Frequently Asked Questions About DNP002

Here are some frequently asked questions and answers that someone like you have been interested in a therapeutic antibody candidate, DNP002.

1. WHAT IS DNP002?

DNP002 is a humanized anti-CEACAM6 antibody. It is a IgG1 isotype.

2. WHAT KIND OF CANCERS ARE INDICATED FOR DNP 002?

CEACAM-6 is known to be expressed in many types of adenocarcinoma. Dinona currently aims to use this antibody to adenocarcinoma of lung, colorectum and stomach. However, usages of DNP002 could be further expanded in the near future to other types of cancer in which CEACAM-6 is expressed.

Regarding the indications for phase I study, our first indications are lung adenocarcinoma, colon cancer and stomach cancer. At now we are vigorously studying and communicating about the detailed protocols for phase I, especially in terms of suitable biomarkers that could reflect the DNP002 efficacy in the patients. Although we have already established the companion diagnostic assay with a IHC format as like Herceptin case, we are trying to expand more systematically for collecting the information about predictive biomarkers from not only histological analysis but also the cutting edged genetic and immunological tools.

3. WHAT IS YOUR STRATEGY FOR CLINICAL STUDY?

Based on the both characteristics of DNP002's target, CEACAM6 expression profile on the various tumor cells and also MDSC targeting, we have a plan to do the multi-national and multi-center oriented phase I study as broadly as we can, mainly in USA, KOREA, and CHINA.

Besides, we should conduct the phase I study quickly in order to not only get the acquisition of safety and important information of patient's responsiveness for DNP002 regimen, but also plan to strategically design the specific phase II trials which can meet the market trends and clinical unmet needs.

4. WHAT IS THE COMBINATORIAL STRATEGY WITH DNP002?

Various trials of combination therapies have been actively developed to maximize the anticancer effect. In keeping with this trend, we are also making efforts to find a concomitant drug to increase the anticancer effect of DNP002. Already, we have published the paper that the combinatorial treatment of Paclitaxel and DNP002

provoked more tumor growth inhibition than each single treatment in xenograft mouse model. In addition, recently we have found the synergistic effect with a STING agonist in vitro. Since a STING agonist induces the innate immunity, when co-treated with DNP002, which induces NK cell activation, NK cells and subsequent immune activation appears to be further increased by immune-networking convergence.

Besides, an important candidates in terms of combination therapy are with immune checkpoint inhibitor blockade as like anti-PD-1 and anti-PD-L1 antibodies and immune agonistic antibodies as like OX-40, 4-1BB, etc. Still we don't have a direct evidence about the synergistic effect in vivo with these T cell activating antibodies, but we are now preparing the appropriate animal model system for testing the synergism.

Taken together, as the potential combinatorial partners with DNP002 treatment, 1) Paclitaxel, and some standard chemo-drugs, 2) a STING agonist as a stimulator of innate immunity, and 3) immune-boosting antibodies are the major three groups of candidates. We will perform the consecutive preclinical and clinical studies in order to acquire the best combination reflecting the more clinical benefit in the patients.

5. WHAT IS THE SAFETY CONCERN ABOUT DNP002?

Because the CEACAM6 antigen is expressed on the neutrophils, the first safety concern by DNP002 treatment is the neutropenia. Actually this neutropenia issue is the common events for all the anti-CEACAM6 antibody therapies. We have observed the neutropenia in cynomolgus monkeys, however through the recovery time for two weeks, the neutrophil level was rebound to close to normal level.

Recently we have found the similar case as like below. Precision Biologics are also developing the anti-CEACAM6 antibody for several solid cancers. They have published their preclinical data in which they described although the neutropenia was shown in monkeys but, some dose could recover to normal level. The results of this company are very encouraging and remarkable in terms of safety in that their antibody is a naked antibody of the same isotype as IgG1 and also act as a major MOA for ADCC. Besides, not only this group, some other groups have also addressed about the neutropenia and recovery.

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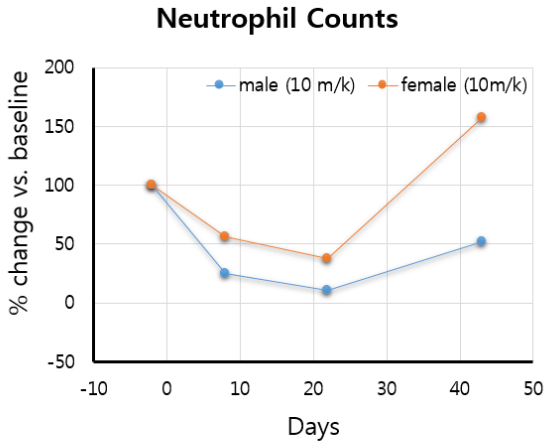
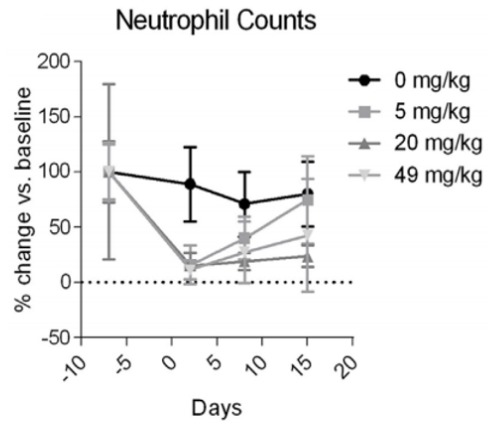
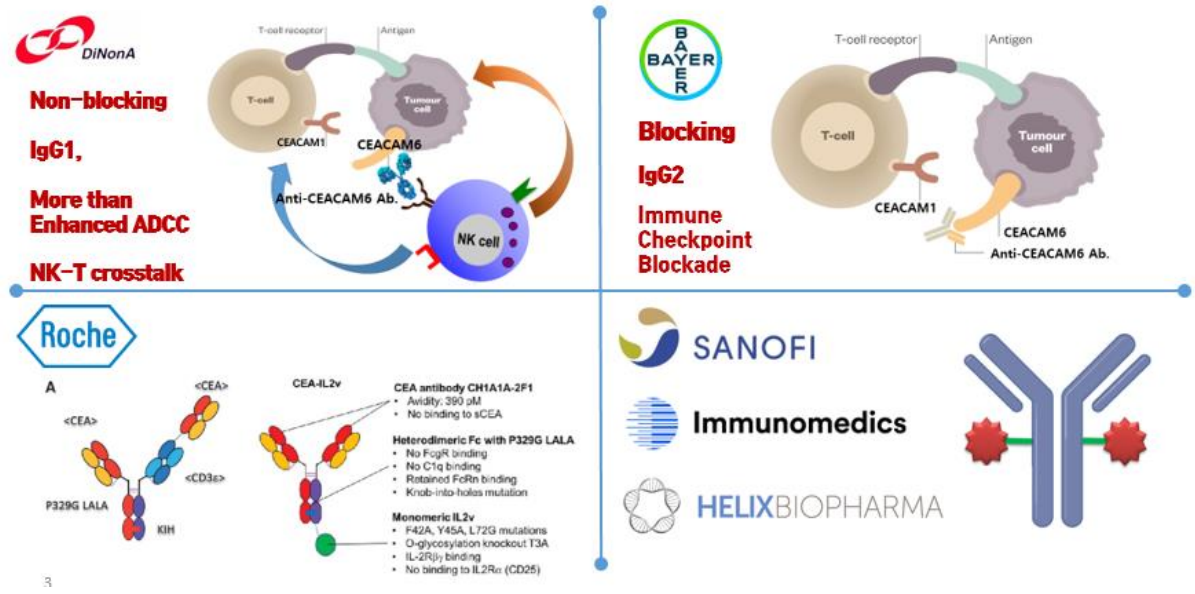
	
• Both are the Toxicity study in Cynomolgus monkeys	

Despite of the neutrophil level could be recovered, we should carefully monitor and manage this phenomenon in clinical stage. So we are actively considering adding a treatment that can help overcome neutropenia, such as G-CSF, to the clinical trial protocol.

6. HOW DIFFERENT IS DNP002 FROM OTHER ANTI-CEACAM ANTIBODY?

In terms of antibody format and mode-of action, DNP002 is different with other competitors.

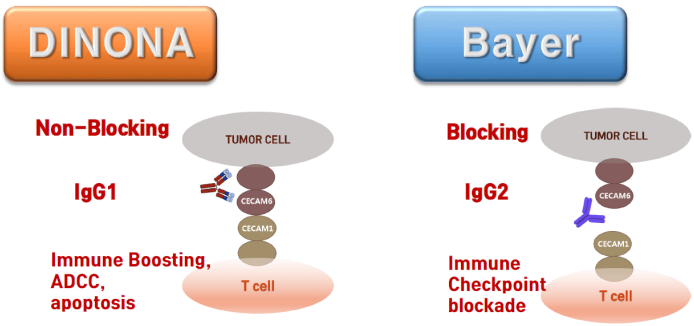
DNP002 is a naked antibody which is strengthened the binding affinity to FcgRIIIa by afucosylaton of antibody glycan. From this Fc modification, DNP002 has an enhanced ADCC potency. Other competitors have been developing 1) antibody-drug conjugates or 2) tumor-targeting antibody, not having the effector function itself as like T-cell binding bispecific antibody, or 3) immune-modulating antibody via blocking of CEACAM1-CEACAM6 interaction.

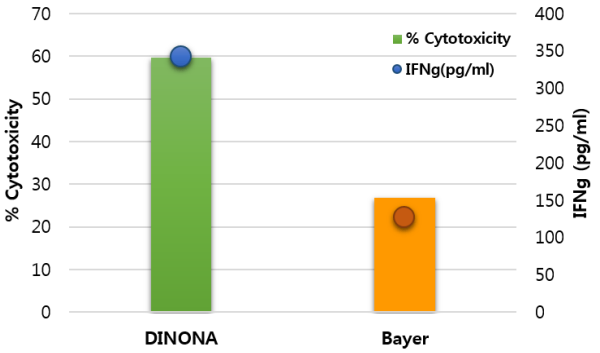


7. YOU INSIST THAT DNP002'S ENHANCED ADCC FUNCTION PROVOKE THE FOLLOWING T CELLS AND OTHER IMMUNE CELLS' ACTIVATION. WHAT IS THE DIFFERENCE BETWEEN BAYER'S IMMUNE CHECKPOINT BLOCKADE AND DINONA'S DNP002 IN TERMS OF FUNCTIONALITY?

Bayer's rationale for their antibody is begun the assumption that the interaction between CEACAM1 on T cells and CEACAM6 on tumor cells is another example as like PD-1/PD-L1 interaction for immune-modulating axis using the cancer cells' survival. However, this interaction seems to have little effect on the regulation of T cell activation. Because MERCK has stopped the phase I study with their anti-CEACAM1 antibody last year. Bayer has designed their anti-CEACAM6 antibody to IgG2 isotype in order to deplete the Fc mediated function and focus to function of blocking. And Bayer has recently addressed the plan to phase I study in 2018.

Unlike Bayer, Dinona's anti-CEACAM6 antibody cannot block the interaction of CEACAM1 and CEACAM6. Rather, DNP002 binds to B domain of CEACAM6 and induces the strong ADCC. Therefore, Dinona has intentionally designed the IgG1, and further Fc glycan-modified IgG1 in order to strengthen the ADCC. We have confirmed that through the direct comparison of both antibodies DNP002 is superior to Bayer's antibody in terms of in vitro cytotoxicity and IFNg secretion.



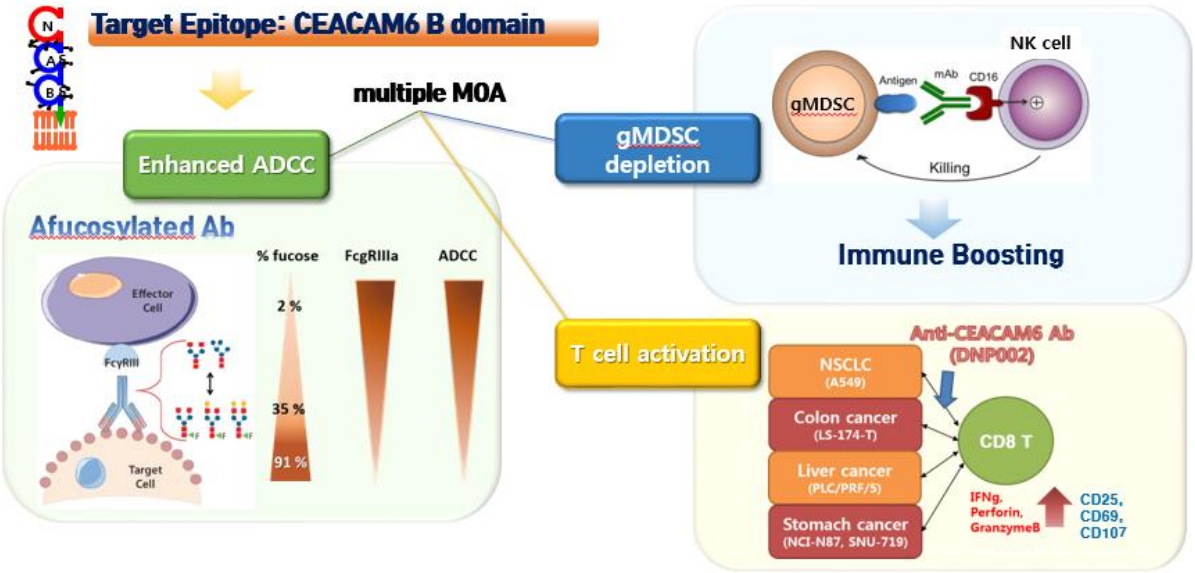


8. WHAT IS THE MODE OF ACTION OF DNP002?

Main mode of action is an enhanced ADCC. The way of showing enhanced ADCC is by afucosylation of antibody.

Afucosylated Fc portion of antibody binds to FcgRIIIa more tightly on NK cells, therefore NK cells become activated and induce the following signal transduction cascade and secreted several inflammatory and cytotoxic cytokines as like IFNg, perforin and granzymeB.

What we notice is that increased ADCC by NK activation does not just kill cancer cells, it can activate peripheral T cells and various immune cells. Through the fine analysis of various genetic and cellular levels we have confirmed that DNP002 is able to activate the T cells and immune cells and accelerate the tumor killing.



In terms of DNP002 binding target, MDSC (Myeloid derived Suppressor Cells) is an another target cells of DNP002. Granulocytic MDSC (gMDSC) which compose of at least more than 60~70% in the total MDSC does express CEACAM6 on the cell surface. So, DNP002 can kill the MDSC efficiently.
MDSC plays a role of helping the survival of tumor cells by immune suppression of tumor microenvironment (TME). Therefore, selective MDSC depletion is able to induce the change of TME from immune suppressive environment to immune reactivation mood. We are verified that from the blood of advanced gastric cancer patients DNP002 can kill the MDSC, and based on these results we applied for a patent this year.

Additionally, we have proved that DNP002 is able to induce the apoptosis of tumor cells in the anoikis conditions which cells is detached from the basement.

9. WHICH METHOD DO YOU USE FOR AFUCOSYLATION?

Using modified sugars in culture media, we produce the afucosylated antibody. Although there are lots of methods modulating the fucosylation level as like expression in FUT8 -/- CHO cells, Coexpression with GnT III and a-ManII in CHO cells, expression in other cells, YB2/0, yeast and even in plant, our method is very convenient and effective manufacturing afucosylated antibody.
Therefore, we are provided the customized cell culture media from a promising CHINA media manufacturing company.

For your further information about antibody afucosylation, you can find this review article.

Natasha A. Pereira, Kah Fai Chan, Pao Chun Lin & Zhiwei Song (2018) The “less-is-more” in therapeutic antibodies: Afucosylated anti-cancer antibodies with enhanced antibody-dependent cellular cytotoxicity, mAbs, 10:5, 693-711

10. HOW ABOUT THE AFFINITY OF DNP002 AND CROSS-REACTIVITY FOR CEACAMS PROTEIN?

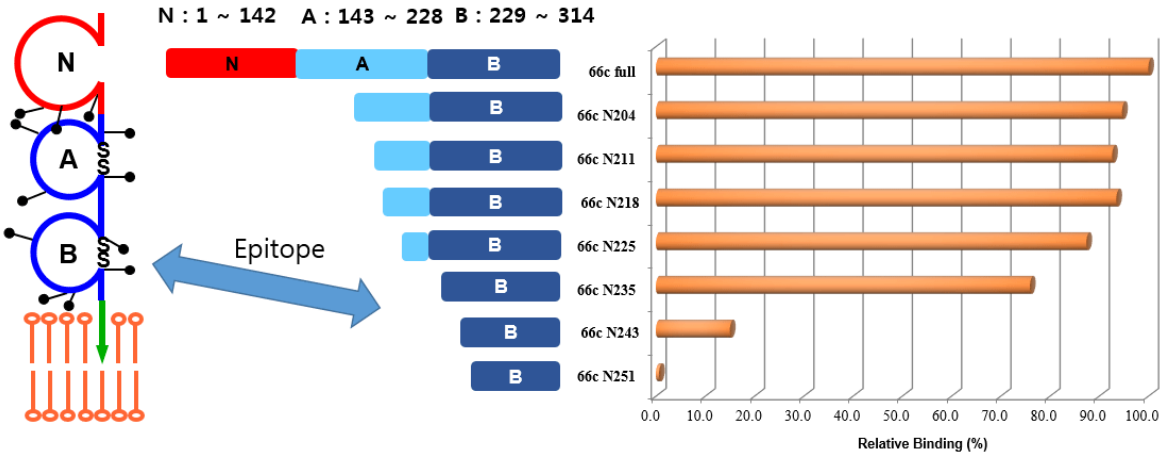
Affinity is KD 6.64E-10 (M) so, DNP002 is very high, competitive binding potential.

DNP002 is able to bind CEACAM5 via B1 domain of CEACAM5, and can bind weakly to CEACAM1. However, despite of having more sequence homology, DNP002 does not bind to CEACAM8. And there are no cross-reactivity on other CEACAM proteins.

11. WHAT IS THE EPITOPE OF DNP002 AND WHAT DOES IT HAVE ON THE PROPERTIES OF THE ANTIBODY?

DNP002 antibody binds to the B domain of CEACAM6 on the contrary of other anti-CEACAM6 antibodies. Because the relative high immunogenicity of N domain, most CEACAM6 antibodies are likely to N domain binding. However, DNP002 can bind to more membrane proximal region of CEACAM6.

Besides, original mouse parental antibody of DNP002 can also exhibit ADCC function, so DNP002 is designed to enhance ADCC function.



12. YOU HAVE CHOSEN THE IGG1 OF DNP002 IN ORDER TO GIVE THE EFFECTOR FUNCTION. WHY YOU CHOOSE THE IGG1 CONTRARY OF COMPETITORS?

One of the important issues in terms of function of antibodies is the isotype issue. In other words, the choice of isotype depends on the MOA of the antibody therapy.

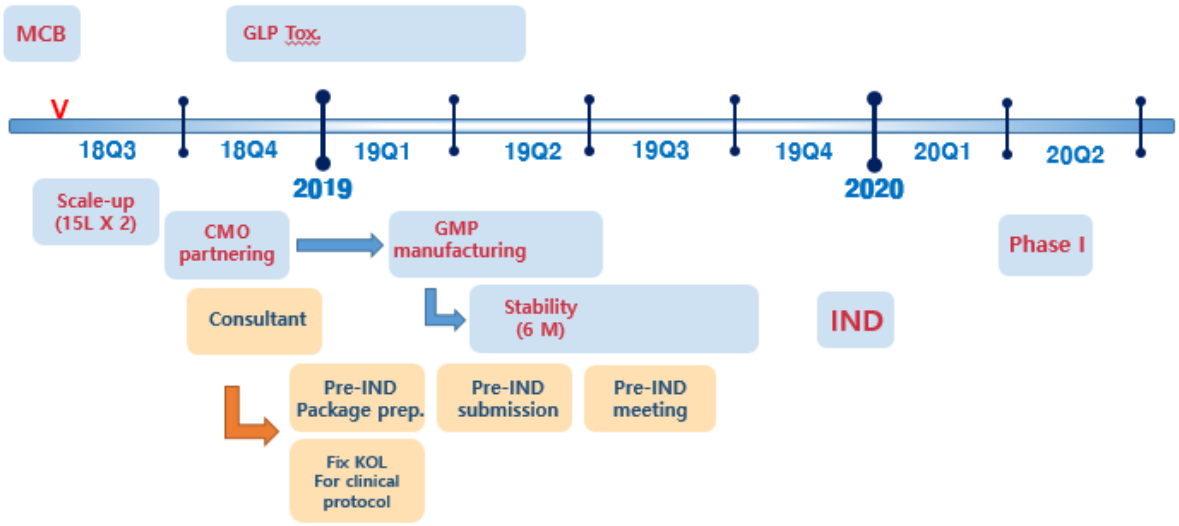
Other competitors selected IgG2, IgG4 or mutant IgG1 isotype to avoid Fc-mediated effector function, but Dinona selected IgG1 isotype to fully functionalize ADCC in antibody.

IgG1	Mutant IgG1	IgG2	IgG4
● **High affinity to FcgRIIIa** ● **ADCC** ● **Dinona, CEACAM6 Ab** ● Rituxan, Herceptin	● Depleting the FcR binding ● No Fc-mediated events, No ADCC ● Roche, CD3-CEACAM5 BsAb :(P329G LALA mutation, silent Fc)	● Very low affinity to FcgRIIIa ● No ADCC ● Bayer, CEACAM6 Ab	● Very low affinity to FcgRIIIa ● No ADCC ● BMS, Opdivo; Merck, Ketruda

13. WHAT IS A DEVELOPMENTAL STAGE OF DNP002?

DNP002 is in the preclinical stage.

Master Cell Bank(MCB) was established and now we are developing the processes. GLP-TOX is going to be begun at November, 2018. In order to GMP manufacturing of DNP002, we have already selected a CMO which has many experience for antibody manufacturing and FDA-inspection. Early next year we will go to the GMP manufacturing. And our goal is USA FDA IND within the end of 2019.



14. HOW ADVANCED ARE YOUR PREPARATIONS IN THE CMC AREA, AND AT WHAT LEVEL?

Since the establishment of MCB(Master Cell Bank), we are currently in the process of characterization of MCB and at the same time development of culture and purification processes is underway. In terms of upstream processes, we have selected the media for fed-batch and are now optimizing the parameters for bioreactor. On the basis of 3 step of chromatography design, also we are optimizing the downstream processes.

Because the antibody titer is more than 4.5 g/L in un-optimized conditions and relatively high processes yield, > 60%, we have a plan to manufacture the 250 L scale in cGMP for phase I study.

From a globally competitive CMO, we are going to manufacture 300 gram of DNP002. It can be used for dosing the patients, stability test, and the compensatory dosing, etc.

Regarding the specifications of DNP002 releasing, we have already set-up all 16 assays design for DS and DP, respectively.

< Remaining questions >

➔ For the successful clinical development of the DNP002 candidate, the following additional questions are very important to us. We will continue to work through early clinical trials to find scientific and clinically reliable answers to the questions below.

- **DOES DNP002 HAVE ANY KIND OF HISTOPATHOLOGIC SUBTYPE OF CANCERS WHICH HAVE SUPERIOR OUTCOME THAN OTHER SUBTYPES?**
- **IF SO, WHICH BIOMARKER WILL BE USED TO DETERMINE THE ADVANTAGE OF DNP002? (EX. CEACAM6 3+, 4+)**

Let's remind that Herceptin is only effective in patients whose HER-2 receptor status is 3+ or 2+ with positive FISH test.

In similar manner, we expect DNP002 would have better outcome in CEACAM-6 highly expressed subtypes. Considering that expression level of CEACAM-6 can be divided into 5 categories from 0 to 4+ and higher expression level naturally leads to higher affinity, superior outcome is anticipated among categories like CEACAM-6 3+ or 4+.

TCGA dataset might be a great potential to acquire reliable data about tumor marker and prognosis. For example, relationships between level of TGF-beta and amount of stroma, or molecular subtypes (ex. CMS4 in rectal cancer, Genomically Stable group in stomach cancer) were analyzed by using TCGA dataset which leads to new immunotherapeutic drug. Therefore, likewise, we would like to figure out how CEACAM-6 is related to prognosis of cancer patients by analyzing reliable dataset. Correlation between expression level of CEACAM-6 and OS, PFS, time to distant metastasis after treatment, initial clinical stage, histology (ex. Poorly differentiated, histologic grade…) and other relevant outcomes should be examined.

- **IS DNP002 SUPERIOR TO OTHER CONVENTIONAL CHEMOTHERAPY OR IMMUNOTHERAPY IN SPECIFIC CANCERS MENTIONED ABOVE?**
- **IF SO, WHAT IS DINONA'S PLAN TO PROVE IT?**
- **HOW DNP002 WILL BE USED IN CLINICAL PRACTICE? WILL IT BE USED ALONE OR IN COMBINATION WITH OTHER THERAPEUTIC AGENTS SUCH AS CHEMOTHERAPY OR RADIOTHERAPY?**
- **IF DNP002 SUPPOSED TO BE APPLIED WITH OTHER THERAPIES, PROPOSE THE OPTIMAL SEQUENCE OF COMBINATION AND DOSE DISTRIBUTION**

This must be verified by in vivo animal study. As cisplatin/etoposide chemotherapy is current treatment of choice in advanced lung cancer without molecular target (ex. EGFR, ALK), comparison of DNP002 against conventional

chemotherapy in animal model is necessary. So, we are now doing the in vivo study for verifying these concepts. Also, outcomes according to treatment sequence should be examined as optimal sequence of radiotherapy and immunotherapy is still unknown territory and variable among immunotherapeutic agents.