NanoCarrier Co. Ltd.
Orient Europharma Co., Ltd.

CLINICAL STUDY REPORT

Phase IIa/IIb Clinical Trial of NC-6004 in Combination with Pembrolizumab in Subjects with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Have Failed Platinum or a Platinum-containing Regimen

Protocol Number:	NC-6004-009
Investigational Medicinal Product:	NC-6004
Indication:	Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck
Phase:	IIa/IIb
Sponsor:	**Nano Carrier Co, Ltd.** Ohnoya-Kyobashi Bldg 1-4-10 Kyobashi, Chuo-ku, Tokyo, 104-0031, Japan **Orient Europharma Co., Ltd.** 7 F, No. 368, Sec. 1, Fu Hsing S. Rd., Taipei, Taiwan, R. O. C.
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First Patient, First Visit:	14. 06. 2019 (IIa) - 12. 10. 2020 (IIb)
Early Study Termination:	02. 06. 2022
Last Patient, Last Visit:	30. 06. 2022
Date of Report:	05. 01. 2023
Report Version:	1.0

The study was conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements, including the archiving of essential documents.

2. SYNOPSIS

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Title of Study: Phase IIa/IIb Clinical Trial of NC-6004 in Combination with Pembrolizumab in Subjects with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Have Failed Platinum or a Platinum-containing Regimen

Protocol Number: NC-6004-009

Study Period: **Study Phase:** IIa/IIb

Date of first patient, first visit: 14. 06. 2019 (IIa) - 12. 10. 2020 (IIb)

Date of last patient, last visit: 30. 06. 2022

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- Prof Anna Kryzhanivska - Municipal Non-Profit Enterprise "Prykarpattia Clinical Oncology Center of the Ivano-Frankivsk Regional Council", 17, Medychna street Ivano-Frankivsk 76018
- Oleksandr Burian - Communal non-profit enterprise "Regional center of oncology", Lisoparkivska str. 4, Kharkiv 61070

Publication(s): None

Objectives:

Primary objectives

Part 1 (Phase IIa):

- To assess (DLTs), and to determine the optimal dose in order to establish the RPIIb dose for the combination of NC 6004 plus pembrolizumab.

Part 2 (Phase IIb):

- To compare Progression-Free Survival (PFS) between NC 6004 plus pembrolizumab and pembrolizumab alone.

Secondary objectives

- To evaluate the safety and tolerability of NC-6004 when combined with pembrolizumab.
- To compare OS between NC 6004 plus pembrolizumab and pembrolizumab alone.
- To compare tumor response between NC 6004 plus pembrolizumab and pembrolizumab alone.
- To assess the pharmacokinetics of NC-6004.

Study Design: This was a Phase IIa/IIb study in subjects with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck Who Have Failed Platinum or a Platinum-containing Regimen, consisting of 2 parts with:

- Experimental arm: NC-6004 + pembrolizumab NC-6004 was to be administered to subjects once every 3 weeks. On Day 1 of each treatment cycle NC-6004 was to be administered first followed by pembrolizumab.
- Active Comparator arm: Pembrolizumab: The recommended dose of pembrolizumab was 200 mg administered as an IV infusion over 30 minutes every 3 weeks.

Part 1 was a Phase IIa, dose-escalation study to determine the optimum tolerated dose and RPIIb dose for use in combination with pembrolizumab in subjects with any of the following:

- Previous treatment with a platinum agent or a platinum-containing regimen for their recurrent or metastatic HNSCC.
- Progressive disease <6 months of multimodal therapy using a platinum agent or a platinum-containing regiment for locally advanced HNSCC.
- Subjects who progressed ≥6 months of multimodal therapy using a platinum agent or a platinum-containing regimen for locally advanced HNSCC could be eligible for the study only if they had subsequently progressed during or after treatment with a platinum agent or a platinum-containing regimen received for recurrent and metastatic stage of disease.

The Part 1 starting dose was 90 mg/m^2, with subsequent dose escalations to 105 mg/m^2, 120 mg/m^2, and 135 mg/m^2. If DLTs were observed at the starting dose, a de-escalation to 60 mg/m^2 occurred.

Part 2 was a Phase IIb, randomized control study between NC-6004 in combination with pembrolizumab versus pembrolizumab alone in the same subject population as Part 1 at the RPIIb dose identified in Part 1.

Part 1/Part 2 (Combination Therapy: NC-6004, Pembrolizumab):

For both Part 1 and Part 2 of the study, each treatment cycle was 21 days (3 weeks) in duration (+3 days). Subjects in both Part 1 and Part 2 continued treatment until progressive disease, unacceptable toxicity, or intercurrent illness that prevented further treatment unless they were discontinued from study treatment.

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All subjects were followed after discontinuation from study treatment for any reason except progressive disease until progressive disease.

Subjects who withdrew from the study due to toxicities or AEs were followed until disease progression.

After disease progression all subjects were followed for overall survival.

Efficacy and activity assessments included disease response assessments and disease progression assessments. Disease progression was assessed at 6 weeks and 12 weeks, and thereafter every 9 weeks after the last imaging through 48 weeks (±1 week) for the evaluation of PFS. For subjects continuing treatment after 48 weeks, the assessment was performed every 12 weeks (±1 week) after the last imaging until PD. Disease response assessments included radiological assessments per RECIST version 1.1 for PFS, ORR, CR/PR, TTR, DOR and SD at 6 weeks and 12 weeks, and thereafter every 9 weeks after the last imaging through 48 weeks (±1 week) and after this every 12 weeks (±1 week) after the last imaging until confirmed PD. PD was confirmed by imaging ≥4 weeks up to 8 weeks after radiologic PD. (Subsequent radiological assessments occurred following the above schedule if PD was not confirmed.) Overall survival was assessed.

Safety was assessed by reported AEs, clinical laboratory tests (hematology and biochemistry), 12-lead ECGs, physical examinations, vital signs (blood pressure, heart rate, respiratory rate, and temperature), and concomitant medications.

Blood was drawn during Part 1 for PK assessments. The following PK parameters were calculated: C_{max}, T_{max}, $AUC_{0-\infty}$, AUC_{0-t}, AUC_{0-tau}, Rac, λz, T½, CL, Vz, and Vss.

Number of Subjects (planned and analyzed):

Phase IIa (Part 1): Number of subjects planned was determined based on medical reasoning; 16 subjects analyzed.

Phase IIb (Part 2): Number of subjects planned 124; 105 subjects analyzed.

Diagnosis and Main Criteria for Inclusion:

1. Be willing and able to provide written informed consent for the trial.
2. Males or females aged ≥18 years at screening.
3. Had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1.
4. Had histologically- or cytologically-confirmed HNSCC.
5. Had recurrent disease not amenable to curative treatment with local or systemic therapy, or metastatic (disseminated) HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx that was considered incurable by local therapies.
6. Had received ≥150 mg/m^2 of a total dose of cisplatin or 2 cycles of carboplatin AUC5 (maximum carboplatin dose per cycle 750 mg).
7. Prior platinum failure as defined by:
   a. Disease progression confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scans using RECIST 1.1 criteria at any time during or after treatment with a platinum agent or a platinum-containing regimen for recurrent/metastatic disease.
   b. Recurrence/progression confirmed by CT or MRI imaging scans using RECIST 1.1 criteria <6 months of prior modal therapy using a platinum agent or a platinum-containing regimen for locally advanced setting,
   c. Recurrence/progression ≥6 months of prior modal therapy in locally advanced HNSCC can be accepted only if subjects have received a further platinum containing regimen for recurrent and metastatic stage of disease and have progressed during or after this regimen.
8. Have a life expectancy of >3 months.
9. Have radiographically measurable disease based on RECIST 1.1.
10. Have adequate bone marrow reserve, defined as:
    a. Absolute neutrophil count ≥1.5 × 10^9/L;

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b. Platelet count ≥100 × 10^9/L; and
c. Hemoglobin ≥10 g/dL (transfusion is allowed to achieve ≥ 10 g/dL).

11. Have adequate liver function, defined as:
    a. Total serum bilirubin ≤1.5 × the upper limit of normal (ULN) or ≤2 × ULN in the cases of subjects with documented hepatic metastasis;
    b. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) <2.0 × ULN or <5.0 × ULN in the cases of subjects with documented hepatic metastasis;
    c. Serum albumin ≥ 3.5 g/dL.
12. Had prothrombin time within normal limits.
13. Had adequate renal function, using the Cockcroft method: Glomerular filtration rate ≥60 mL/min.
14. Had results from central laboratory testing of HPV (defined as p16 IHC testing using CINtec p16 Histology assay and a 70% cutoff point).

    Note: HPV stratification was performed in subjects with oropharynx cancer. Oral cavity, hypopharynx, and larynx cancer were not required to undergo HPV testing by the central laboratory.
15. Had provided tissue for PD-L1 biomarker analysis from a newly obtained core, excisional biopsy or an archived specimen. Repeat samples could be required if adequate tissue was not provided or for indeterminate results.

    Note: If emerging data indicated a high concordance in PD-L1 expression scores between newly obtained and archival samples, archived samples could be acceptable.
16. Female subjects of childbearing potential should have a negative serum pregnancy test within 72 hours prior to receiving the first dose of study medication. A urine test could be considered if a serum test was not appropriate.
17. Female subjects of childbearing potential must be willing to use 2 methods of birth control or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study therapy according to local standard of care.

    Note: Abstinence was acceptable if this was the established and preferred contraception for the subject.
18. Male subjects must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy according to local standard of care.

Note: Abstinence was acceptable if this was the established and preferred contraception for the subject.

Study Treatment, Dose and Mode of Administration:

- Study treatment: NC-6004

NC-6004 was administered to subjects once every 3 weeks. On Day 1 of each treatment cycle NC-6004 was administered first followed by pembrolizumab.

Other Name: Nanoplatin

- Study treatment: Pembrolizumab

The recommended dose of pembrolizumab is 200 mg administered as an IV infusion over 30 minutes every 3 weeks.

Subjects were administered with NC-6004 first followed by pembrolizumab in both parts of the study.

The Part 1 phase IIa portion, starting dose was 90 mg/m^2, with subsequent dose escalations to 105 mg/m^2, 120 mg/m^2, and 135 mg/m^2. In phase IIb portion, the dose was to be determined RPII dose in phase IIa portion.

NC-6004 drug product was provided in vials of 5 mL containing the equivalent of 50 mg cisplatin. NC-6004 was mixed with 500 mL of 5% dextrose solution for IV infusion over 60 minutes.

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Duration of Treatment:

For both Part 1 and Part 2 of the study, each treatment cycle was to be 21 days (3 weeks) in duration (+3 days). The treatment of the individual subject was limited to 24 months, calculated from the first received treatment cycle.

Criteria for Evaluation:

Efficacy:

Efficacy and activity assessments included disease response assessments and disease progression assessments. Disease progression was assessed at 6 weeks and 12 weeks, and thereafter every 9 weeks after the last imaging through 48 weeks (±1 week) for the evaluation of PFS. For subjects continuing treatment after 48 weeks (±1 week) the assessment was performed every 12 weeks (±1 week) after the last imaging until PD. Disease response assessments included radiological assessments per RECIST version 1.1 for PFS, ORR, CR/PR, SD, TTR and DOR at 6 weeks, 12 weeks, thereafter every 9 weeks after the last imaging through 48 weeks and after this every 12 weeks after the last imaging until confirmed PD. PD was confirmed by imaging ≥4 weeks up to 8 weeks after radiologic PD. (Subsequent radiological assessments occurred following the above schedule if PD was not confirmed.) Overall survival was also assessed.

Safety:

Safety was assessed by reported adverse events (AEs), clinical laboratory tests (hematology and biochemistry), 12-lead ECGs, physical examinations, vital signs (blood pressure, heart rate, respiratory rate, and temperature), and concomitant medications.

AEs were graded according to the NCI-CTCAE v5.0 criteria (only abnormal laboratory results deemed to be clinically significant were recorded as AEs or SAEs).

Statistical Methods:

Efficacy:

The assessment of the treatment efficacy was primarily based on the treatment response as measured by the RECIST (version 1.1). Based on the RECIST outcomes for CR, PR, SD and PD, the times from start of treatment to any of these outcomes will be determined. Apart from summarizing the frequency distributions for each treatment group at the scheduled assessment times during the study, the primary analysis focused on the times to these events. As these times were not directly observable due to censoring, statistical methods for survival time analysis was used for the description and analysis of these times and the time of overall survival.

In particular, the survival time distributions in each treatment group was estimated using the product-limit method and graphically displayed in Kaplan-Meier curves.

Treatment comparisons of the time variables (e.g. time to disease progression) was performed in the context of a proportional hazards (Cox) regression model, estimating and testing the hazard ratio. The results of these inferences (p-values, 95% confidence intervals) was supplemented by figures.

If the model assumption of proportional hazard did not hold for a particular time to event, then the nonparametric log-rank test was used for treatment comparison in this case.

The time to event analyses was performed separately for each study part.

Safety:

The analysis of safety was based on the occurrence of AEs, the results of the safety laboratory tests, vital signs, ECG measurements and results of Physical Examination.

AEs were coded according to the version of MedDRA current at the start of the study. The analysis included only TEAEs, i.e., AEs that started or worsened after the start of IMP. All TEAEs, related TEAEs (i.e., TEAEs probably or possibly related to the IMP), and serious TEAEs were summarized and tabulated according to MedDRA primary system organ class and preferred term.

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Subject listings were provided for subjects with SAEs, AEs leading to withdrawal from study, and AEs leading to death.

Time profiles of the safety laboratory parameters were analyzed by presenting sampling statistics for the values as well as their difference to baseline at each time point. Additionally, frequency tables for values outside the normal ranges as well as shift tables were presented.

Vital signs and continuous ECG measurements were analyzed by presenting sampling statistics for the values as well as their difference to baseline at each time point. Additionally, frequency tables were presented for classified QTC values and differences (according to ICH-E14) as well as ECG interpretations.

Subjects disposition:

A total of 220 subjects were screened in this study, 16 subjects in Phase IIa and 204 subjects in Phase IIb.

In Phase IIa, dose escalation (Part 1), dose-limiting toxicities (DLTs), to determine the optimal dose recommended for Phase IIb (RPIIb), 16 subjects screened were enrolled and received treatment (trt) as follow:

- NC-6004 90 mg/m² + Pembrolizumab (trt1) (3 subjects),
- NC-6004 105 mg/m² + Pembrolizumab (trt2) (4 subjects),
- NC-6004 120 mg/m² + Pembrolizumab (trt3) (3 subjects),
- NC-6004 135 mg/m² + Pembrolizumab (trt4) (6 subjects).

Of 204 subjects screened for Phase IIb, 136 subjects were randomized and 68 subjects were screen failure. Of the 136 subjects, 31 subjects were excluded from the Full analysis Set (FAS) and 105 subjects received trt as follow:

- NC-6004 + Pembrolizumab (trt5) (53 subjects),
- Pembrolizumab alone (trt6) (52 subjects).

Of the 105 subjects in Phase IIb, 5 subjects (4.1%) completed the study and 100 subjects discontinued the study. The most common reasons for treatment discontinuation were disease progression (76 subjects [62.8%]) and death (65 subjects [53.7%]).

Demographic data:

In Phase IIa (Part 1) study, majority of subjects were male (14 subjects [87.5%]) and not Hispanic or Latino (14 subjects [87.5%]). All the subjects (100.0%) were white. Most of the subjects (13 subjects [81.25%]) enrolled were from Serbia.

In Phase IIb (Part 2) study, majority of subjects were male (90 subjects [85.71%]) and not Hispanic or Latino (104 subjects [99.05%]). Most of the subjects (93 subjects [88.57%]) were white.

Efficacy Results:

Approximately, similar proportion of subjects in the NC 6004 + Pembrolizumab treatment group and Pembrolizumab treatment group achieved overall response: 12 subjects (22.64%) in the NC 6004 + Pembrolizumab treatment group and 12 subjects (23.08%) patients in the Pembrolizumab treatment group had progression. Majority of patients did not achieve the overall response rate.

Higher proportion of subjects in the NC 6004 + Pembrolizumab treatment group (43 subjects [81.13%]) had progression in comparison to the Pembrolizumab treatment group (36 subjects [72.0%]). The median time to progression was similar across both the treatments groups: 4.90 months (95% C.I: 2.89, 6.18) in the NC 6004 + Pembrolizumab treatment group and 4.86 months (95% C.I: 2.83, 8.97) in the Pembrolizumab treatment group (HR [95% CI]: 1.20 [0.77, 1.89]; p=0.4233). The progression-free estimates were similar in the NC 6004 + Pembrolizumab and in the Pembrolizumab treatment group (60.09% and 38.64%). The KM-estimate for progression after 3 months, after 6 months, 9 months and

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12 months were higher in the Pembrolizumab treatment group in comparison to the NC 6004 + Pembrolizumab group.

Safety Results:

Safety population consisted of 121 subjects.

Extent of Exposure

In Phase IIa (Part 1) study, the median total dose of NC-6004 105 mg/m² + Pembrolizumab, NC-6004 135 mg/m² + Pembrolizumab, NC-6004 90 mg/m² + Pembrolizumab, and NC-6004 120 mg/m² + Pembrolizumab administered was 90.1, 135, 90.2, and 120.

In Phase IIb (Part 2) study, the median total dose of NC-6004 + Pembrolizumab was 135.

Adverse Events:

- In Phase IIa (Part 1), a total of 15 (93.8%) subjects experienced at least one AE. The most commonly reported AEs by PTs (occurring in ≥10% of overall subjects) were anaemia: thrombocytopenia, hypothyroidism, hyperglycaemia, hyperkalaemia, hypomagnesaemia, stomatitis, blood creatinine increased, creatinine renal clearance decreased, and weight decreased. In Phase IIa (Part 1) study, a total of 13 subjects (81.3%) experienced at least one TEAE and all of the TEAEs were of ≥Grade 3 intensity.
- In Phase IIb (Part 2), a total of 99 (94.3%) subjects experienced at least one AE: 52 (100.0%) subjects in NC-6004 + Pembrolizumab, and 47 (90.4%) subjects in Pembrolizumab treatment group. The most commonly reported AEs by PTs (occurring in ≥10% of overall subjects) were anaemia, hypothyroidism, hypomagnesaemia, asthenia, and blood creatinine increased.
- In Phase IIb (Part 2) study, a total of 98 (93.3%) subjects reported 730 TEAEs. Of these, 47 subjects (44.8%) experienced TEAE with ≥Grade 3 intensity
- In Phase IIa (Part 1) study, a total of 13 subjects (81.3%) experienced TEAEs of ≥Grade 3 intensity.
- In Phase IIb (Part 2) study, a total of 47 subjects (44.8%) experienced TEAE with ≥Grade 3 intensity.
- In Phase IIa (Part 1) study, 1 (6.3%) subject in NC-6004 105 mg/m² + Pembrolizumab treatment group reported a TEAE (PT: Hypophosphatemia) which was considered as dose limiting toxicity (DLTs).
- In Phase IIb (Part 2) study, 13 (12.4%) subjects experienced TEAEs which were considered as DLTs with higher proportion of subjects in NC-6004 + Pembrolizumab treatment group compared to the subjects in Pembrolizumab treatment group.

Overall, 5 subjects experienced TEAEs that lead to death. These TEAEs reported by PTs were Suspected COVID-19 infection, Pneumonia, death, Pneumonia viral, and Acute coronary syndrome.

Conclusions:

- The efficacy objective of the study was not met. There was no difference in the NC 6004 + Pembrolizumab and in the Pembrolizumab treatment groups.
- There was no clinically meaningful difference in safety between the NC-6004 + Pembrolizumab treatment group and Pembrolizumab treatment group.

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