

## NanoCarrier Co. Ltd.

(4571 TSE Mothers)

December 25 2017

## Focusing on the Value Enhancement of the VB-111 Brain Tumour Gene Therapy

Now shifting from DDS drug discovery venture to discovering bio-drugs for cancer treatment

## Basic Report

Fair Research Inc.

Tsuyoshi Suzuki

NanoCarrier Co., Ltd. started out as a drug discovery venture for DDS preparations, using its own micellar nanoparticle technology. The company has subsequently undertaken research and development to apply this technology to widely used anti-cancer drugs in order to increase their therapeutic effect and reduce side effects.

In recent years, moreover, the company has used its knowledge in the area of cancer for applications in areas other than existing cancer drugs. These include applications involving new drug candidates, nucleic acid approaches, targeting of micelles, investments in outside ventures with distinctive characteristics and the licensing-in of cutting-edge drugs. By so doing the company aims to flesh out its cancer drug line-up and thereby transform itself from a DDS drug discovery venture into a bio-drug discovery company. Hence, for example, the company is laying a lot of stress on VB-111, a ground breaking gene therapy drug for intractable brain tumours, which the company announced in November 2017 it was licensing in from the Israeli company VBL Therapeutics.

## Company Overview

|           |                       |
|-----------|-----------------------|
| Location  | Kashiwa, Chiba        |
| CEO       | Ichiro Nakatomi       |
| Founded   | June 1996             |
| Capital   | ¥11,089 mil.          |
| Listing   | March 2008            |
| URL       | www.nanocarrier.co.jp |
| Industry  | Pharmaceuticals       |
| Employees | 60 (consol.)          |

## Main indicators (22/Dec./2017)

|                               |              |
|-------------------------------|--------------|
| Stock price                   | ¥667         |
| 52-week high                  | ¥917         |
| 52-week low                   | ¥623         |
| Shares issued                 | 43 million   |
| Trading unit                  | 100 shares   |
| Market cap                    | ¥28,814 mil. |
| Div. forecast                 | 0.0          |
| EPS-forecast net profit basis | -112.2       |
| Forecast PER                  | n. a.        |
| Actual BPS                    | 181.5        |
| Actual PBR                    | 3.67X        |

(Note: EPS,PER,BPS,PBR: shares issued basis excl. Treasury shares)

| Results trend          | Sales JPY mil. | Change (%) | Operating Profit (JPY mil.) | Change (%) | R.P. (JPY mil.) | Change (%) | Net profit (JPY mil.) | Change (%) | EPS (Yen) | FY share price (¥) |     |
|------------------------|----------------|------------|-----------------------------|------------|-----------------|------------|-----------------------|------------|-----------|--------------------|-----|
|                        |                |            |                             |            |                 |            |                       |            |           | High               | Low |
| 2015/3 Actual          | 676            | 43.1       | -1,108                      | na         | -171            | na         | -207                  | na         | -5.1      | 1,914              | 900 |
| 2016/3 Actual          | 243            | -64.0      | -2,083                      | na         | -2,381          | na         | -2,537                | na         | -59.5     | 1,389              | 824 |
| 2017/3 Actual          | 219            | -10.1      | -2,712                      | na         | -2,619          | na         | -2,676                | na         | -62.1     | 2,019              | 735 |
| 2018/3 1H actual       | 71             | -15.9      | -2,080                      | na         | -2,054          | na         | -2,049                | na         | -48.5     | 727                | 623 |
| 2018/3 2H Co. forecast | 126            | -6.7       | -2,704                      | na         | -2,652          | na         | -2,798                | na         | -63.7     |                    |     |
| 2018/3 annual forecast | 197            | -9.9       | -4,784                      | na         | -4,706          | na         | -4,847                | na         | -112.2    |                    |     |

## Market cap could double when value of breakthrough drug VB-111 is discounted

The NanoCarrier share price has continued to be almost flat, and hardly reacted even after the announcement in November of the licensing in, mentioned above, of the breakthrough drug VB-111. In other words, the market has not yet discounted the value of VB-111. On the basis of certain assumptions we posit a value of JPY31.2 billion for VB-111, and adding this to the company's current market value (JPY28.8 billion) we estimate a total value of around JPY60 billion, or approximately double the current level.

In the January-March period of 2018 the preliminary results of US Phase 3 trials are due to be announced and a repetition of the favourable results of Phase 2 would mean the possible expansion of applications to other types of cancerous tumour, which would be a catalyst for the company's value in the market place.

## Three reasons given for slumping share price not necessarily relevant

Three reasons have been posited for NanoCarrier's continuous share price weakness so far. First is the temporary discontinuation of development of NK105, which it was hoped would be the company's first success. Secondly, a concern that the arrival in the market of Opdivo and other immuno-therapeutic drugs would eliminate conventional cancer drugs. And thirdly, worries about the company's ability to finance its own new drugs and to invest externally or license in.

As to the first point, NK105, licensed out to Nippon Kayaku, is a first generation technology while other significant pipeline drugs are second generation. This, together with the fact that the two companies have different development policies, means that the temporary suspension of NK105 has no effect on the development of the other main drugs in the company's pipeline. Moving on to the second point concerning the attention being paid to immuno-therapeutic treatment of cancer, there are differences in efficacy depending on the type of cancer and many cases where they have no effect at all. Many recent clinical trials have therefore involved concomitant administration of conventional cancer drugs, pointing to the continued importance of DDS preparations of such drugs. And on the third point concerning financial concerns, as of the end of September 2017, liquidity in hand amounted to JPY9.6 billion. The company is carefully staggering outgoings to ensure that for the next two years or more it has sufficient funds to finance milestone payments for externally sourced drugs and to cover the R&D costs for in-house drugs.

As investors acquire a correct understanding of the above three factors it will facilitate the discounting.

## Company Outline – Core Technology

**Outline of operations**

NanoCarrier Co., Ltd. started out as a drug discovery venture for DDS preparations, using its own micellar nanoparticle technology, but is now shifting away from DDS preparations only and becoming a bio-drug company in the area of cancer treatment.

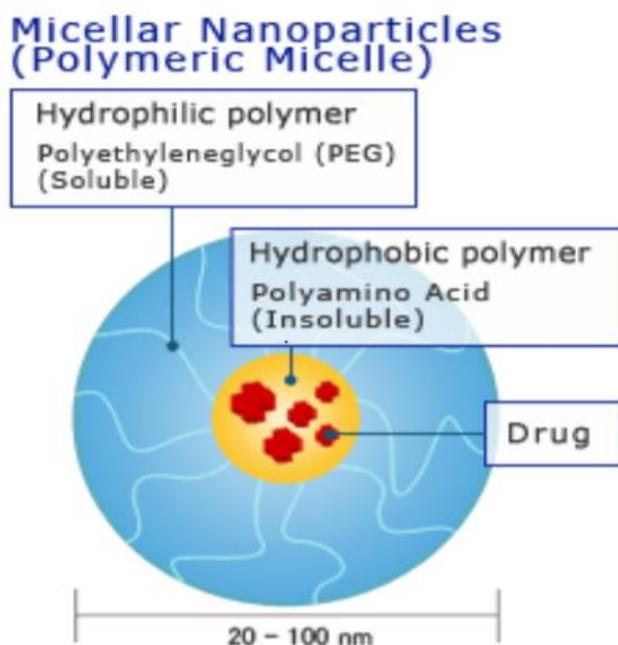
NanoCarrier Co., Ltd., a drug discovery venture company that develops DDS (Drug Delivery System) formulations capable of adjusting dispersion and timing, was the first company in Japan to use nano-technology (micellar nano particles, described later) to directly deliver drugs such as anti-cancer agents at target cells (notably cancer cells). Conventionally, in the case of many cancer types, the anti-cancer agents which form an integral part of standard chemotherapies do in many cases induce serious side-effects in patients. Preparations using NanoCarrier's technology, however, are expected to provide improved drug efficacy and a better quality of life for the patient. The company has licensed out in-house developed DDS formulation to major Japanese pharmaceuticals companies and will receive milestone payments and royalties. Additional sources of revenue are expected to come from R&D collaboration with major pharmaceuticals companies on the application of its in-house technology to new drug candidates, and making use of its knowledge of drug development to invest in bio-ventures which have promising synergistic technologies, and otherwise to generate external growth through tie-ups on the development and introduction of new products. In other words, it is aiming beyond its current status as simply a drug development venture to being a bio-drug company in the cancer area.

**Core Technology**

Micellar nanoparticles

Micellar nanoparticles, the company's core technology, are polymers formed as single molecules consisting of a water-soluble (hydrophilic) part and a water-insoluble (hydrophobic) part. Mixed in water the drug is encased in the hydrophobic part and covered with the insoluble part, forming the micellar nanoparticle.

Fig. 1-1 Micellar Nanoparticles



Source: Company IR meeting materials

By rendering poorly soluble drugs soluble this technique enables the drug release to be controlled in the human body, making for reduced side-effects while raising drug efficacy.

Provides anti-cancer drugs with greater therapeutic efficacy and reduced side-effects

This technology makes it possible to easily disperse poorly soluble drugs in water, and thereby provides superior release control (improved stability and safety) leading to better retention in the bloodstream and sustained efficacy. In addition, in cancer tissues subject to a fast rate of cell proliferation there is considerable angiogenesis and wider spaces between blood vessel cells, allowing ease of access to micellar particles. It has been observed that this causes accumulation and retention in blood flow. Further, when modified with a sensor (antibody or peptide) micellar nanoparticles take on the characteristics of the cancer tissue, developing a mechanism for accumulating at the cancer site, thereby providing superior targeting.

Many conventional cancer drugs act not only on cancerous tissue but also on normal tissue and can cause serious side-effects, but the company's technology has the effect of enhancing the drug's therapeutic efficacy and reducing its side effects.

Fig. 1-2 Characteristics of Micellar Nanoparticles

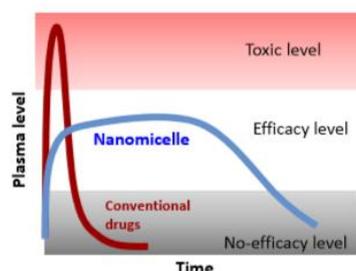
**Enhanced solubility**

Dissolve the hydrophobic drug in water

| Drug (mg/mL)               | Itraconazole       | Paclitaxel        |
|----------------------------|--------------------|-------------------|
| water                      | <0.001             | <0.1              |
| Micelle                    | >2                 | >50               |
| Solubility (Micelle/water) | 2000 times or more | 500 times or more |

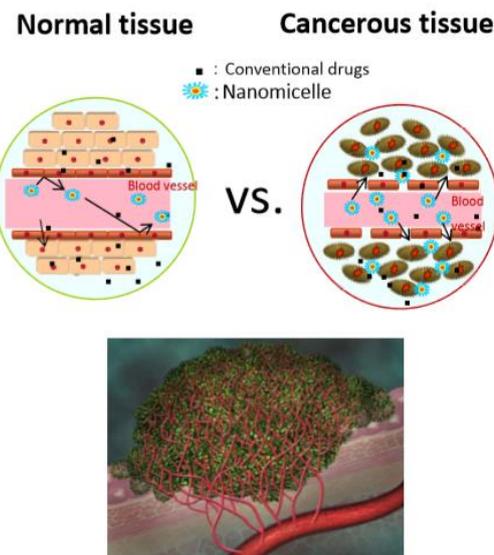
**Controlled release**

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



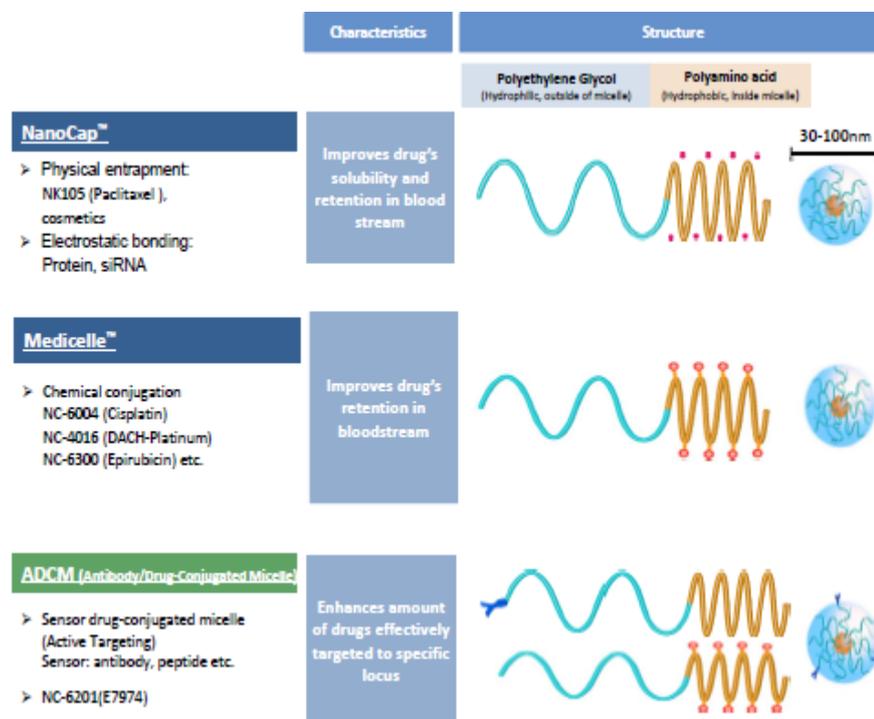
Source: Company IR meeting materials

This core technology has three design types. The first generation involves the physical adsorption of the drug in the micelle, the second generation involves the chemical binding of the drug to the micelle, and the third is the use of an ADCM (antibody/drug conjugated micelle) in which a sensor such as an antibody is modified in the hydrophilic part of the micellar particles, providing greater accuracy in targeting the affected cells.

The company holds that, compared to the first generation type, the second generation type makes for a much longer drug half-life (retention time) in the blood and a dramatic improvement in the precision of drug release controls, leading to reduced side effects and a big improvement in drug efficacy. Further, compared to the ADC which directly binds a drug to an antibody, the ADCM allows for an increase in the volume of drug that can be carried per single antibody, and can reliably deliver a large volume of the

drug to the cytoplasm and nucleus. For example, in the field of nucleic acid medicine which is now attracting attention, it had been difficult to deliver nucleic acid directly to the site of the lesion because it would break up immediately after administration, but using this technology macromolecular nucleic acid drugs can now be delivered in a stable manner, invading specific cells and providing a pharmaceutical effect.

Fig.2-3 System Designs



Source: Company IR meeting materials

**History**

Full-fledged development of micellar cancer drugs from 2000

The company was set up by the current president, Ichiro Nakatomi, who hails from the same family as the founder of Hisamitsu Pharmaceutical. He initially worked on R&D in Hisamitsu's research institute before transferring in 1991 to Utah University's first pharmaceuticals venture business, TheraTechnologies Inc. After successfully expanding the company's operations he got to thinking about opportunities in Japan and set up NanoCarrier in 1996. At an international symposium in Salt Lake City in 1993 he had come into contact with the research results on macromolecular micelle nanoparticles produced by Professor Kazunori Kataoka of Tokyo University and Professor Mitsuo Okano of Tokyo Women's Medical College, and the new venture was set up with a view to commercialisation. In 1999 the company raised funds from JAFCO and other venture capital funds and full-scale operations commenced in 2000.

To begin with the company began development of DDS preparations for cancer drugs which had already seen worldwide exposure, and expanded activities related to licensing out. In 2002 the company signed a basic licensing agreement with Nippon Kayaku covering the cancer drug paclitaxel (trade name Taxol), and in 2004 Nippon Kayaku began Phase 1 clinical trials of paclitaxel micelle (NK105). In 2005, the company signed a joint development and options agreement with the Swiss company Debiopharm S.A., famous for its development of the cancer drug oxaliplatin (trade name El Prat), to develop Dahaplatin (NC-4016). This is a substance produced by oxaliplatin in vivo. Further, in 2006, the company itself initiated

Listed on T.S.E Mothers in March 2008, development finance falls short

Fund procurement helps the company push forward on development from around 2012

Following capital raising in 2015 the company moved its focus to bio-discovery in the area of cancer through external growth

Concrete results emerged in 2017 – investment in Tocagen and licensing-in of VBL's gene therapy drug

Phase 1 clinical trials in the UK for cisplatin micelle (NC-6004), based on cisplatin, which is the standard therapy in many cases of cancer chemotherapy. In 2007, Developments included a licensing agreement covering NC-4016 with Debiopharm, and Nippon Kayaku's commencement of Phase 2 clinical trials (below, Ph2, stomach cancer) for NK105, leading up to the company's listing on the T.S.E. Mothers market in March 2008. However, the weakness of the market prevented the company from raising sufficient capital and they therefore had to discontinue clinical testing in Europe and the US of NC-6004. Development was continued by the Taiwanese pharmaceuticals and cosmetics company, Orient Europharma Co., Ltd. (below OEP Co.) under a licensing-out agreement concluded in September 2008.

Subsequently, the company engaged in several fund raising activities to finance an acceleration in its in-house development program. Thus, in 2011 it issued a third party allocation of shares to Kowa, in March 2012 it received large-scale infusions from funds run by Whiz Partners Inc., and in October issued a third party allocation to Shin-Etsu Chemical. Meanwhile, the company's contract with Debiopharm had run its course and NC-4016 was moved to in-house development in 2011, with US Phase 1 clinical testing beginning in 2013. In November of that year, in order to expedite development of its main pipeline drugs and also its pipeline of new products, the company carried out a worldwide share offering aimed at foreign investors, raising JPY8.6 billion. NC-6004 also saw a number of developments, with Phase 2 trials for Asia (ex-Japan) beginning in 2011 and Phase 1 for Japan in 2012, Phase 3 clinical trials for Asia with Japan participation in 2014, and basket Phase 3 targeting 3 cancer types started in the US in 2015 before being expanded to Europe. Further, from the results of domestic Phase 1 trials, domestic participation began in Asia Phase 3 trials, with NanoCarrier involved in international joint clinical trials. The company entered a licensing agreement with Kowa in 2011 covering Epirubicin micelle (NC-6300), which is epirubicin (trade name Farmorubicin) with an added pH-responsive function and incorporated in micelles. Phase 1 domestic trials began in 2013. The agreement with Kowa was dissolved in December 2016 and development was moved in-house. (Note: pH-responsiveness: a decline in the pH value=when the acidity rises the preparation in the micelles is released). It is reported that results of Japanese Phase 1 trials have been favourable. As for the next generation pipeline, development has begun on using sensors to improve targeting in new drug candidates. In 2014, the company licensed in a new drug candidate, E-7974, from Eisai for the treatment of solid tumours and began developing an ADCM function (pre-clinical). In addition, the company in 2015 began basic research on the treatment of solid tumours by fusing its technology with antibody and siRNA drugs from Chugai.

The next new development began with the conclusion in September 2015 of an agreement with funds managed by Whiz Partners Inc. for the issue of convertible bonds (JPY3 billion) and stock subscription rights, for a maximum infusion of JPY9.4 billion. The main purpose of this was to supplement capital and fund tie-ups and M&A, with the aim of strengthening the company's development and production functions, including overseas. In March 2017 the company announced it was making an investment in the Taiwanese company TPG Biologics (below, TPG), with whom it would also be doing joint development research. The company is aiming to establish a new technological base by developing sensors suitable for TPG's ADCM. The company also announced in April an investment in the US company, Tocagen. Tocagen is a bio-venture listed on Nasdaq and is well known for its development of a specific gene therapy for cancer sites. Toca 511 & Toca FC is now in Phase 3 and in February 2017 was designated by

the FDA as a “breakthrough therapy” with respect to recurrent malignant brain tumours. Further, in November 2017 the company signed an agreement with the Israeli company VBL Therapeutics to bring the gene therapy drug VBL-111 to Japan.

Reference: Outline of VBL

**Vascular Biogenics Ltd. (VBL) operation as VBL Therapeutics**

|                           |  |   |
|---------------------------|--|---|
| Founded                   | 2000   |  |
| Head office               | 8 Hasat St., Modiin, Israel  |   |
| Market                    | Listed on NASDAQ, U.S., VBL Therapeutics (VBLT)  |   |
| Issued shares, and others | Total number of issued shares: 27,058,869<br>Market capitalization: \$120 M, as of June 30, 2017<br>Cash flow: \$33.8 M, as of June 30, 2017                             |   |
| Representative            | Dror Harats, MD, Chief Executive Officer   |   |
| Business outline          | Bio-venture focusing on development, manufacture, and distribution of gene drugs mainly in the cancer field  |   |
| Pipeline                  | VP-111: Non-replicating adenovirus vector that drives apoptosis in newborn blood vessel cells.<br>VB-201: Low-molecular-weight Lecinoxoid that inhibits TLR, and others. |   |

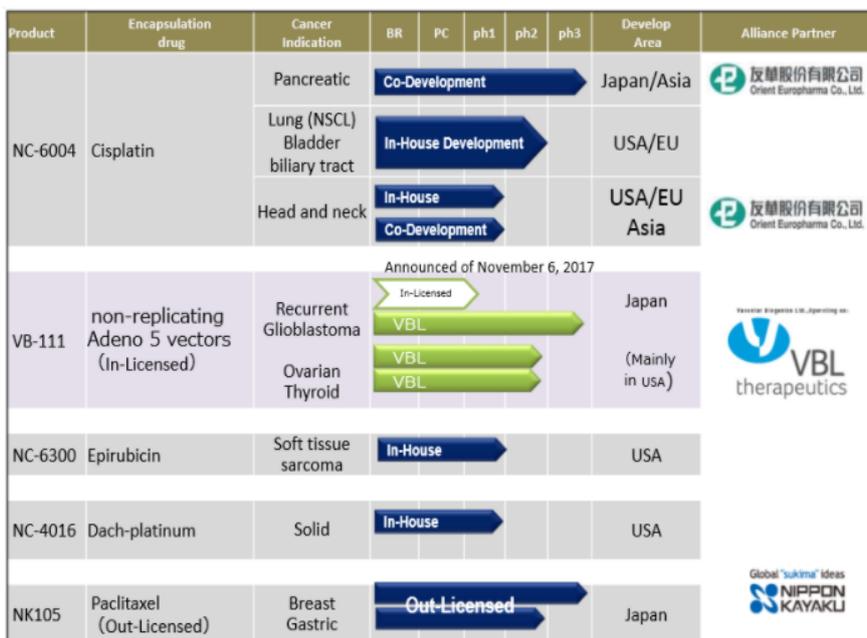
Source: Company IR meeting materials

**Current Pipeline Status**

The company has 4 main drugs

The main products in the company’s drug pipeline are 3 DDS preparations (NC-6004, NC-4016, and NC-6300) for anti-cancer drugs used worldwide, and the recently licensed-in VB-111. An additional preparation, NK105, was licensed out at an early stage and since the contract did not include milestone success payments it will in the future have only a small impact on the company’s revenue.

Fig. 3 Status of Main Pipeline Drugs



Source: First half FY2017 results meeting materials

Among the company's products the most advanced in terms of development is NC-6004, which OEP is subjecting to Phase 3 trials in Asia for pancreatic tumours. The company is now registering patients for Phase 3 pancreatic cancer trials in Japan also. In the US, the company has begun Phase 2 basket-style trials of in-house developed drugs directed at three types of cancer.

NC-4016: Phase 1 data now being analysed

NC-6300 developed in-house, now applying for US Phase 1/2 trials targeting soft tissue sarcoma, ready for full-scale development

### 1. NC-6004 (Cisplatin Micelle)

Cisplatin micelle is a DDS preparation based on the anticancer agent cisplatin. Although cisplatin is an important platinum-based drug in the chemotherapy treatment of many cancers its use can sometimes cause serious side effects in the liver and other parts of the body. For this reason, before administration it is necessary to infuse intravenously large quantities of electrolytic replenisher over a protracted time period. NanoCarrier technology makes it possible to avoid the large infusions and reduce side effects while enhancing the anti-tumour effect.

In terms of the current development status, OEP is now conducting Phase 3 trials in Asia for pancreatic cancer, and NanoCarrier is registering patients in Japan. In Japan, Phase 1 trials were carried out on a combination therapy with radiation for head and neck cancer, but this was terminated in December 2016 due to severely adverse outcomes, and patient registration for pancreatic cancer subjects was also temporarily suspended. However, it was then judged that the cause of the problem was the radiation, and patient registration was reopened in August 2017. The company thinks patient registration will now be completed during FY2018, about a year behind the initial plan.

In addition, the company is looking to expand worldwide beyond Asia, and to that end is itself conducting basket-style Phase 2 trials in the US on three cancers (non-small cell lung cancer, biliary tract cancer and bladder cancer). It completed patient registration for one cancer type and expects to complete registration for the other two within 2017. It should be noted that in July 2017 this product received orphan drug designation for biliary tract cancer from the FDA.

### 2. NC-4016 (Dahaplatin Micelle)

Dahaplatin micelle is a micelle of Dahaplatin produced in vivo by the platinum-based anticancer drug oxaliplatin, which is widely used worldwide for breast cancer and other conditions. In this form the side-effects of oxaliplatin are alleviated and the anti-cancer efficacy increased. The company conducted Phase 1 trials on solid tumours in the US and data analysis is now underway.

### 3. NC-6300 (Epirubicin Micelle)

Epirubicin, an anti-cancer agent with applications to a broad variety of tumours, inserts into the helical DNA structure inhibiting synthesis or cleaving DNA, but the cardiotoxicity side-effect is a problem. The company's technology (pH-responsive micelles) controls the release of epirubicin, thereby suppressing its accumulation in the heart and enhancing accumulation in cancer cells, leading to reduced side effects and improved anti-tumour efficacy. In Japan, Phase 1 trials targeting solid cancers were almost completed in November 2016 with favourable results. Analysis of those results and in order to accelerate development led the company in December of the same year to apply to the FDA for Phase 1/2 examination targeting soft tissue sarcoma. The drug received orphan drug designation in July 2017.

VB-111 is one type of gene therapy drug which is expected to have a breakthrough effect on malignant glioblastoma, a refractory brain tumour.

#### 4. VB-111

VB-111 is a gene therapy drug targeting a refractory brain tumour known as recurrent malignant glioblastoma (below, rGBM). As earlier mentioned, the company in November 2017 concluded an agreement with VBL Therapeutics for exclusive development and sales rights in Japan. The drug is a non-proliferative adenoviral vector which selectively leads to tumour vasculature in cell tumours and induces tumour immunity. It has the potential to be widely used to treat solid cancers (e.g. rare cancers such as platinum-resistant ovarian cancer, Iodine-resistant thyroid cancer, and lung cancer). It has been given fast-track status by the FDA, giving it access to preferred approval adjudications, and in both the US and Europe has been given orphan drug status.

In Phase 2 tests on rGBM conducted by VBL it was verified that the overall survival time approximately doubled when used in combination with the anti-cancer drug Avastin.

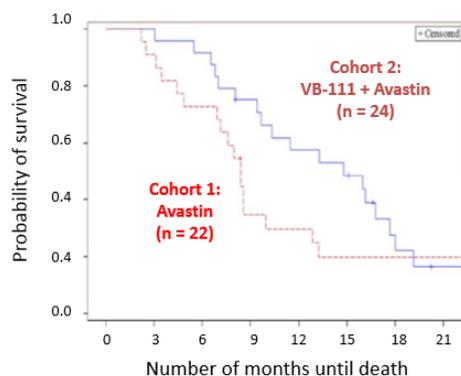
NanoCarrier’s purpose in licensing in VB-111 is to fill out its line-up of anticancer drugs for refractory cancers evidencing a variety of action mechanisms, and thereby enhance its profile as a drug discovery company in the cancer field.

In addition, while VB-111 acts on new blood vessels, subjecting the cancer cells to starvation attack, NanoCarrier’s technology acts on the cancer cells directly, raising the possibility of using both concomitantly. VB-111 has a particle size of 80nm, about the same as other intravenous micellar particles. This facilitates inferring the in vivo dynamics of the drug and the possibility of extending to a wide variety of cancer types, and explains the company’s interest in licensing in.

The preliminary results of Phase 3 are expected in the January-March period of 2018.

VBL has already completed patient registration for clinical trials in the US, Canada and Israel and plans to have preliminary trial results in January-March of 2018.

Fig. 4 Phase 2 Trials for Recurrent Malignant Glioblastoma



Study details:

VB-111 ( $1 \times 10^{13}$  VPs) was administered every eight weeks. Upon recurrence, the following treatment was given.

- ◆ Cohort 1: Switched to Avastin (every two weeks) (n = 22)
- ◆ Cohort 2: Continue use of VB-111 every eight weeks and use Avastin (every two weeks) simultaneously (n = 24)

|                                   | Cohort 1 | Cohort 2  |
|-----------------------------------|----------|-----------|
| Median value of OS                | 8 months | 15 months |
| Long survival (12 months or more) | 23%      | 54%       |

➔ Phase III (GLOBE study) Patient enrollment completed

Source: First half FY2017 results meeting materials

**Background to lacklustre stock price**

The temporary suspension of NK105's development does not negate NanoCarrier's technology and has no effect on the company's main pipeline development.

The market is now focusing almost entirely on cancer immunotherapies but it is unlikely that the anticancer formulations used in chemotherapy will disappear. There is still considerable potential for drug delivery systems using conventional formulations.

As of December 22 2017 NanoCarrier's market capitalisation stood at JPY 28.8 billion, around half its level at the end of 2014, and around one-third the level of mid-mid-2016 when hopes for the success of NK105 peaked. Three reasons for this stock price weakness can be proffered.

**(1) The effect of the temporary suspension of NK105's development**

NK105 was out licensed to Nippon Kayaku and from July 2012 Phase 3 trials were conducted targeting metastatic and recurrent breast cancer. Eventually, from around early 2016, judging from the results, it was expected that the company had its first drug development success. However, in July 2016 Nippon Kayaku announced that an important evaluation yardstick had not been met. This announcement gave rise to concern in the stock market about the whole of NanoCarrier's core micelle technology. As mentioned earlier, the company represented that NK105 is first generation technology while the other products making up its development pipeline are second generation with no effect on the former.

Looking at the development of DDS formulations, it is important to demonstrate greater effectiveness than the anticancer drug matrix, even when the cancer develops a resistance to the matrix. We may often encounter cases in which the trial cannot demonstrate greater effectiveness (including survival longevity) although the DDS clearly reduces side effects in comparison with the anticancer drug matrix.

Even if a drug does not meet its endpoint at Phase 3, analysis of the data and discriminating between the patient cohort exhibiting the most obvious pharmaceutical effects and the cohort not doing so, in additional and repeated trials, may produce more supportive cases.

**(2) Reduced focus on the potential for conventional anticancer drugs and related DDS**

There has recently been increased attention paid to immunotherapy drugs in the treatment of cancer, representative examples being Opdivo and Keytruda, giving rise to the assumption that conventional anticancer drugs used in chemotherapy will disappear. However, chemotherapy using such anticancer drugs as cisplatin and paclitaxel are still the first line standard regimen for cancer treatment. The drugs recently receiving attention are targeted at specific genotypes and are often ineffective in the case of many other cancers. This means that conventional chemotherapy drugs will continue to be used. In addition, there are examples of successful DDS formulations incorporating such drugs. Abraxane is a drug administered with paclitaxel bound with artificial albumin in a suspended state. It is conceptually similar to NanoCarrier's products in the sense that it is a DDS formulation of a modified conventional anticancer drug. Applications have expanded since its launch in 2005 and it now commands a market of JPY100 billion. NanoCarrier's micellar nanoparticles are smaller than the albumin formulations used in abraxane and elsewhere, and have superior release control and targeting of the encapsulated drugs.

Fig. 5: Comparison with Abraxane (albumin nanoparticle preparation)

|         |   | Controlled release | Targeting | Bioavailability |
|---------|---|--------------------|-----------|-----------------|
| Passive | Albumin nanoparticle (Abraxane, etc.)   | Low                | Low       | Low             |
|         | liposome (Doxil, ONIVYDE, Lipodox etc.) | Low                | High      | Medium          |
|         | PEG-PLA (Genoxol-PM, etc.)              | Medium             | Low       | Medium          |
|         | Passive Micelle (NC-6004, NC-6300 etc.) | High               | High      | High            |
| Active  | Active PEG-PLA (BIND-014, etc.)         | Medium             | Very high | High            |
|         | Active Micelle, ADCM (NC-6201, etc.)    | High               | Very high | Very high       |

Source: Company IR meeting materials

### (3) Pros and cons of two-front strategy - in-house development and outside investment/licensing-in

The company is carefully controlling its scheduling to ensure its two-front strategy of in-house development and external investment/licensing-in does not exhaust available funds.

R&D costs are rising year by year. In the company's 2017 financial year there was a full-tilt effort to complete US Phase 2 basket trials for NC-6004 and Phase 1/2 trials for NC-6300, such that the company announced R&D costs would exceed the initial estimate of JPY2.2 billion by around JPY400 million. In the Spring of 2017, the company paid a total of around JPY400 million to TPG and Tocagen. On top of that it must pay a one-off licensing-in fee of JPY1.7 billion (USD15 million) for VB-111, and VBL has announced total payments including this and development and sales milestones will amount to USD100 million (around JPY11 billion). Elsewhere, development of the company's most advanced project, NC-6004, is, as mentioned earlier, about one year behind schedule on Phase 3 for Japan, meaning that revenue from licensing out, etc. will not occur until FY2021 at the earliest. Meanwhile, the results of the US Phase 2 basket test should be released in the second half of 2018 and, depending on those results, a lump sum licensing-out fee will be receivable. As of the end of September 2017 the company still has sufficient funds (cash in hand of JPY9.6 billion - outstanding CB's of JPY2.5 billion), but the possibility of development capital being depleted by VB-111 milestone payments and adverse timing of revenues is still a concern. On the other hand, milestone payments over approximately the next two years amount to around JPY100-200 million with bigger such payments coming into force when sales grow. However, VB-111 will come to market relatively earlier and because it is targeted at rare cancers will be particularly profitable, such that the company claims that in the second year after launch it will recoup the milestone payments made up to that time. Further, it is directed at rare cancers so the number of hospitals involved will be small and the hospitals where the clinical trials were conducted will automatically be recipients of the drug. Large-scale promotion activities will not therefore be necessary, and in fact are expected to be extremely small. In overall terms, therefore, fund availability is not a major concern.

## Liquidity in Hand and Trend in R&amp;D costs

(million yen)

| End of Month     | Mar.2015    | Mar.2016    | Mar.2017    | Sept.2017                 |
|------------------|-------------|-------------|-------------|---------------------------|
| Liquidity        | 13,772      | 13,760      | 11,769      | 9,630                     |
| CB's outstanding | 0           | 3,000       | 2,475       | 2,475                     |
| FY               | FY2015/Mar. | FY2016/Mar. | FY2017/Mar. | FY2018/Mar.<br>(Forecast) |
| R&D Costs        | 1,053       | 1,833       | 2,252       | 2,529                     |
| Lump sum to VBL  |             |             |             | 1,700                     |
| Operating Profit | -1,108      | -2,083      | -2,712      | -4,784                    |
| Recurring Profit | -171        | -2,381      | -2,619      | -4,706                    |
| Net Profit       | -207        | -2,537      | -2,676      | -4,847                    |

Source: Fair Research Inc. using official filings

**Focusing on the value of VB-111**

The announcement that the company was licensing-in VB-111 triggered almost no change in its market value. In other words, the market has effectively not discounted the value of VB-111.

Despite the announcement in November 6<sup>th</sup> 2017 that NanoCarrier was licensing-in the ground breaking drug VB-111, the company's share price remained almost becalmed. That is to say, the market more or less declined to factor in the value of VB-111. We believe that a broader understanding of the three factors behind the company's desultory share price would make it easier to discount this value. We have therefore carried out a trial valuation of VB-111.

A number of assumptions were made for the trial calculation, and it should be noted that the result is a yardstick based on these multiple assumptions

There are approximately 2,000 new cases a year of malignant glioblastoma. We assume that medication is administered for one and a half years to 3,000 patients per year. We also factor in the assumption of competition with drugs being developed by Tocagen. However, since it is necessary in the case of Tocagen's formulations to perform a craniotomy for the injection, VB-111 (intravenous injection) places a lower physical burden on the patient, and allows us to assume a 70% selection rate. We estimate peak sales of JPY45 billion on the assumption that per-patient costs are JPY20 million annually. In addition, the royalty percentage paid to VBL will probably depend on the level of sales but we assume it will initially be 15%, rising gradually thereafter. The gross margin is posited at around 50% since the raw materials must be bought from VBL.

We have disregarded marketing costs since, as noted earlier, they are likely to be minor. We have assumed a milestone payment schedule starting at USD15 million, and USD1-2 million after two years or so, and subsequently in accordance with events such as applications and approvals and in line with growth in sales. We are assuming the total sum paid will be USD100 million. Finally, we are assuming test costs will be around JPY400 million (40 cases) per year and, given its Phase 3 status, a success probability of 80%.

We have set the discount rate at 12%, slightly on the high side but justified by the fact that NanoCarrier is a bio-venture whose products have not yet been tested in the market. Peak sales we expect to be attained in around the fourth year after going on the market, and

We posit a value for VB-111 of approximately JPY31.2 billion. Given a current market capitalization of JPY28.8 billion this totals up to JPY60 billion.

The announcement of Phase 3 results for VB-111 in the January to March period could be a catalyst for the company's stock price.

subsequently sales will start declining at a rate of around 5% until the tenth year, with sales falling at a sharp rate of 10% from the eleventh year onwards.

As a result of our simulation we posit the value of VB-111 at JPY31.2 billion (it should be noted in this connection that if we lower the discount rate to 8%, which is the level of ROE required by the market for the general run of companies, then the value reading rises to JPY42.3 billion). If we add the value of VB-111 to the current market value we arrive at a revised market value of JPY60 billion, more than twice its current value.

As mentioned earlier, the preliminary announcement of results for Phase 3 trials are scheduled for release between January and March 2018. We anticipate that this will provide the opportunity for the market to factor in the value of VB-111 and re-evaluate NanoCarrier.

Needless to say, the progress in the development of NC-6300 and other early stage drugs will continue to act as upside drivers.

#### Reference: DCF Calculation of VB-111's Value

| VB-111<br>r-BM                              | Mar-18  | Mar-19 | Mar-20        | Mar-21        | Mar-22 | Mar-23 | Mar-24 | Mar-25 | Mar-26 | Mar-27 | Mar-28 | Mar-29 | Mar-30           | Milestone total => | DCF value |
|---|---|--------|---------------|---------------|--------|--------|--------|--------|--------|--------|--------|--------|------------------|--------------------|-----------|
|   | US P13 file   | JP P13 | file approval | file approval |        |        |        |        |        |        |        |        | After March 2030 |                    |           |
| Dev. costs (Japan only)                     |   | 4      | 2             | 2             |        |        |        |        |        |        |        |        |                  |                    |           |
| Milestone payments                          | 17  | 2      | 2             | 17            | 17     | 20     | 20     | 20     | 20     | 20     | 20     | 20     | 20               | 367                | 115       |
| Sales (Japan)                               | 0   | 0      | 0             | 75            | 150    | 300    | 450    | 450    | 428    | 406    | 386    | 367    |                  |                    |           |
| Gross Margin                                |   |        |               | 55%           | 53%    | 50%    | 50%    | 50%    | 50%    | 50%    | 50%    | 50%    |                  |                    |           |
| Success prob. 100%                          |   | -17    | -6            | -4            | 24     | 63     | 130    | 205    | 205    | 214    | 203    | 193    | 183              | 150                | 619       |
| Net Revenue                                 |   | -17    | -6            | -4            | 16     | 47     | 100    | 160    | 160    | 171    | 162    | 154    | 147              | 120                | 480       |
| Success prob. 80%                           |   | -17    | -6            | -4            |        |        |        |        |        |        |        |        |                  |                    |           |
| Net Revenue                                 |   | -17    | -6            | -4            |        |        |        |        |        |        |        |        |                  |                    |           |
| Success prob. 80%                           |   | -17    | -6            | -4            |        |        |        |        |        |        |        |        |                  |                    |           |
| Net Revenue                                 |   | -17    | -6            | -4            |        |        |        |        |        |        |        |        |                  |                    |           |
| Market share 70%<br>(competing with Toegun) |   | -17    | -6            | -4            | 6      | 28     | 64     | 106    | 106    | 120    | 114    | 108    | 103              | 84                 | 312       |
| Discount rate                               | 12%   |        |               |               |        |        |        |        |        |        |        |        |                  |                    |           |
|   | Assuming sales falling at 10% p.a. in final stage (from 11th year after coming to market) |        |               |               |        |        |        |        |        |        |        |        |                  |                    |           |

Source: Calculation by Fair Research Inc.

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