 14 days in the event of any DLT or at the discretion of the investigator for any toxicity possibly related to NC-6004 that did not meet DLT criteria. A dose delay of more than 14 days required a patient to be removed from the trial, except in the case of potential patient benefit. Following recovery to \geq Grade 1, treatment was resumed at 50% of the original dose based on the investigator's discretion.

Bayesian continual reassessment model

The dose selection from the Bayesian N-CRM was based on point estimates for the probability of a DLT at each dose and the model was continually updated. In the single patient, run-in phase, the model was updated whenever a patient experienced a DLT or completed the first cycle. Following single patient run-in

and for the remainder of the dose escalation, the model was updated when all four patients enrolled in a cohort experienced a DLT or complete the first cycle without a DLT. The dose escalation ended when: (i) 10 cohorts were completed, (ii) two cohorts were treated at the MTD, or (iii) no dose level controlled the probability of excessive or unacceptable toxicity to be no more than 25%. The MTD was identified by the dose level that has the greatest probability of controlling excessive or unacceptable toxicity to be no more than 25%.

Results

Patient characteristics

A total of 22 patients, 11 males and 11 females, were enrolled at four sites in the United States during the phase Ib dose escalation (stratification by gender was not used). The median age was 55 (range, 21–69) years and a majority were Caucasian ($N = 13$, 59%). Lung cancer was the most common tumor type ($N = 11$, 50%) followed by SCCHN ($N = 3$, 14%). Half of the patients were previously treated with a platinum-containing regimen ($N = 11$, 50%). The number of prior systemic regimens were: 1 in 12 patients (55%), 2 in 2 patients (9%), 3 in 3 patients (14%), 4 in 2 patients (9%), and 5 or more in 3 patients (14%). Patient demographics and baseline characteristics are summarized in Table 1.

Dose escalation

The number of patients treated at each dose level of NC-6004 is shown in Table 1. The median treatment duration was 9 weeks (range, 0–50). The median treatment duration at the MTD, which was determined to be 135 mg/m² was 15 weeks (range, 3–50). The longest treatment duration observed was almost 1 year (50 weeks) in a Caucasian, female patient with non-small cell lung cancer (NSCLC) previously treated with one prior platinum-containing regimen. This patient was treated with NC-6004 at the MTD. Duration of treatment for each individual patient by dose level is shown in Figure 1. No patients required withdrawal of NC-6004 or a dose reduction at doses lower than 150 mg/m².

Safety

All 22 patients treated with NC-6004 and gemcitabine were assessed for safety. Treatment-emergent adverse events (TEAEs) for all grade and grade 3 to 4 at the MTD and overall are reported in Table 2. All abnormal laboratory and clinical assessments, including those that worsened from baseline were recorded as TEAEs regardless of clinical significance. No treatment-emergent death was observed. The most common grade 3 and 4 hematologic TEAEs overall and at the MTD were leukopenia (68%; 78%), thrombocytopenia (59%; 44%), neutropenia (55%; 67%), lymphopenia (45%; 44%), and anemia (27%; 33%) respectively as shown in Figure 1. No grade 3 or 4 nonhematologic TEAEs were observed at a frequency higher than 18% overall and 22% in patients treated at the MTD. A majority of patients received prophylaxis for nausea and vomiting (73%) and 60% received a neurokinin-1 antagonist as part of their prophylaxis regimen. The incidence of grade 3 or 4 nausea or vomiting overall, was 9% and 5%, respectively. No grade 3 or 4 nausea or vomiting was observed at the MTD. The change in creatinine clearance for each patient treated with NC-6004 is shown in Figure 2. Prolonged administration of NC-6004 at all dose levels was not associated with any clinically significant changes in renal function. Among patients with a reduction in creatinine clearance, all occurrences

Table 1. Patient demographics and baseline characteristics

Characteristics	Study Population ($N = 22$)
Age, year (median, range)	55 (21–69)
Gender, N (%)	
Male	11 (50)
Female	11 (50)
Race, N (%)	
White	13 (59)
Black	5 (23)
Asian	1 (4)
Other	3 (14)
Tumor type, N (%)	
Lung cancer	11 (50)
Squamous cell head and neck cancer	2 (9)
Endocrine cancer	2 (9)
Sarcoma	2 (9)
Colorectal cancer	2 (9)
Gastro/esophageal cancer	2 (9)
Breast cancer	1 (5)
Prior chemotherapy	
Platinum-containing regimen, N (%)	11 (50)
Prior lines of therapy	Mean: 2.5 (1 = 12; 2 = 2; $\geq 3 = 8$)
NC-6004 dose level (mg/m ²), N (%)	
60	1 (5)
75	1 (5)
90	1 (5)
105	1 (5)
120	1 (5)
135	9 (41)
150	6 (27)
165	1 (5)
180	1 (5)

were after the first cycle of treatment and all patients recovered and remained stable throughout the remainder of treatment.

The occurrence of DLTs is summarized in Table 2. No DLTs were observed in patients treated at doses lower than 150 mg/m². During the single patient run-in, there was a single case of grade 4 febrile neutropenia in a patient treated with NC-6004 at 180 mg/m². The dose of NC-6004 was subsequently reduced and the single patient run-in phase ended. Further dosing was determined by the N-CRM, additional DLTs observed were: one case of Grade 3 nausea at 165 mg/m² where no action was taken, one case of Grade 3 vomiting at 150 mg/m² where NC-6004 was withdrawn and three cases of grade 4 thrombocytopenia at 150 mg/m², where the NC-6004 dose was reduced to 75 mg/m² in all three patients for the remainder of the trial. One patient had a study drug dose delay of more than 14 days due to a Grade 4 GGT elevation and was discontinued at cycle 5. Two patients did not receive a Day 8 gemcitabine dose due to hematologic adverse events but remained on treatment.

Quality of life

Patients with at least two EORTC QLQ-C30 scores (at baseline and last assessment) were analyzed for deterioration, improvement, or stability and are presented in Figure 1 (supplement; $N = 18$). Absolute score changes ≥ 0 were classified as improved or stable and < 0 were classified as deterioration. Of the 18 evaluable patients, a greater proportion was observed to have an improvement or stability in their scores from baseline.

Antitumor activity

Twenty of the 22 patients were evaluable for radiographic tumor response assessment. Maximum tumor shrinkage

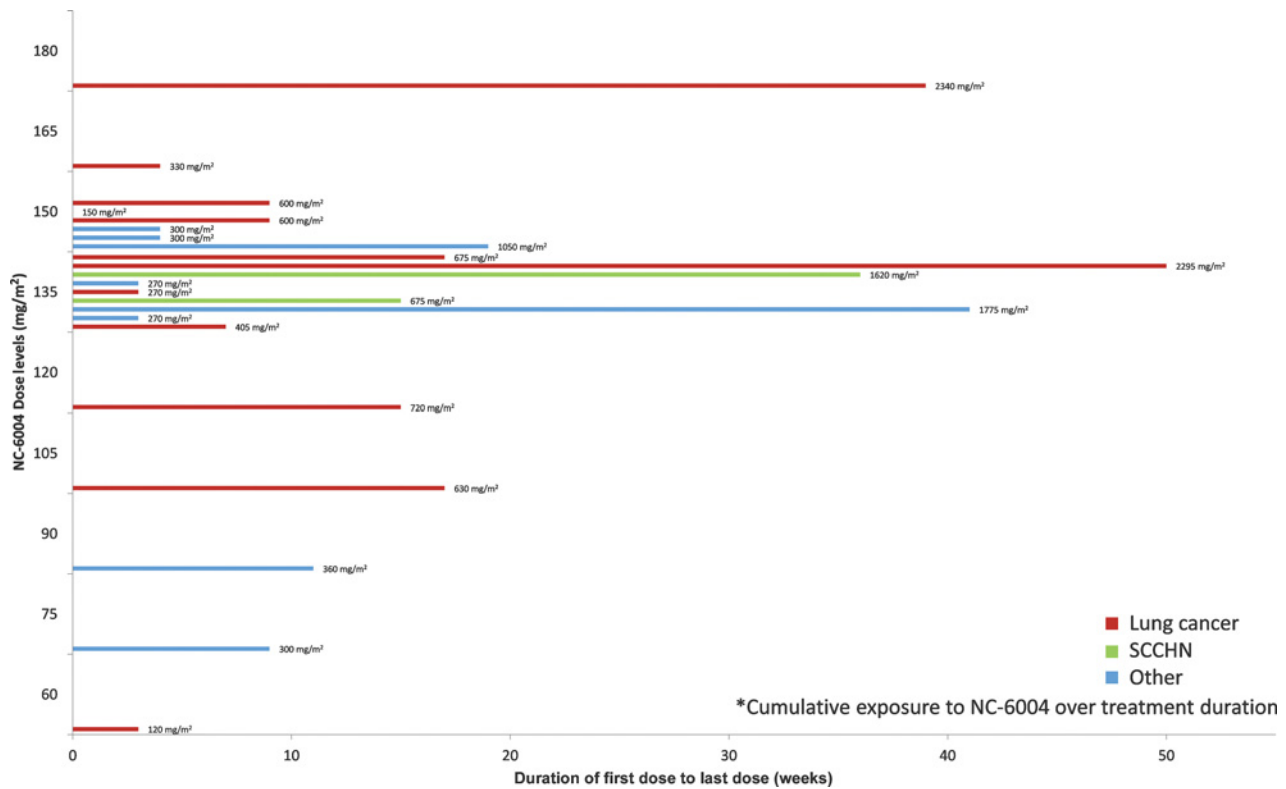


Figure 1.
Duration of treatment ($N = 22$).

displayed as percent change from baseline is presented in Figure 3. Activity was observed in heavily pretreated patients, half of whom were pretreated with a prior platinum agent. Tumor shrinkage was observed in 11 patients (55%) whose NC-6004 doses ranged from 90 to 180 mg/m², 67% of these patients received prior platinum therapy. Stable disease was observed in 14 patients (70%) overall and in four patients at the MTD. The disease control rate was 85%. Partial responses were observed in three patients (15%), two with nonsquamous NSCLC (one patient treated at the MTD and the other at 180 mg/m²) and one with SCCHN (treated at the MTD) with a median duration of response of 16 weeks. The patient with SCCHN who received three prior lines of chemotherapy was treated for 15 weeks had a partial response. The two patients with nonsquamous NSCLC with partial responses each had one prior line of a platinum-containing chemotherapy regimen and were treated for 39 and 50 weeks. Durable response was observed in four patients (SCCHN, $N = 2$; NSCLC, $N = 2$). One of the NSCLC patients with durable response had been previously treated and progressed on a checkpoint inhibitor. A spider plot illustrating change in tumor size is presented in Figure 3.

Discussion

NC-6004 is a nanoparticle designed to provide sustained release of cisplatin and utilizes the enhanced permeability retention-effect (EPR) to target the release of platinum to tumors (23). Nanoparticles capitalize on the EPR effect by exploiting abnormalities of tumor vasculature, namely hypervascularization,

fenestrated vasculature, and retaining intratumorally via a lack of a tumor lymphatic drainage system (24). The micelle-based drug delivery system of NC-6004 has allowed for administration of cisplatin at much longer durations than used in practice with cisplatin in a heavily pretreated population. The median treatment duration was 9 weeks with one patient treated for approximately 1 year (range, 0–50 weeks). Notably, we observed no cumulative cisplatin-related toxicities in some patients with durable antitumor activity. Using the N-CRM instead of a traditional 3+3 modified Fibonacci dose escalation design employed in previous studies of NC-6004, we determined an MTD for NC-6004 in combination with gemcitabine of 135 mg/m², which is higher than that currently approved for cisplatin monotherapy, where the highest dose used in routine practice is 100 mg/m² per cycle. Dose reductions of NC-6004 were due to hematologic toxicities and vomiting and only occurred at doses exceeding the MTD. Dose escalation using the N-CRM allowed for greater exploration of the pharmacologic zone of interest and projected a higher MTD of NC-6004 and gemcitabine versus a 3+3 design.

Nausea and vomiting are often significant concerns for a patient undergoing chemotherapy and can affect overall quality of life. The 2016 Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology guideline for the prevention of chemotherapy-induced nausea and vomiting classifies cisplatin as a highly emetogenic chemotherapy and recommend the prophylactic use of antiemetic regimens (25). In this trial, we did not require the prophylactic use of antiemetic agents but a majority of patients received prophylaxis based on standard

Table 2. Treatment emergent adverse events (TEAE)

Adverse event, N (%)	NC-6004	NC-6004	Overall all grade (N = 22)	Overall grade 3-4 (N = 22)
	135 mg/m ² All Grade (N = 9)	135 mg/m ² Grade 3-4 (N = 9)		
Total TEAEs	516	77	139	183
At least one TEAE	9 (100)	8 (89)	22 (100)	18 (82)
Leukopenia	9 (100)	7 (78)	21 (95)	15 (68)
Thrombocytopenia	9 (100)	4 (44)	21 (95)	13 (59)
Neutropenia	8 (89)	6 (67)	18 (82)	12 (55)
Lymphopenia	5 (56)	4 (44)	12 (55)	10 (45)
Anemia	6 (67)	3 (33)	16 (73)	6 (27)
Fatigue	6 (67)	2 (22)	12 (55)	4 (18)
Hypomagnesemia	9 (100)	1 (11)	22 (100)	3 (14)
Hyponatremia	5 (56)	1 (11)	12 (55)	3 (14)
Decreased appetite	5 (56)	1 (11)	9 (41)	2 (9)
Dehydration	1 (11)	0	4 (18)	2 (9)
Hyperglycemia	2 (22)	1 (11)	8 (36)	2 (9)
Hypokalemia	5 (56)	0	14 (64)	2 (9)
Nausea	9 (100)	0	16 (73)	2 (9)
Prolonged APTT	1 (11)	0	2 (9)	1 (5)
Increased GGT	4 (44)	1 (11)	13 (59)	1 (5)
Increased AST	6 (67)	0	18 (82)	1 (5)
Increased ALT	4 (44)	0	13 (59)	1 (5)
Weight loss	1 (11)	0	4 (18)	1 (5)
Abdominal distension	0	0	1 (5)	1 (5)
Abdominal pain	1 (11)	1 (11)	2 (9)	1 (5)
Diarrhea	3 (33)	0	9 (41)	1 (5)
Dysphagia	0	0	1 (5)	1 (5)
Vomiting	4 (44)	0	9 (41)	1 (5)
General edema	0	0	1 (5)	1 (5)
Pneumonia	1 (11)	1 (11)	1 (5)	1 (5)
Dyspnea	1 (11)	0	3 (14)	1 (5)
Dose-limiting toxicities (DLT)				
NC-6004 dose		DLT		NC-6004 action taken
150 mg/m ²		Grade 4 Thrombocytopenia		Dose reduced
150 mg/m ²		Grade 4 Thrombocytopenia		Dose reduced
150 mg/m ²		Grade 4 Thrombocytopenia		Dose reduced
150 mg/m ²		Grade 3 Vomiting		Drug discontinued
165 mg/m ²		Grade 3 Nausea		None
180 mg/m ²		Grade 4 Febrile neutropenia		Dose reduced

treatment center protocols. Most patients received both an NK1 antagonist and a 5-HT3 antagonist; however, several patients were managed on a 5-HT3 antagonist alone. Overall, we observed a low incidence of severe nausea and vomiting with only 9% of patients (2/22) experiencing grade 3 nausea or vomiting, all following doses higher than the MTD. Although we are not able to directly compare the emetogenicity between NC-6004 and cisplatin, NC-6004 was moderately emetogenic and allowed patients to be well managed on a 5-HT3 antagonist and a corticosteroid alone. Most patients reported an improvement or stability in EORTC QLQ-C30 scores related to nausea and vomiting from baseline.

Dose-related and cumulative renal insufficiency is a major dose-limiting toxicity of cisplatin therapy. Renal toxicity occurs in 28% to 36% of patients treated with a single dose of cisplatin at 50 mg/m² without the use of hydration regimens and becomes more prolonged and is exacerbated by repeat treatment courses with cisplatin (5). When cisplatin is administered with prophylactic intravenous hydration, nephrotoxicity is reduced but not eliminated with patients experiencing a persistent 10% to 25% mean reduction in glomerular filtration rate with subnormal recovery suggestive of irreversible damage (26). No patients in this trial experienced neuro-, oto-, or nephrotoxicity when NC-6004 was administered with pre- and postintravenous hydration. In addition, we observed relatively stable renal function through-

out the course of treatment in all patients: no patients treated with NC-6004 had a clinically significant decline in renal function that was classified as grade 3 or higher by the NCI CTCAE. Four patients experienced a modest reduction in renal function during the first cycle of treatment but all recovered to baseline at the next cycle and renal function remained stable throughout the remainder of treatment. The incidence of acute kidney injury with NC-6004 compared to cisplatin has been evaluated in a previous phase I population pharmacokinetic and pharmacodynamic modeling study. Compared to a mean cisplatin dose of 100 mg/m², 70% of patients who received 100 mg/m² of NC-6004 did not experience acute kidney injury. With each increasing stage of acute kidney injury, cisplatin had a proportionally greater number of cases of acute kidney injury compared to NC-6004 (27). A nanoparticle cisplatin that demonstrates favorable pharmacokinetics, potential for longer duration of tolerability, promising dose-proportional activity and reduced toxicity, particularly nephrotoxicity and neurotoxicity, may expand the successful delivery and use of platinum agents in the clinic. In addition, we have observed no known micelle-related adverse events in this trial or in preceding trials enrolling over 300 patients to date (28). Polyethylene glycol, a major component of the nanoparticle has been utilized in many other drug delivery systems and is approved globally with no known associated toxicities (29). These

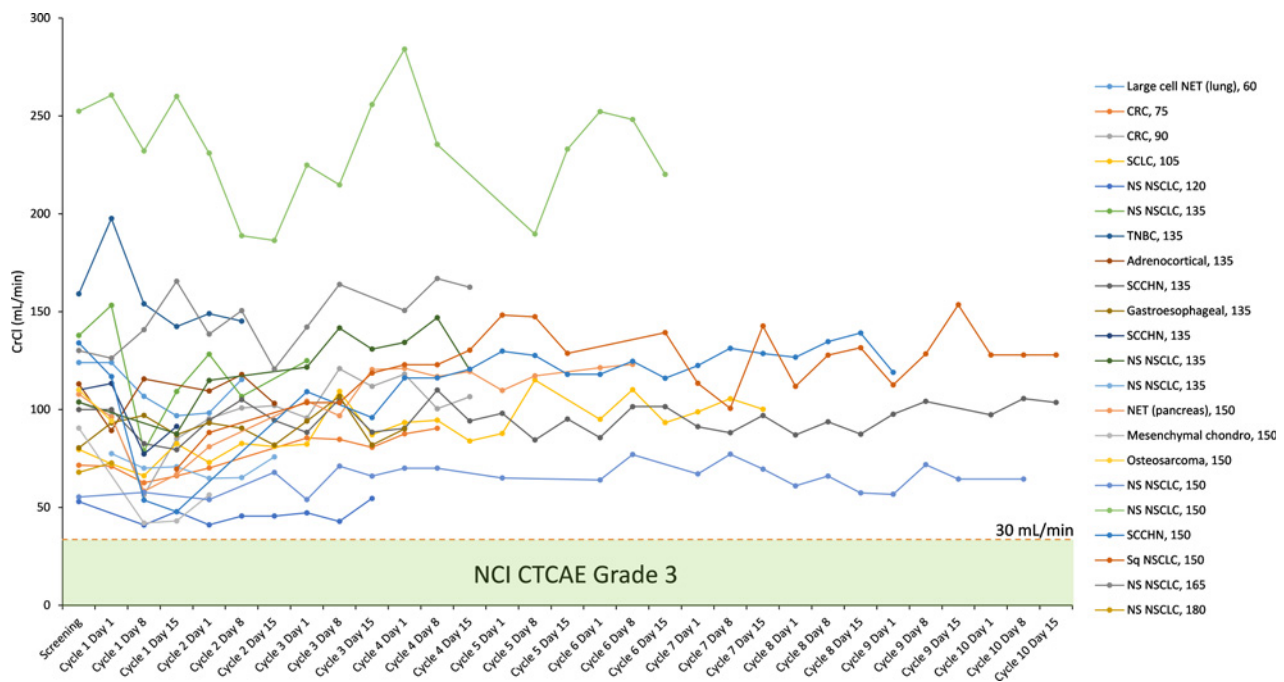


Figure 2. Change in CrCl over treatment duration (N = 22).

characteristics may be especially important in indications where high doses of cisplatin are used in practice (SCCHN) and in indications such as bladder cancer where cisplatin is the most

effective agent, but approximately half of patients are unable to tolerate it due to poor renal function. Nanoparticle cisplatin may also provide an advantage over cisplatin in patients with

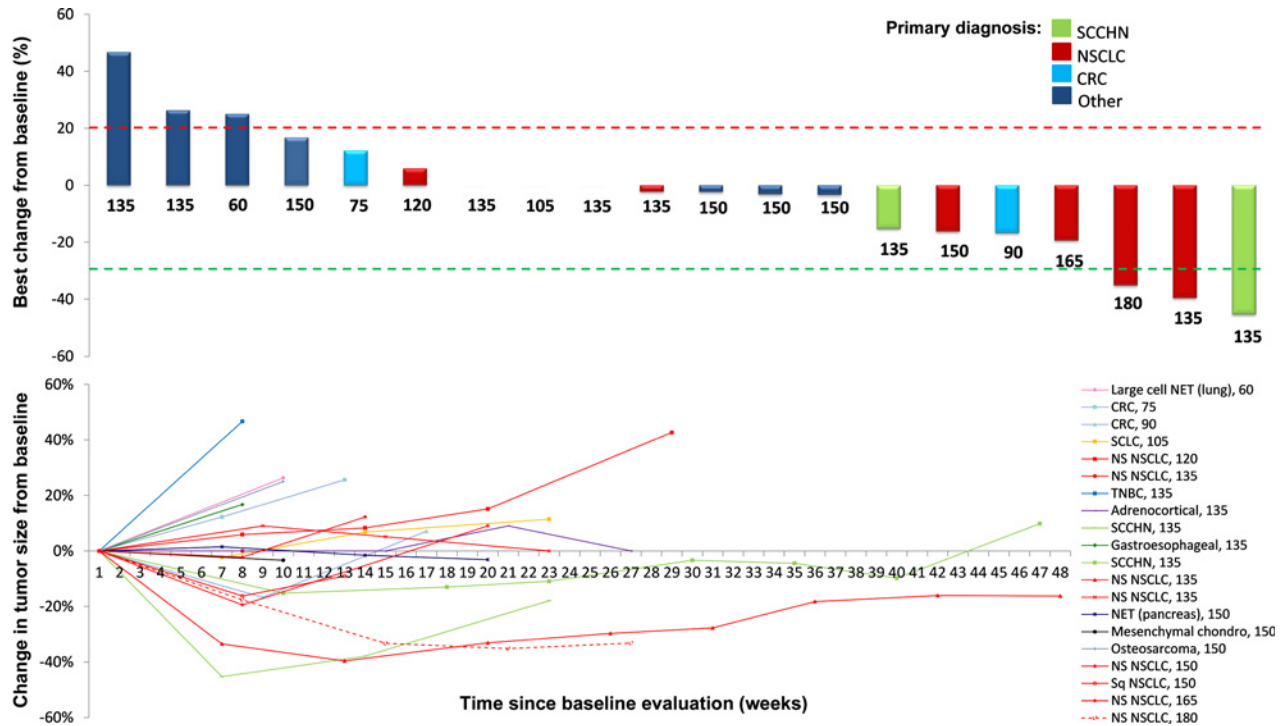


Figure 3. Best response by dose and tumor type and spider plot of change in tumor size (N = 20).

comorbidities who are older, have poor performance status and are unable to tolerate cisplatin.

This trial determined an MTD and RP2D of 135 mg/m² for NC-6004 in combination with gemcitabine using an adaptive Bayesian N-CRM. This was 50% higher than the MTD previously determined in the NC-6004 trial in Asia that used a traditional 3+3 modified Fibonacci dose escalation design. When designing clinical studies, there is substantial uncertainty about the appropriate design and how to optimally escalate the drug doses in patients. A traditional design defines all key trial parameters *a priori* and all parameters are held constant throughout the trial. However, this may not be the optimal design as shown by the outcome of this trial. As patients are enrolled and treated, information accumulates that reduces the uncertainty regarding the MTD. Adaptive designs such as the Bayesian N-CRM allow for dynamic modification of key trial parameters based on the accumulating information using a set of predefined rules. By continually updating the model, we were able to determine an MTD that was substantially higher than was previously determined and was well-tolerated in patients with advanced solid tumors without any additional clinically significant adverse events (30). Traditional 3+3 modified Fibonacci design may underestimate the true MTD, however there are few examples comparing actual MTDs from two dose escalation trials (one 3+3 and one N-CRM) evaluating the same regimen (31). Here we present one example of a trial where the N-CRM design optimized the dose and expedited the trial (largely due to the single-patient run-in) in contrast to prior NC-6004 phase I trials which used a traditional 3+3 modified Fibonacci trial. One limitation of making a direct comparison is our trial was performed in patients with all advanced solid tumors from the United States, while the 3+3 trial was conducted in Asia in patients with metastatic pancreatic cancer. Despite this, it is an interesting comparison illustrating the promise of N-CRM designs in practice. A phase I case study used simulations to evaluate a N-CRM design versus the 3+3 method in determining the MTD and found that on average the N-CRM design had a smaller average sample size and greater chance at determining the correct MTD under almost any dose-toxicity assumption (32). While only nine patients were treated at the MTD, we observed extended treatment duration in several patients suggestive of tolerability and disease control with NC-6004. Part 1 presented here represents a dose finding study in a heavily pretreated population, and additional data from the phase II portion of this trial will allow for a stronger understanding of the long term effects and activity of NC-6004 treatment at the RP2D in first-line patients. The 135 mg/m² dose was determined to the RP2D based on the tolerability profile and the observation of a dose–response relationship. This dose warrants further investigation in first-line locally advanced/metastatic bladder cancer, squamous cell NSCLC and biliary tract cancers which is ongoing in the phase II portion of this trial.

References

1. Piccart MJ, Lamb H, Vermorken JB. Current and future potential roles of the platinum drugs in the treatment of ovarian cancer. *Ann Oncol* 2001; 12:1195–203.
2. Socinski MA, Schell MJ, Peterman A, Bakri K, Yates S, Gitten R, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. *J Clin Oncol* 2002;20: 1335–43.

Conclusion

The results of the phase Ib portion of this trial have determined an MTD of NC-6004 that is 50% higher using a Bayesian design compared to a traditional 3+3 modified Fibonacci dose escalation design in a previous trial of NC-6004 with no clinically significant neuro, oto-, or nephrotoxicity. These data demonstrate promising activity and tolerability of NC-6004 and gemcitabine in heavily pretreated patients. On the basis of the tolerability and preliminary signal of activity observed, the combination of NC-6004 and gemcitabine warrants further investigation in the ongoing phase II trial enrolling NSCLC, biliary tract and bladder cancer.

Disclosure of Potential Conflicts of Interest

V. Subbiah reports receiving other commercial research support from ABBVIE, Bayer, Nanocarrier, and Novartis. N. Sharma is an employee of Novartis, reports receiving other commercial research support from Astellas Pharma, Bristol-Myers Squibb, Cleveland Biolabs, GlaxoSmithKline, Halozyme, Incuron, and Plexikon; speakers bureau honoraria from NCCN, and is a consultant/advisory board member for Bionest Partner, C1 consulting, and LEK. No potential conflicts of interest were disclosed by the other authors.

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Acknowledgments

The authors acknowledge the patients and their families for participating in this study.

This study was funded by Nanocarrier. The University of Texas MD Anderson Cancer Center was supported by the NIH Cancer Center Support grant no. CA016672. The Department of Investigational Cancer Therapeutics is supported by U11 TR000371, NCATS Center for Clinical and Translational Sciences.

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Received April 19, 2017; revised July 19, 2017; accepted October 10, 2017; published OnlineFirst October 13, 2017.

3. Park JO, Kim SW, Ahn JS, Suh C, Lee JS, Jang JS, et al. Phase III trial of two versus four additional cycles in patients who are nonprogressive after two cycles of platinum based chemotherapy in non-small-cell lung cancer. *J Clin Oncol* 2007;25:5233–39.
4. Plesken CV, Bergman B, Andersen O, Bremnes RM, Sundstrom S, Gillyery M, et al. Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. *B J Cancer* 2006;95:966–73.

5. Platinol® (cisplatin for injection, USP) [package insert]. Corden Pharma Latina S.p.A.: Sermoneta, Italy; 2011.
6. Hartmann JT, Lipp H-P. Toxicity of platinum compounds. *Expert Opin Pharmacother* 2003;4:889–901.
7. Alberts D. New perspectives on an old friend: optimizing carboplatin for the treatment of solid tumors. *Oncologist* 1997;3:15–34.
8. Bellmunt J, Ribas A, Eres N, Albanell J, Almanza C, Bermejo B, et al. Carboplatin-based versus cisplatin-based chemotherapy in the treatment of surgically incurable advanced bladder carcinoma. *Cancer* 1997;80:1966–72.
9. Dogliotti L, Carteni G, Siena S, Bertetto O, Martoni A, Bono A, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. *Eur Urol* 2007;52:134–141.
10. Petrioli R, Frediani B, Manganelli A, Barbanti G, De Capua B, De Lauretis A, et al. Comparison between a cisplatin containing regimen and a carboplatin-containing regimen for recurrent or metastatic bladder cancer patients. A randomized phase II study. *Cancer* 1996;77:344–351.
11. Forastiere AA, Metch B, Schuller DE, Ensley JF, Hutchins LF, Triozzi P, et al. Randomized comparison of cisplatin plus fluorouracil and carboplatin plus fluorouracil versus methotrexate in advanced squamous-cell carcinoma of the head and neck: a Southwest Oncology Group study. *J Clin Oncol* 1992;10:1245–51.
12. De Andrés L, Brunet J, López-Pousa A, Burgués J, Vega M, Tabernero JM, et al. Randomized trial of neoadjuvant cisplatin and fluorouracil versus carboplatin and fluorouracil in patients with stage IV-M0 head and neck cancer. *J Clin Oncol* 1995;13:1493–500.
13. Galsky MD, Chen GJ, Oh WK, Bellmunt J, Roth BJ, Petrioli R, et al. Comparative effectiveness of cisplatin-based and carboplatin based chemotherapy for treatment of advanced urothelial carcinoma. *Ann Oncol* 2012;23:406–10.
14. Guan J, Li Q, Zhang Y, Xiao N, Chen M, Zhang Y, et al. A meta-analysis comparing cisplatin-based to carboplatin-based chemotherapy in moderate to advanced squamous cell carcinoma of head and neck (SCCHN). *Oncotarget* 2016;7:7110–19.
15. 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.
16. Cabral H, Matsumoto Y, Mizuno K, Chen Q, Murakami M, Kimura M, et al. Accumulation of sub-100 nm polymeric micelles in poorly permeable tumours depends on size. *Nat Nanotechnol* 2011;6:815–23.
17. Nishiyama N, Okazaki S, Cabral H, Miyamoto M, Kato Y, Sugiyama Y, et al. Novel cisplatin-incorporated polymeric micelles can eradicate solid tumors in mice. *Cancer Res* 2003;63, 8977–83.
18. Baba M, Matsumoto Y, Kashio A, Cabral H, Nishiyama N, Kataoka K, et al. Micellization of cisplatin (NC-6004) reduces its ototoxicity in guinea pigs. *J Control Release* 2012;157:112–7.
19. Uchino H, Matsumura Y, Negishi T, Koizumi F, Hayashi T, Honda T, et al. Cisplatin-incorporating polymeric micelles (NC 6004) can reduce nephrotoxicity and neurotoxicity of cisplatin in rats. *Br J Cancer* 2005;93:678–87.
20. Plummer R, Wilson RH, Calvert H, Boddy AV, Griffin M, Sludden J, et al. A phase I clinical study of cisplatin-incorporated polymeric micelles (NC-6004) in patients with solid tumours. *Br J Cancer* 2011;104:593–8.
21. Reece PA, Stafford I, Russell J, Khan M, Gill PG. Creatinine clearance as a predictor of ultrafilterable platinum disposition in cancer patients treated with cisplatin: relationship between peak ultrafilterable platinum plasma levels and nephrotoxicity. *J Clin Oncol* 1987;5:304–9.
22. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. *Stat Med* 2008;27:2420–39.
23. 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.
24. Greish K. Enhanced permeability and retention (EPR) effect for anticancer nanomedicine drug targeting. *Methods Mol Biol* 2010;624:25–37.
25. Roila F, Molassiotis A, Herrstedt J, Aapro M, Gralla RJ, Bruera E, et al. MASCC and ESMO consensus guidelines for the prevention of chemotherapy and radiotherapy-induced nausea and vomiting: ESMO clinical practice guidelines. *Ann Oncol* 2016;27:v119–33.
26. Lauritsen J, Mortensen MS, Kier MGG, Christensen IJ, Agerbaek M, Gupta R, et al. Renal impairment and late toxicity in germ-cell cancer survivors. *Ann Oncol* 2015;26:173–8.
27. Doi T, Hamaguchi T, Shitara K, Iwasa S, Shimada Y, Harada M, et al. NC-6004 phase I study in combination with gemcitabine for advanced solid tumors and population PK/PD analysis. *Cancer Chemother Pharmacol* 2017;79:569–78.
28. NanoCarrier Investigator Brochure Edition 9.0, August 2015.
29. D'souza AA, Shegokar R. Polyethylene glycol (PEG): a versatile polymer for pharmaceutical applications. *Expert Opin Drug Deliv* 2016;13:1257–75.
30. Hansen A, Graham D, Pond G, Siu LL. Phase 1 trial design: is 3+3 the best? *Cancer Control* 2014;21:200–208.
31. Reitsma DJ, Hummel J, Simmons AE, Combest AJ. We can improve trials using adaptive designs. *Applied Clinical Trials* 2015;35.
32. Hummel J, Wang S, Kirkpatrick J. Using simulation to optimize adaptive trial designs: applications in learning and confirmatory phase trials. *Clin Invest* 2015;5:401–13.