Antibody/Drug-Conjugated Micelle (ADCM): the Next Generation of Active Targeting Technology
This presentation may include forward-looking statements pertaining to the business and prospects of NanoCarrier Co., Ltd. (the “Company”). These statements reflect the Company’s current analysis of existing information and trends. Actual results may differ from expectations based on risks and uncertainties that may affect the Company’s businesses. Although this presentation includes information regarding pharmaceuticals (including products under development), the information is not intended as any advertisement and/or medical advice.
FY1996: Incorporation of the company to develop innovative nanomedicine based on cutting-edge polymer technology from Japan
FY2000: Started real activity of the company at Kashiwa-city to develop innovative anti-cancer nanomedicine
FY2008: Listing at Tokyo Stock Exchange (TSE) Mothers Market
FY2014: Relocation of a head office and a laboratory to a new facility at Kashiwanoha Campus
FY2016: In promoting several clinical trials in the world (Japan, the United States, Europe, Asia)

HQ and Research Lab: Kashiwa, Chiba, Japan
Tokyo office: Chuo-ku, Tokyo, Japan
iCONM Lab: Kawasaki, Kanagawa, Japan
NanoCarrier Highlights

Core Technology - Nanomicelle

Robust Oncology Pipelines

Antibody/Drug-Conjugated Micelle (ADCM)
Core Technology - Nanomicelle

Poly-Ethylene Glycol (Hydrophilic, outside of micelle)

Poly-Amino Acid (Hydrophobic, inside micelle)

- Payloads (LMW to HMW)

Loading and Releasing:
- Physical entrapment
- Electrostatic bonding
- Chemical conjugation

Self assembly

Average of 30-100nm
NanoCarrier - All in One Delivery Technology

Enhanced solubility
Dissolve the hydrophobic drug in water

<table>
<thead>
<tr>
<th>Drug (mg/mL)</th>
<th>Itraconazole</th>
<th>Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>&lt;0.001</td>
<td>&lt;0.1</td>
</tr>
<tr>
<td>Micelle</td>
<td>&gt;2</td>
<td>&gt;50</td>
</tr>
<tr>
<td>Solubility (Micelle/water)</td>
<td>2000 times or more</td>
<td>500 times or more</td>
</tr>
</tbody>
</table>

Controlled release
Superior controlled release (improved stability and safety) and improved retention in bloodstream

Enhanced Targeting
Nanomicelle accumulate in cancerous tissue by taking advantage of characteristics of cancer cells

Normal tissue  Cancerous tissue

- : Conventional drugs
- : Nanomicelle

Enhanced solubility
Dissolve the hydrophobic drug in water

Controlled release
Superior controlled release (improved stability and safety) and improved retention in bloodstream
Improvement of Product value for POC drugs & NCE

Add significant value to existing drugs

- Controlled release
  Improve efficacy and reduce toxicity

- Targeting
  Enhance delivery into cancer cells

- Increased bioavailability\(^1\)
  Enhance solubility of insoluble drugs

Improve of patients' QOL

- Enhance efficacy
  Increase delivery into cancer cells

- Reduce side effects
  Reduce toxicity by releasing drugs in a controlled manner

- Improve accessibility
  No overnight hospitalization,
  Reduce treatment to mollify side effects,
  Reduce medical cost

Note: \(^1\) The rate and extent to which the active substance is absorbed from a drug product and becomes available at the site of action
NanoCarrier's micellar nanoparticles have potential to address the limitations of existing nanomedicine. The table below compares the advantages of different nanoparticles and micelles, categorized by passive and active technologies, based on their controlled release, targeting, and bioavailability:

<table>
<thead>
<tr>
<th>Micelle Type</th>
<th>Controlled release</th>
<th>Targeting</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Passive</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin nanoparticle (Abraxane, etc.)</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>liposome (Doxil, ONIVYDE, Lipodox etc.)</td>
<td>Low</td>
<td>High</td>
<td>Medium</td>
</tr>
<tr>
<td>PEG-PLA (Genoxol-PM, etc.)</td>
<td>Medium</td>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>Passive Micelle (NC-6004, NC-4016, etc.)</td>
<td>High</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Active</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active PEG-PLA (BIND-014, etc.)</td>
<td>Medium</td>
<td>Very high</td>
<td>High</td>
</tr>
<tr>
<td>Active Micelle, ADCM (NC-6201, etc.)</td>
<td>High</td>
<td>Very high</td>
<td>Very high</td>
</tr>
</tbody>
</table>
NanoCarrier Highlights

Core Technology - Nanomicelle

Robust Oncology Pipelines

Antibody/Drug-Conjugated Micelle (ADCM)

Japan Technology
Micellar Nanoparticle
# Current Status of Pipelines

<table>
<thead>
<tr>
<th>Product</th>
<th>Encapsulation drug</th>
<th>Cancer Indication</th>
<th>BR</th>
<th>PC</th>
<th>ph1</th>
<th>ph2</th>
<th>ph3</th>
<th>Develop Area</th>
<th>Alliance Partner</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC-6004</td>
<td>Cisplatin</td>
<td>Pancreatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Co-Development</td>
<td>Japan/Asia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lung (NSCL)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In-House Development</td>
<td>USA/EU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bladder</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Co-Development</td>
<td>USA/EU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>bile duct</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Co-Development</td>
<td>USA/EU</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Head and neck</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Co-Development</td>
<td>USA/EU/Latin/Asia</td>
</tr>
<tr>
<td>NC-4016</td>
<td>Dach-platinum</td>
<td>Solid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In-House</td>
<td>USA</td>
</tr>
<tr>
<td>NC-6300</td>
<td>Epirubicin</td>
<td>Solid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Co-Development</td>
<td>Japan</td>
</tr>
<tr>
<td>K-912</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NC-6201</td>
<td>E7974 (in-licensed)</td>
<td>Solid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In-House</td>
<td>USA</td>
</tr>
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</tr>
<tr>
<td>Active</td>
<td>siRNA</td>
<td>Solid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In-House</td>
<td></td>
</tr>
<tr>
<td>NanoFect</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>NK105</td>
<td>Paclitaxel</td>
<td>Gastric</td>
<td>Out-Licensed</td>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
NanoCarrier Recent Press Release

October 11, 2016

Results of a Phase Ib Clinical Study of NC-6004 in the US

We are pleased to announce that on October 10, 2016 local time at the European Society for Medical Oncology (ESMO) 2016 Congress held in Copenhagen (Denmark) from October 7 to 11, 2016.

We confirmed safety profile and efficacy of NC-6004 (cisplatin-encapsulated nanoparticle) in the Phase Ib clinical study conducted in the United States. In terms of the adverse reactions such as neurotoxicity, auditory damage, and nephrotoxicity, which are known to be observed in cisplatin treatment, no clinically significant event of those was observed even when NC-6004 was administered at 1.5 times higher dose than the standard dose of conventional cisplatin. In addition, although the subjects for Phase I clinical study are usually patients who have received standard therapies but have not shown sufficient efficacy, NC-6004 was well tolerable and showed efficacy in patients who had previously received platinum-based chemotherapy including cisplatin.
NanoCarrier Highlights

Core Technology - Nanomicelle

Robust Oncology Pipelines

Antibody/Drug-Conjugated Micelle (ADCM)
Next Generation of Active Targeting System

eg. More than 70 ADCs are under clinical developments (PI 46, PII 26, PIII 5) and markets (3) world wide.
- Has limits of use on Mabs and payloads.
- Has limits of use for indications

NanoCarrier provides the solution by enabling to use many kinds of targeting ligands and payloads.

eg. ADCM
(Antibody/Drug-Conjugated Micelle)

Expands the market opportunity
Basic Structure of ADCM

Polymer with ligand-binding site

- PEG
- Poly-amino acid derivative

Drug-conjugated polymer

Self-assembly

~ 50 nm

~100 drug /antibody
### Differences in Key Requirements

<table>
<thead>
<tr>
<th></th>
<th>ADC</th>
<th>ADCM</th>
</tr>
</thead>
</table>
| **Ligand molecule** | • Incompatible with Fab and scFv  
• Internalization required | • Fab and scFv applicable  
• Protein, peptide, and small molecule also applicable  
• Internalization preferable |
| **Drug** | • Highly potent agents (IC₅₀: 10⁻¹⁰~10⁻¹¹ M)  
• Low Ab-drug ratio | • Moderately potent agents (IC₅₀: ~10⁻⁹ M)  
DAR: ~100  
• High Ab-drug ratio |
| **Linker** | • Must be stable in plasma to avoid premature release of the drug | • Enable slow release of payload in plasma |
## Advantages of ADCM

### Experimental results of ADCM

<table>
<thead>
<tr>
<th>Study</th>
<th>ADC* vs. ADCM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustainable drug release in the plasma</td>
<td>ADC &lt; ADCM</td>
</tr>
<tr>
<td>Drug distribution in the tumor **</td>
<td>ADC &lt; ADCM</td>
</tr>
<tr>
<td>Anti-tumor activity**</td>
<td>ADC &lt; ADCM</td>
</tr>
<tr>
<td>Mab internalization</td>
<td>Mab &lt; ADCM</td>
</tr>
</tbody>
</table>

*ADC was made in NanoCarrier  
**Studies were performed in triple-negative human breast cancer xenograft models.
Improving Therapeutic Window by Active Targeting

- Increase drug delivery to tumor
- Reduce normal-tissue drug exposure

MTD (Maximum Tolerated Dose)

MED (Minimum Effective Dose)

Free drug

Micellar nanoparticle

ADCM
Flexibility in Ligand Molecules

- **Antibodies:** Mab, F(ab’)₂, Fab
- **Proteins:** Transferrin
- **Peptides:** Cyclic RGD
- **Small molecules:** Folic acid
Flexibility in Payloads/Linkage Modes

- Anthracyclines
- Taxanes
- Platinums
- Camptothecins
- Hemiasterlins
- TKIs
- Maytanisinoids
- MMAE/MMAF
- Others

- Ester bond linkage
- pH sensitive linkage
- Enzyme cleavable linkage
- others
Clinically approved payload with novel ligand
Ex: E7974 / Anti-EGFR Ab, Anti-HER2 Ab

Clinically approved ligand with novel payload
Ex: Epirubicin / Anti-Tissue Factor Ab
NC-6201 : NCAB001-conjugated E7974-incorporating Micelle

- Tubulin binder
- Synthetic analog of hemiasterlin
- Poor PgP substrate
- Cytotoxic activity (IC50): ca. 4 nM
- MTD in human: 0.45 mg/m2 (DLT: neutropenia)
Antitumor Activity of NC-6201 on EGFR-positive BxPC-3 Pancreatic Cancer Cell Line Xenograft (sc/iv)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dose (mg/kg)</th>
<th>Therapeutic Index (MTD/ED$_{50}$)</th>
<th>Ratio to E7974</th>
</tr>
</thead>
<tbody>
<tr>
<td>E7974 (Drug alone)</td>
<td>1.8</td>
<td>0.41</td>
<td>1.0</td>
</tr>
<tr>
<td>E7974 nanomicelle</td>
<td>2.7</td>
<td>0.93</td>
<td>2.3</td>
</tr>
<tr>
<td>NC-6201</td>
<td>0.2</td>
<td>12.5</td>
<td>30</td>
</tr>
</tbody>
</table>
Antitumor activity of NC-6201 on EGFR and KRAS Mutation-positive MDA-MB-231 Breast Cancer Cell Line Xenograft

![Graph showing antitumor activity](image)

- **Cetuximab (4 mg/kg)**
- **E7974 nanomicelle (1 mg E7974 eq./kg)**
- **Vehicle control**
- **E7974 nanomicelle + cetuximab**
- **NC-6201 (1 mg E7974 eq./kg)**

Mean ± SE (n=6)
Antitumor Activity of NC-6201 on EGFR and KRAS Mutation-positive HCT116 Colorectal Cancer Cell Line Xenograft

Mean ± SE (n=6)

Tumor volume (mm$^3$)

Body weight change (%)

Days after initial dose

Days after initial dose

- : Vehicle control
- : NC-6201 (1 mg E7974 eq./kg)
- : NC-6201 (2 mg E7974 eq./kg)

Mean ± SE (n=6)
Antitumor Activity of NC-6201 on EGFR vIII-expressing LN229 glioblastoma

Vehicle control
NC-6201 q7dx3 (2 mg/kg)
NC-6201 q2dx3 (2 mg/kg)
Mean ± SE (n=6)
Pharmacokinetics

a) Rat

Plasma concentration-time courses in rats and monkeys receiving NC-6201 or E7974 at 1 mg and 0.15 mg of E7974/kg, respectively.

b) Monkey

Plasma concentration-time courses in rats and monkeys receiving NC-6201 or E7974 at 1 mg and 0.15 mg of E7974/kg, respectively.
NC-6201 and E7974 showed similar toxic profiles in rats and monkeys.

- Class effect of tubulin inhibitor
  - Major side-effects: Myelosuppression, Anemia
- No dermatitis
- No anaphylactoid symptoms
- Toxic intensity in monkeys
  - NC-6201 0.45 mg/kg ≤ E7974 0.15 mg/kg
ADCM is the next-generation platform technology for tumor-targeted delivery, which has superior versatility of the combination of payload, linker, and antibody, compared to ADC.

NC-6201 exhibited the anti-tumor activity against cetuximab-insensitive KRAS-mutated tumors.

Preclinical studies of NC-6201 are ongoing to move into clinical next year, and the toxicity studies are indicating there is no ADCM specific toxicity.
More Opportunities by NanoCarrier

- Approved drugs
- Compound hold in clinical/nonclinical
- ADC products
- New drug targets

Enhances:
- Target specificity
- Safety
- Solubility
- PK profile

Enables to:
- Focus on activity

Reprofiling

Simplifying and accelerating drug discovery

New drugs to meet high UMN

Increase QOL of patients

Innovative Drug
NanoCarrier Highlights

Core Technology - Nanomicelle

Robust oncology pipelines

Antibody/Drug-Conjugated Micelle (ADCM)

New research and Business

Be continued to challenge
NanoCarrier Keeps on Evolving

**Passive to Active Delivery**

**Chemicals to Bio**

- Small molecule
- Antibody
- Nucleic acid
- Protein Peptide
- Active NanoFect™ siRNA
- ADCM
- BBB-penetrating ligand

New generation of CNS drug

Vaccine, Intracellular antibody therapy

Skin essence

Nano cosmetics

Hair growth tonic

Nano cosmetics

Skin essence
Acknowledgement

Research Division, NanoCarrier Co., Ltd.

• Mitsunori Harada
• Masami Tsuchiya
• Ryusuke Miyazaki
• Tadashi Inoue
• Ryosuke Tanaka
• Yuuki Yanagisawa
• Masayoshi Ito
• Yu Ito
• Kenichiro Naito
Thank you very much

We put on the market a new drug based on a proprietary platform technology

Contact
E-mail: mori@nanocarrier.co.jp
Product Development Scheme

Chemistry Development
Drug conjugation (Polymer, linker)

Formulation Development
Polymer, ingredients etc.

Development of scale up manufacturing

Technical transfer to CMO

GMP manufacturing by CMO

NanoCarrier with CMO, CRO

Development of testing methodology

Technical transfer to CRO

Quality test by CRO

Supply of investigational drug for clinical test
<table>
<thead>
<tr>
<th>Products</th>
<th>Stage of clinical trial</th>
<th>Patent period (^1)(^2)</th>
<th>Market opportunity (^3) (Million $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC-6004 Cisplatin Conjugated Micelle</td>
<td>Asia&amp;Japan PIII, USA&amp;EU PII, Japan PI</td>
<td>2029</td>
<td>Oxaliplatin (Eloxatin etc.) 2,272 (2007)</td>
</tr>
<tr>
<td>NC-4016 Dachplatin Conjugated Micelle</td>
<td>USA PI</td>
<td>2026</td>
<td>Oxaliplatin (Eloxatin etc.) 2,272 (2007)</td>
</tr>
<tr>
<td>NC-6201 (ADCM) Antibody/Drug Conjugated Micelle</td>
<td>Pre Clinical</td>
<td>2029</td>
<td>Trastuzumab Emtansine (Kadcyla) 2,700 (2018)</td>
</tr>
</tbody>
</table>

\(^1\) Time through which exclusivity through patents or license is effectively secured.
\(^2\)The patent period does not take into account potential extensions to the patent term that may be available in certain jurisdictions after regulatory approvals have been obtained.
\(^3\)Peak annual global sales of similar products (Source: EvaluatePharma. Based on peak actual or estimated global sales for all application areas.)
<table>
<thead>
<tr>
<th>Features</th>
<th>Basic ADCM platform</th>
<th>Modified ADCM platform</th>
<th>Novel antibody applicable for ADCM ligand</th>
<th>pH sensitive linker conjugates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Features</strong></td>
<td>The ADCM is constituted by a sensor (antibody) attached block-copolymer and a drug conjugated block-copolymer. Any sensor and drug is applicable.</td>
<td>The ADCM further constitutes a modulator block-copolymer (free from a sensor and drug). Any sensor and drug is applicable.</td>
<td>An anti-human tissue factor antibody that exhibits: 1) $\text{KD} \leq 2 \times 10^{-10} \text{M}$; 2) internalization activity. Non-clinical study of the ADCM using NC-6300 and this antibody is ongoing at COINS and NCC Japan.</td>
<td>A drug conjugated block-copolymer applicable to any drug having a carbonyl group (C=O) through hydrazide bonding. A clinical study is ongoing as our NC-6300/K-912 pipeline.</td>
</tr>
<tr>
<td><strong>Principal patent terms</strong></td>
<td>2029</td>
<td>2034</td>
<td>2035</td>
<td>2027</td>
</tr>
</tbody>
</table>
Company Strategy

**Pharmaceutical products, approved and/or under clinical development**
We establish new efficacy and dosage regimen by improving pharmacokinetics to extend therapeutic field.

**Drug with increased needs and an increased marketability**
We aim to globally market our drug products depending on treatment purposes.

**Own Development, Collaborative R&D and in-or-out license**
We value alliances as well as self-development to balance financial risks.

**Drugs with exclusiveness and prolonged lifecycle management**
- We secure the superiority of platform technology by patents.
- We ensure the company remains unrivalled by means of patents.
- We secure the prolongation of patent right.

**Global market**

POC drugs for merit

Development & Alliance

Intellectual Property
NC-6004: Phase I/II results

Combination therapy of NC-6004 with Gemcitabin

Safety/Tolerability
- Superior against cisplatin
  - The incidence rate of nausea and vomiting was 33.3% and 20.8% respectively in phase II part and was clearly low compared to cisplatin risk over 90%.

Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Phase I part</th>
<th>Phase II part</th>
<th>Phase I/II</th>
</tr>
</thead>
<tbody>
<tr>
<td>(month)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.1</td>
<td>3.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Median OS</td>
<td>12.2</td>
<td>7.4</td>
<td>8.2</td>
</tr>
</tbody>
</table>

- Phase I/II clinical trial OS\(^1\) median: 8.2 months, PFS\(^2\) median: 3.8 months
- Efficacy was approximately the same compared to literature data of existing therapies (Abraxane+Gemcitabine), but more significant level compared to Gemcitabine alone.

Measures to improve efficacy
- Since this trial was conducted without hydration, which is generally a standard practice with Cisplatin therapy, mild kidney damage was detected when NC-6004 was administered. The low efficacy level of OS in Phase II part was considered to be caused by reducing administration dose in half for 11 out of 24 patients due to observations of nephrotoxicity. Therefore, a low volume of hydration will be added in the Phase III clinical trial protocols in order to improve efficacy.

Advantage/Benefit
- Possibility for lower doses to reduce side effects
- Potential for ambulatory treatment with reduced administration time
- Improves patients’ QOL and reduces their medical expenditure
- Contributes to national medical expenditure reduction

Note: \(^1\) OS: Overall Survival \(^2\) PFS: Progression-Free Survival
Applies micellar technology to Cisplatin, a leading chemotherapy cancer treatment, to increase efficacy and patients’ QOL during treatment.

Clinical value of Cisplatin
- Cisplatin is widely used as a standard regimen to treat various types of cancers, such as ovarian, head and neck, NSCLC and gastric cancers.

Major issues with Cisplatin
- Cisplatin is known to be highly toxic (renal toxicity, gastrointestinal toxicity and neurotoxicity), which is dose-limiting, thereby reducing its potential effectiveness.
- Patients who are administered Cisplatin may need to be hospitalized for hydration for an extended period of time.
- Although Bristol-Myers Squibb developed Carboplatin to lessen the serious side effects of Cisplatin, it has not been able to replace Cisplatin because it is less effective.

Development concept for NC-6004 (Cisplatin-conjugated micellar nanoparticles)
- Enhance Efficacy
- Reduce Side Effect
- Improve Accessibiiy

Time-dependent release
Replace with nucleophile such as Cl⁻ and release with low pH environment.