The annual meeting of the American Association for Cancer Research, one of the major cancer-related associations, will be held in New Orleans, Louisiana, USA from April 16 to 20, 2016. On April 18, we will present about NC-6201, which is our new pipeline using the ADCM where anti-EGFR\(^1\) antibody, NCAB001, is attached on the surface of the micelle, and the new anticancer agent, E7974\(^2\) is incorporated in the inner core. ADCM is a next-generation technology to realize a novel targeted delivery platform for anticancer therapy, and NC-6201 has been studied with a view to initiating a clinical trial.

ADCM is NanoCarrier’s proprietary technology that enables the creation of breakthrough pharmaceutical products. Using ADCM, anti-tumor effect is improved by retaining a large amount of the drug in the micelle and controlling its release. In addition, drug targeting to cancer cells and normal cell damage are significantly improved by ADCM. It was revealed that the therapeutic index of NC-62001 was improved approx. 30 times in comparison with E7974 itself. Non-clinical studies of NC-6201 are currently being conducted, and we are preparing for filing an IND by the end of 2016 to initiate a phase I clinical trial in the United States.

In parallel with internal development of pipeline using ADCM, we are actively promoting collaborations using ADCM with pharmaceutical companies, bio-ventures, and research institutions.

\(^1\) EGFR
A receptor protein that is over-expressed on the surface of various types of cancer cells.

\(^2\) E7974
Tubulin depolymerization inhibitor, A highly active anticancer agent candidate introduced by Eisai Co., Ltd.
It also demonstrates an effect for multidrug-resistant cancers.
Title: Preclinical evaluation of NC-6201, an antibody/drug-conjugated micelle incorporating novel hemiasterlin analogue E7974

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Abstract:

Background
Antibody-drug conjugates (ADCs) have been recognized as a promising anticancer agent. There have been a lot of registered clinical trials for ADCs. However, not all ADC compounds were successful. To overcome the difficulties and drive the next generation of ADCs, we have recently developed Antibody/Drug-Conjugated Micelle (ADCM) system. ADCM is composed of polyethylene glycol-poly (amino acid derivative) polymers, which can form a micellar nanoparticle spontaneously in aqueous media with a diameter of 20-100 nm. Antibodies are attached to the surface of the nanoparticle, while payloads are incorporated in the inner core at a payload-to-antibody molecular ratio of 100-200. In this study, anti-EGFR monoclonal antibody NCAB001 and novel hemiasterlin analogue E7974 were used as a targeting sensor and a payload of the ADCM (NC-6201), respectively. Here we report the results of in vitro evaluation and in vivo efficacy and toxicity studies.

Methods
NC-6201 was prepared as described previously (Japan Patent No.4538666) with slight modification. The antigen affinity and the cytotoxicity of NC-6201 were evaluated using a Biacore system and Cell Counting Kit-8, respectively. NC-6201 was administered intravenously to BALB/c-nu/nu mice xenografted with various human tumor cell lines. Tumor volumes and animal body weights were monitored 2 or 3 times a week. Also, the dose- and schedule-dependency of the antitumor effect were evaluated. Single-dosed toxicological studies of NC-6201 in SD rats and cynomolgus monkeys were performed.

Results
NC-6201 showed similar antigen affinity to the unconjugated NCAB001 and had a broad range of in vitro cytotoxicity against a panel of tumor cells. NC-6201 potently suppressed tumor growth in nude mice bearing subcutaneous human tumor xenografts expressing EGFR, such as BxPC-3 (pancreas) and MDA-MB-231 (triple-negative breast) tumor models. The efficacious NC-6201 dose schedules were achieved at one tenth or two fifth of its MTD. In an EGFR-null tumor model, NC-6201 and untargeted micelle incorporating E7974 showed comparable tumor growth inhibition. Overall, NC-6201 at efficacious doses was well tolerated without significant body weight loss, indicating that NC-6201 has an excellent therapeutic window. Relative to E7974, NC-6201 showed an unaltered toxicity profile in rats and monkeys, and the potential for reduced toxicity and an improved therapeutic window.

Conclusion
Based on these promising results, NC-6201 is advanced in our project pipeline as a clinical candidate for cancer therapy.