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To whom it may concern:

NanoCarrier Co., Ltd.
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NC-6300: Positive Results of Phase 1b/II Clinical Study in the US published on Clinical Cancer Research

We are pleased to announce that NC-6300 (epirubicin-encapsulated nanoparticle) phase 1b portion result was published in *Clinical Cancer Research*, which is an official journal of the American Association for Cancer Research, on May 7th, 2020 as follows. NanoCarrier has developed NC-6300 for soft tissue sarcoma and been running a phase 1b/II study in the US.

- There were no adverse events specific to NC-6300. Although epirubicin-related adverse reactions such as nausea/vomiting and myelotoxicity were observed, both the incidence and severity tended to decrease.
- No clinically significant decrease in cardiac function was observed, even in patients with long-term administration.
- Partial Response (PR) was observed in two cases out of two enrolled patients with angiosarcoma, a type of soft tissue sarcoma.
- Long term Stable Disease (SD) was observed in a patient with malignant melanoma refractory to several immune checkpoint inhibitor therapies.

NC-6300 has been designated as an orphan drug for soft tissues sarcoma in the U.S. Based on the phase 1b result, NanoCarrier has initiated angiosarcoma expansion cohort from October 2019 enrolling 10 angiosarcoma patients in order to pursue developmental strategies toward early approval in an area where no robust standard of care available.

Title : A Phase 1b Dose-Escalation Trial of NC-6300 (Nanoparticle Epirubicin) in Patients with Advanced Solid Tumors or Advanced, Metastatic, or Unresectable Soft Tissue Sarcoma
Author: Sant P Chawla, Sanjay Goel, Warren Chow, Fadi Braiteh, Arun S Singh, Juneko E Grilley Olson, Atsushi Osada, Iulian Bobe and Richard F. Riedel
Online : https://clincancerres.aacrjournals.org/content/early/2020/05/07/1078-0432.CCR-20-0591.abstract

**[Abstract]**

**Purpose:**
NC-6300 is a novel nanoparticle formulation of epirubicin that has a pH sensitive linker conjugated to epirubicin. It exhibits selective tumor accumulation owing to enhanced permeability and retention effect. We conducted a phase 1b trial to determine maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of NC-6300 monotherapy in advanced, metastatic, or unresectable solid tumors, including soft tissue sarcomas.
Experimental Design:
This Phase 1b dose escalation trial of NC-6300 monotherapy employed a Bayesian continuous reassessment method design. NC-6300 was administered on Day 1 of every 21-day cycle, with epirubicin-equivalent dose increments from 125 mg/m² to 215 mg/m². Safety, efficacy, quality-of-life, and pharmacokinetic profile of NC-6300 monotherapy were evaluated.

Results:
Twenty-nine subjects (16 male) were enrolled: 17 with soft tissue sarcoma, 1 with osteosarcoma and 11 with other solid tumors. Observed dose-limiting toxicities included thrombocytopenia, stomatitis, lung infection and febrile neutropenia. The most common grade 3/4 adverse events were neutropenia (59%), anemia (24%), thrombocytopenia (24%) and febrile neutropenia (21%). MTD and RP2D were determined to be 185 mg/m² and 150 mg/m², respectively. The objective response rate in the evaluable population was 11%. Partial response was observed in angiosarcoma and endometrial stromal sarcoma. A dose-dependent increase was observed in both total and released epirubicin concentrations.

Conclusions:
NC-6300 was well tolerated with a manageable side effect profile, despite the MTD and RP2D being higher than conventional epirubicin doses. A signal of preliminary activity was observed in angiosarcoma. NC-6300 warrants further investigation in patients with advanced solid tumors, including sarcoma.

*NC-6300 (epirubicin micelle)
NC-6300 is one of NanoCarrier’s pipeline products using our proprietary micellar nanoparticle technology. It is a pH-sensitive micelle compound that incorporates the anticancer drug epirubicin and selectively releases a large amount of epirubicin by sensing the intracellular environment after being absorbed into cancer cells. Epirubicin is classified to a drug class so called anthracyclines. NanoCarrier promotes the development of this novel micellar compound under the concept of further reducing the impact on normal cells and enhancing the antitumor effect through a massive release of the anticancer drug inside the cells.

*Soft Tissue Sarcoma
Soft tissue sarcomas are a type of malignant solid tumor arising in soft tissue, such as fat, muscle and blood vessels. According to the U.S. National Cancer Institute, the number of new-onset adult patients with soft tissue sarcoma in the U.S. is estimated to be around 12,000 cases/year. Soft tissue sarcoma is globally recognized as a rare cancer. Angiosarcoma is one of the soft tissue sarcoma subtypes comprising 2-3% of the entire soft tissue sarcoma population.

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