ONO PHARMACEUTICAL CO., LTD.

R&D Meeting

February 22, 2024

[Number of Speakers]	4	
	Gyo Sagara	President, Representative Director, and Chief Executive Officer
	Toichi Takino	Member of the Board of Directors, Senior Executive Officer, Executive Director of Discovery & Research
	Tatsuya Okamoto	Corporate Officer, Deputy Executive Director, Clinical Development
	Ryuta Imura	Senior Director, Corporate Communications

Presentation

Imura: First, President Sagara will give an opening speech, and then Mr. Okamoto, Deputy Executive Director of Clinical Development, will introduce the development status of ONO-4578. Finally, Dr. Takino, Executive Director of Discovery and Research, will introduce the progress of open innovation and ONO-8250.

Change in Representative Directors

Details of the change in directors as of April 1, 2024

Name	New Role	Current Title
Gyo Sagara	Representative Director, Chairman of the Board and Chief Exective Officer	Representative Director, President
Toichi Takino	Representative Director, President and Chief Operating Officer	Director, Senior Executive Officer / Exective Director, Discovery and Research
Toshihiro Tsujinaka	Representative Director, Exective Vice President / Executive Directorr, Corporate Strategy & Planning / Director, Sustainability Promotion	Director, Senior Executive Officer, Exective Director, Corporate Strategy & Planning / Director, Sustainability Promotion

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Sagara: I would like to begin by saying a few words about the changes we have decided to make to our top management structure from April onward.

As you know, ONO is currently facing the expiration of patents for Opdivo and the diabetes-related Glactiv and Forxiga in the near future and is currently working to strengthen its pipeline and how to overcome these patent expirations. Also, we are working on how to grow further, and I think this will be everything for the next few years.

As I have mentioned in the past, the first and most important issue is to obtain approval and sell the products overseas, in the US and Europe by ourselves.

Of course, we are taking this initiative from a place where we have never obtained approval, have never dealt with production and logistics regulations, and have no experience in marketing or sales, so we are prepared for difficulties, but we know that we need to accomplish this.

The Japanese market is currently 5% of the global market. Of that 5%, we obtain approval and sell the products ourselves, but the remaining 95% are licensed out, from which we receive royalties, and that is the model we have adopted.

I won't say the remaining all 95%, but it will be 50% in the United States and 15% in major European countries, and plus extra, but it is time for us to try and sell the products by ourselves in those markets. The entire company is working diligently toward this goal.

In terms of the US, we have been planning to launch Velexbru in 2026. The target year is 2026, which is two years from now, and when the entire company is working together to achieve this target, I wondered if the current structure is really the best way to achieve this goal. The current system is that I am the president and have only one representative, and the rest are handled by the departments, department directors, and the person in charge.

We have been moving forward under this structure, but we decided to create this new structure to move forward with the last two years until 2026 with the entire company united as one. The idea was that two or three cylinders would be more propulsive, more successful, and more feasible than one cylinder.

Of course, we felt that having only one representative was not a desirable system when considering various accidents, etc. The background of this change is that we decided on this type of structure to move forward toward the most important milestone of the next two years with a three-cylinder engine.

So, what role will each of us three play? Naturally, the president will be in charge of internal operations, and Dr. Takino will be responsible for day-to-day operations and decisions within the Company. I, Sagara will be involved in the Company's policies, direction, and decision-making, and will also bear responsibility for such decisions.

Dr. Takino oversees the whole thing and has a long and proven track record of BD and licensing experience overseas, given his background. As you know, I became president in 2008, and the timing was such that the percentage of long-term listed products would be about 90% in three or four years. The research institute did not have anything suitable for the time.

Therefore, we decided to strengthen the license and overcome this problem, and I asked the BD team at the time to take on a difficult task. At that time, Dr. Takino and I worked in tandem to find partners overseas and in Japan to acquire the compounds.

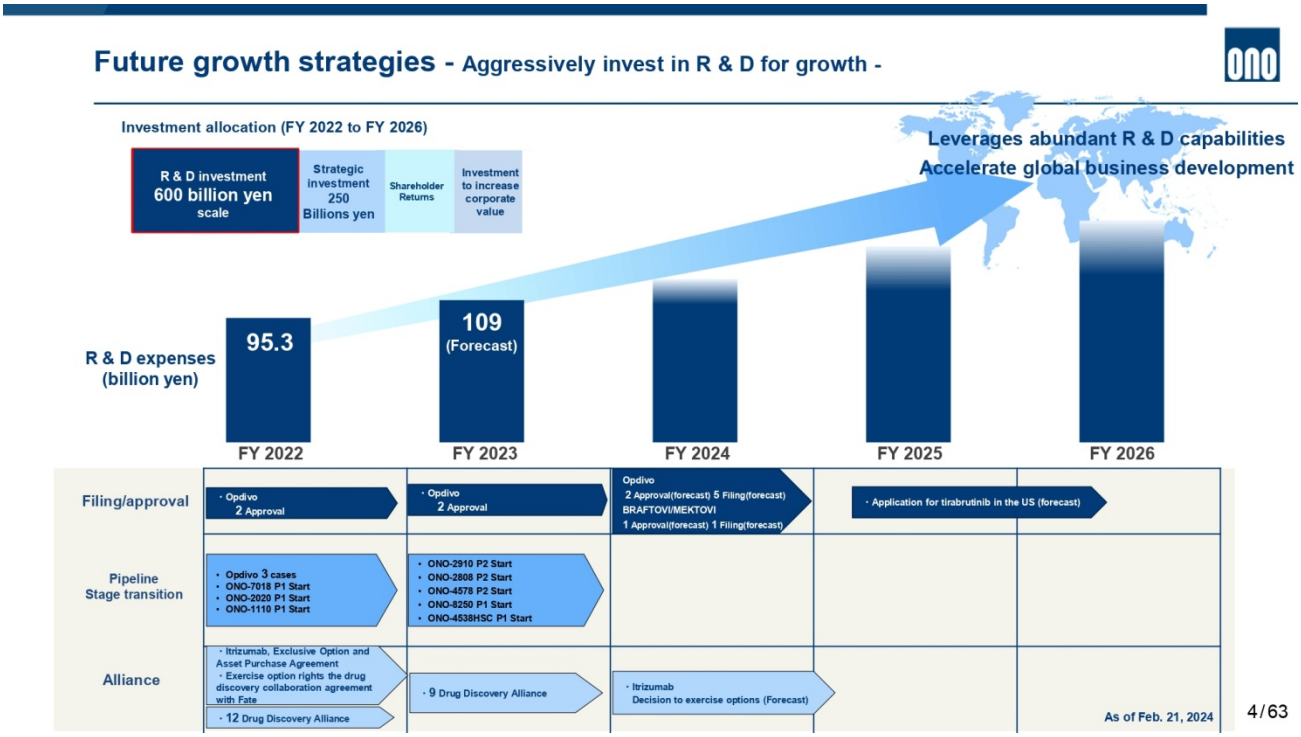
I think we can say that most of the compounds for which we obtained the rights at that time are now available, except for Opdivo and Velexbru, the long-term listed products. We obtained more than a dozen compounds in our hands, and those compounds are now supporting the Company.

In the meantime, our investment in Opdivo paid off, and we launched it for melanoma in 2014 and took the indication for lung cancer in 2016, and so far, that has allowed us to grow steadily. We are determined to go through these difficult times with a new mindset to deal with the situation as it was 15 years ago, and we will have the new President Dr. Takino oversees our overseas expansion.

Although he does not have any experience of working in clinical development overseas, I am sure that he will be able to make good use of his long career working overseas.

This is the background for the new structure that will be in place as of April 1. As for Mr. Tsujinaka, who will become vice-president, will be responsible for the solid operation of the domestic entities. In addition, I, Sagara will continue to be responsible for industry activities, business activities, and external relations.

I have not had a chance to talk to the analysts since the announcement on January 11, so I have spoken to you today.



I am showing you the rough operation of the Company until the approval and start of sales of Velexbru in the United States in FY2026.

What I would like to say with this is that we are entering a difficult period in terms of sales. Royalties will be decreasing next year, and as you know, unfortunately, we will be taking the Opdivo tailgated price cut on April 1. This is something we have to overcome, though. Period performance will be a bit tougher compared to the steady growth of the last few years.

However, we will continue to invest in research and development as much as possible. Although I would not go so far as to say that we will sacrifice profit and loss for the period and performance for the period, we intend to make solid investments with a certain degree of preparedness.

About 15 years ago, we continued to invest in R&D despite three to four years of slow performance. We have been criticized by many of you, but we have accumulated a certain amount of funds over the past several years, and we intend to make good use of them.

In the current medium-term plan for FY2022 to FY2026, we will invest JPY600 billion in R&D, which will be an average of JPY120 billion per year. We invested JPY95 billion in FY2022 and the amount is expected to be JPY109 billion this fiscal year. We would like to work hard to steadily move forward with R&D investment on the scale of JPY600 billion.

For details, please refer to the document.

Imura: Now, Mr. Okamoto of Clinical Development will continue with an explanation of the development status of ONO-4578.

Okamoto: I would like to introduce the development status of ONO-4578, including the most recently published conference report.

ONO-4578

Compound	**ONO-4578（In-house, Small molecule）**
Mechanism	**Prostagrandin receptor (EP4) antagonist**
Formulation	**Tablet**
Stage	**Phase2：GC*（JP・KR・TW）** **Phase1：Colorectal cancer*, Pancreatic cancer*, NSCLC*, Hormone receptor-positive, HER2-negative breast cancer（JP）** **（*：Combination with OPD）**

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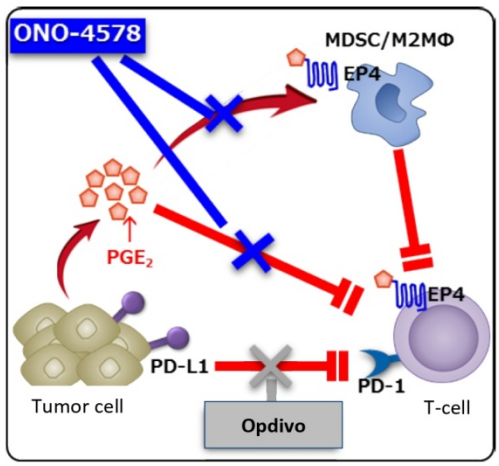
First, we present ONO-4578, an overview of the compound.

This is a small molecule compound created in-house for oral use. The mechanism of action is antagonism against EP4, one of the four receptors for prostaglandin, PGE2. I will explain the development status in detail later.

ONO-4578 Mechanism of Action

- **Prostaglandin E_2 (PGE_2) is produced from arachidonic acid through cyclooxygenase-2 (COX-2)**
- **COX-2 is overexpressed in solid cancer[1]. PGE_2 has been reported to induce myeloid-derived suppressor cells (MDSC) and M2 macrophages in the tumor microenvironment through one of its receptors, EP4, and suppress activation of cytotoxic T cells[2].**
- **ONO-4578, a novel selective EP4 antagonist, is expected to have an antitumor effect by abolishing the tumor immunosuppressive mechanism that PGE_2 constructs via EP4.**



1) Bing L, et al. Cancer Cell Int; 2015:15:106
2) Yukinori T, et al. Front Immunol. 2020;11:324

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Here is the mechanism of action of ONO-4578.

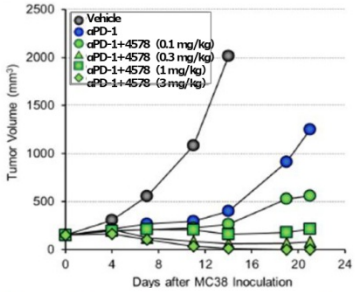
As I just mentioned, ONO-4578 is an antagonist of EP4, one of the receptors for the bioactive substance PGE2. This bioactive substance, PGE2, has various functions.

In the cancer microenvironment, cancers utilize PGE2 produced by themselves to induce a group of cells that negatively regulate tumor immunity, such as MDSCs or M2 macrophages, to escape from tumor immunity. It is thought that they create a tumor microenvironment that is comfortable for them to live in.

On the other hand, Opdivo, acts on CD8-positive T cells, which are the main players in the anti-tumor immunity, the side that attacks cancer, and suppresses the inactivation of T cells. However, we believe that ONO-4578 activates tumor immunity by suppressing the activation of other tumor immunity suppressing factors such as MDSCs and M2 macrophages, which cannot be inhibited by Opdivo.

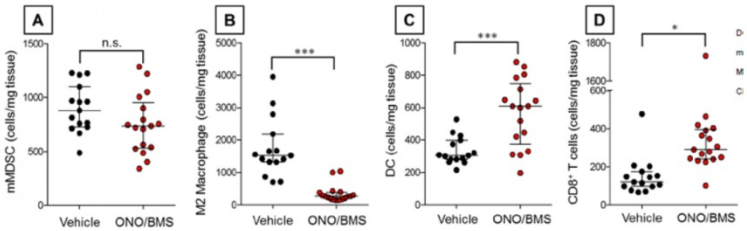
ONO-4578 Non-clinical data

Fig 1. Time course of median tumor volume in syngeneic mouse colorectal cancer MC38 tumor-bearing model



- **In syngeneic mouse tumor-bearing model, ONO-4578 improved immunosuppressive tumor microenvironment and showed antitumor effects (Figs. 1 and 2).**
- **Furthermore, ONO-4578 enhanced its antitumor effect by co-administration with anti-mouse PD-1 antibody (αPD-1) (Fig. 1).**

Fig 2. Effect of ONO-4578 on intra-tumoral immune cells in syngeneic mouse colorectal cancer MC38 tumor-bearing model



A : No. of mMDSC
B : No. of M2 macrophage
C : No. of dendritic cells
D : No. of CD8-positive T cells

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Here is some non-clinical and basic data.

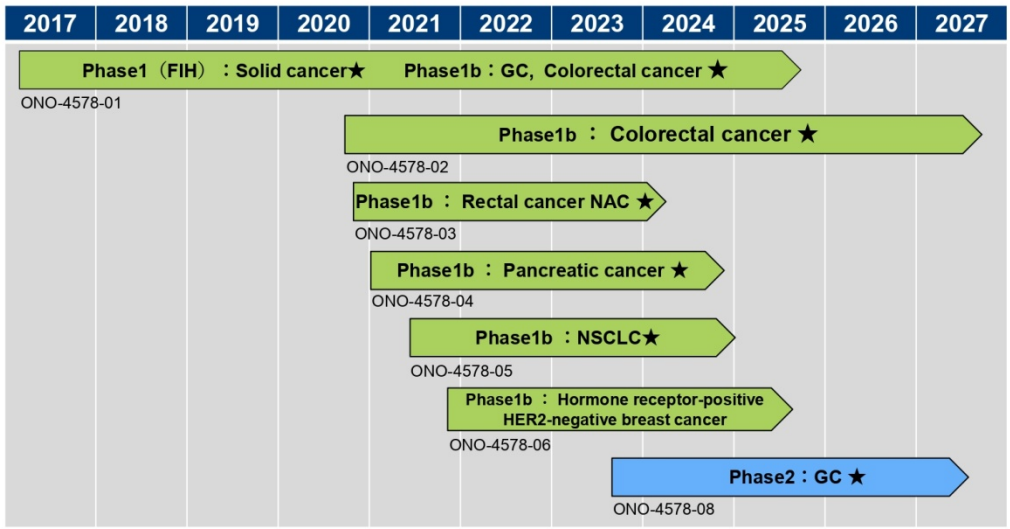
As I mentioned earlier, Opdivo and ONO-4578 have different points of action. Therefore, we believe that the combination of both drugs will enhance anti-tumor immunity and provide stronger anti-tumor effects.

Figure 1 shows the results of the combined administration of ONO-4578 in a syngeneic mouse tumor-bearing model and PD-1 antibody to mice. As you can see, the combination of both drugs has shown a strong anti-tumor effect as expected.

I would like you to take a look at the diagram below to see if the movement in line with the concept, in line with the mechanism of action I mentioned earlier, is actually occurring. It has been confirmed that the number of CD8 T cells on the right-side increases by reducing the number of bad cells, such as M2 macrophages and MDSCs, which negatively induce tumor immunity.

Based on these preclinical results, we believe that the combination of Opdivo and ONO-4578 has the potential to show high efficacy not only in cancers where the efficacy of PD-1 antibodies has already been established, but also in some cancers where the efficacy of PD-1 antibodies alone or in combination with chemotherapy has not been easily observed, for example, pancreatic cancer, colorectal cancer.

ONO-4578 Development stage



★Combination with OPD

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Here is the status of clinical development.

As shown here, we are currently developing the drug in combination with Opdivo for multiple solid tumors.

Today, I will present the results in detail later of the Phase I trial shown at the top of this list, Part C, which targets advanced and recurrent gastric cancer, and Part D, which targets colorectal cancer after third-line treatment.

On the other hand, as I mentioned earlier, we believe that combination therapy can be expected to enhance the efficacy for colorectal cancer. We are conducting the ONO-4578-02 trial, which is a trial in which Opdivo and ONO-4578 are used in combination with chemotherapy, which is the standard treatment, for first-line colorectal cancer. Also, we are conducting the ONO-4578-04 trial, which is a trial in which Opdivo and ONO-4578 are used in combination with chemotherapy, which is the standard treatment, for first-line pancreatic cancer.

As for ONO-4578-05 trial, this is a trial for non-small cell lung cancer. As you all know, PD-1 or PD-L1 antibody-containing regimens are currently the standard of care for first-line treatment of non-small cell lung cancer, but for those who experienced exacerbations after receiving this standard regimen, we are now conducting a trial in which we will administer Opdivo and ONO-4578 again in combination with the standard regimens.

Regarding gastric cancer, it is indicated by a blue bar at the bottom. Based on the results of Part C, which I will talk about later, we have already announced that we have started a Phase II study in Japan, South Korea and Taiwan, in which ONO-4578 is added to the standard treatment of gastric cancer, the combination of Opdivo and chemotherapy.

ONO-4578-01 Part C Results

Safety, efficacy, and biomarkers for ONO-4578 plus nivolumab in unresectable advanced or recurrent gastric or gastroesophageal cancer

Hidekazu Hirano[1], Akihito Kawazoe[2], Kensei Yamaguchi[3], Tetsuya Hamaguchi[4], Yukiya Narita[5], Shogen Boku[6], Takashi Oshima[7], Hiroki Hara[8], Yasuo Hamamoto[9], Taito Esaki[10], Kenji Ishido[11]

[1]Department of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Chuo-ku, Japan; [2]Gastroenterology and Gastrointestinal Oncology Department, National Cancer Center Hospital East, Kashiwa, Japan; [3]Gastroenterological Chemotherapy Dept., The Cancer Institute Hospital of JFCR, Koto-ku, Japan; [4]Gastroenterological Oncology Dept., Saitama Medical University International Medical Center, Hidaka, Japan; [5]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan; [6]Cancer Treatment Center, Kansai Medical University, Hirakata, Japan; [7]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; [8]Gastroenterology, Saitama Cancer Center, Ina, Japan; [9]Cancer Center, Keio University School of Medicine, Shinjuku-ku, Japan; [10]Clinical Research Department, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [11]Department of Gastroenterology, Kitasato University East Hospital, Sagamihara, Japan

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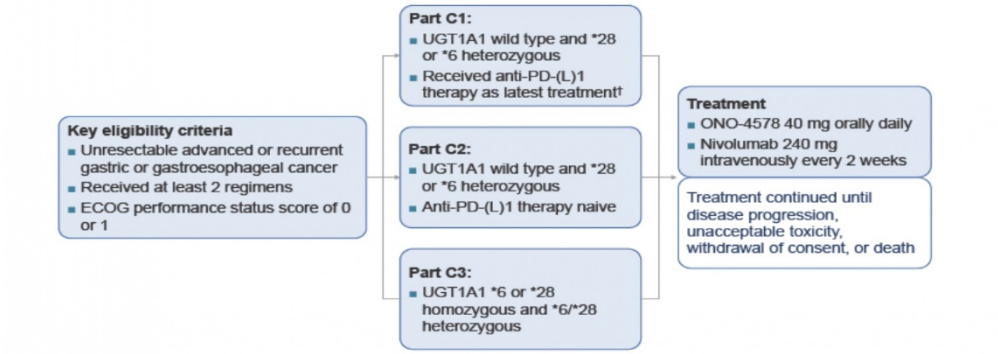
I would like to present the results of Part C, the ONO-4578-01 study in gastric cancer.

The results of this study were presented at ESMO last year.

Methods

Study Design

- Part C of the ONO-4578-01 phase 1 study (NCT03155061) was an open-label, uncontrolled study, conducted at 22 sites in Japan
- Recruited patients were categorized into three parts (C1, C2, C3) on the basis of prior anti-PD-1/
- PD-L1 therapy and UGT1A1 genotype (Figure 2)
- All subgroups received 40 mg of ONO-4578 orally every day and 240 mg NIV intravenously every two weeks; one cycle consisted of 4 weeks



†Patients assessed to have a progressive disease on the first image evaluation after the latest anti-PD-(L)1 antibody therapy were excluded

ECOG, Eastern Cooperative Oncology Group; PD-(L)1, programmed death-1 or programmed death ligand-1

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This is a brief overview of the study design. This is different from the slide presented at the conference but is available as supplementary materials. I will use this to explain the study design.

In Part C of the ONO-4578-01 study, Opdivo was not yet approved for first-line gastric cancer treatment at the time of the study's initiation. At that time in Japan, Opdivo monotherapy, was approved for gastric cancer patients after the third-line treatment and it was the standard treatment.

In Part C of the study, patients who had received the standard of care, Opdivo, for the third-line treatment and had a certain level of clinical benefit but subsequently developed disease progression or PD, in other words, patients who were considered to have developed resistance to Opdivo, were divided into two cohorts**:** Part C1, in which patients were re-treated with Opdivo in combination with ONO-4578, and Part C2, in which patients were treated with the standard of care, Opdivo plus ONO-4578.

Since this was a phase I study, the primary endpoints were to confirm tolerability and safety. Today I will talk including effectiveness.

Efficacy Results

	C1 (n=30)	C2 (n=30)
Objective Response Rate, % [90% CI]	10.0 [2.8–23.9]	16.7 [6.8–31.9]
Disease Control Rate, % [90% CI]	73.3 [57.0–86.0]	40.0 [25.0–56.6]
Best Overall Response, n (%) [90% CI]		
Complete Response	0 (0) [0.0–9.5]	0 (0) [0.0–9.5]
Partial Response	3 (10.0) [2.8–23.9]	5 (16.7) [6.8–31.9]
Stable Disease	19 (63.3) [46.7–77.9]	7 (23.3) [11.5–39.4]
Progressive Disease	7 (23.3)	18 (60.0)
Not Evaluable	1 (3.3)	0 (0)
Progression-Free Survival[a]		
Median, months [90% CI]	3.88 [2.79–4.17]	1.56 [1.41–2.76]
At 6 months, % [90% CI]	26.3 [13.7–40.8]	21.8 [10.7–35.4]
At 12 months, % [90% CI]	7.5 [1.9–18.6]	3.6 [0.5–13.0]
Overall Survival[a]		
Median, months [90% CI]	16.13 [10.18–18.92]	5.49 [4.27–10.68]
At 6 months, % [90% CI]	93.3 [80.2–97.9]	46.7 [31.3–60.6]
At 12 months, % [90% CI]	62.6 [46.1–75.4]	30.0 [17.2–43.9]

90% confidence intervals (CI) on both sides were calculated using the Clopper-Pearson method
[a]Analysis using Kaplan-Meier method

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Efficacy Results.

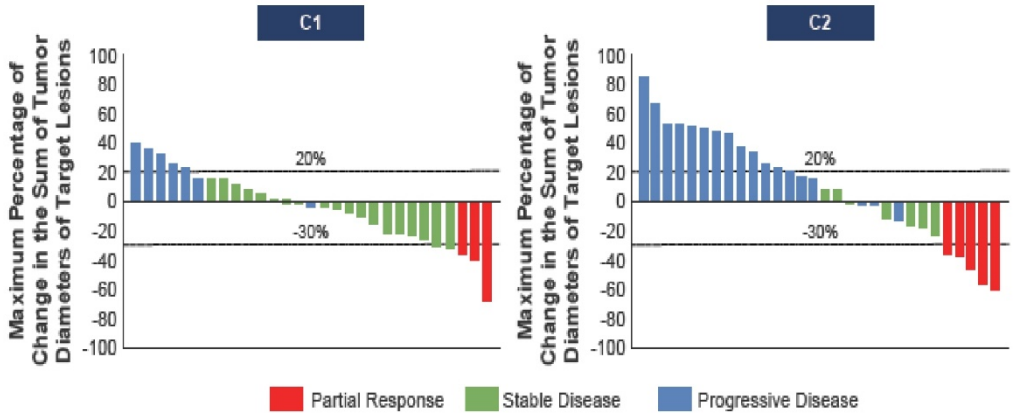
Part C1, which I mentioned earlier, is on the left side, and Part C2, on the right side, is the addition of ONO-4578 to the standard of care, Opdivo monotherapy.

The response rate for Part C1 was 10.0%, and the disease control rate was 73.3%. On the other hand, the response rate in Part C2, in which naïve patients with no prior experience with PD-1 antibody drugs were treated with Opdivo and ONO-4578, was 16.7%, and the disease control rate was 40.0%.

For your information, the ATTRACTION-2 trial, or ONO-4538-12 trial, a Phase III study in gastric cancer patients after the third-line treatment who had not received PD-1 antibody drugs, showed a response rate of 11.2% and a disease control rate of 40.3%.

Efficacy Results

Waterfall Plot by Best Overall Response



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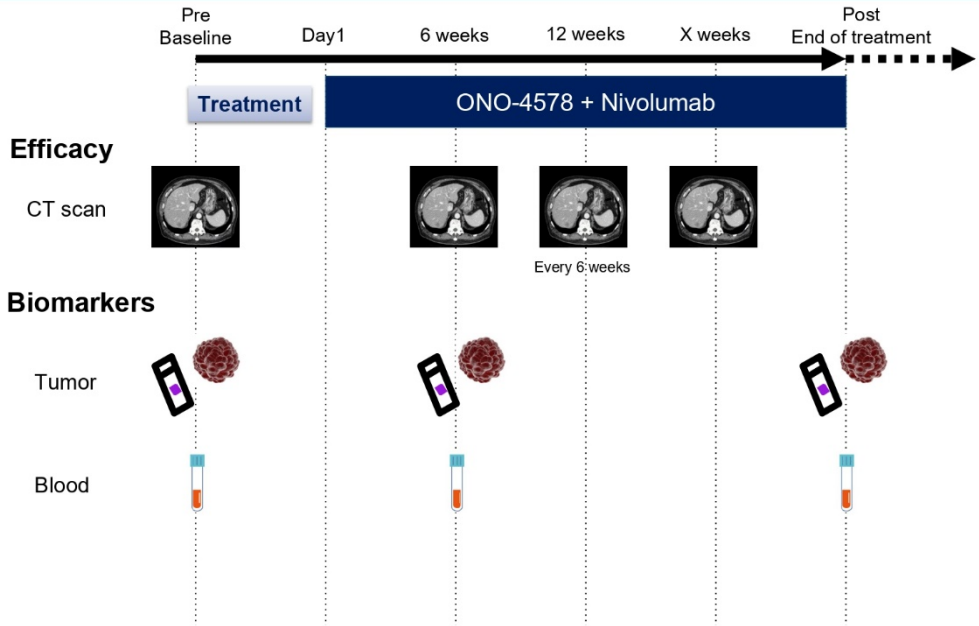
This is a waterfall plot.

The left side is C1, and the right side is C2. Now I would like you to focus on this C1. As I have mentioned repeatedly, patients eligible for C1 are those who were once treated with Opdivo as the standard of care and had a certain level of benefit, but whose tumors subsequently grew.

In Part C1, more than half of the patients again showed tumor shrinkage after re-administration of Opdivo in combination with ONO-4578.

Study schedule of ONO-4578-01 Part C (3rd or later line, GC)



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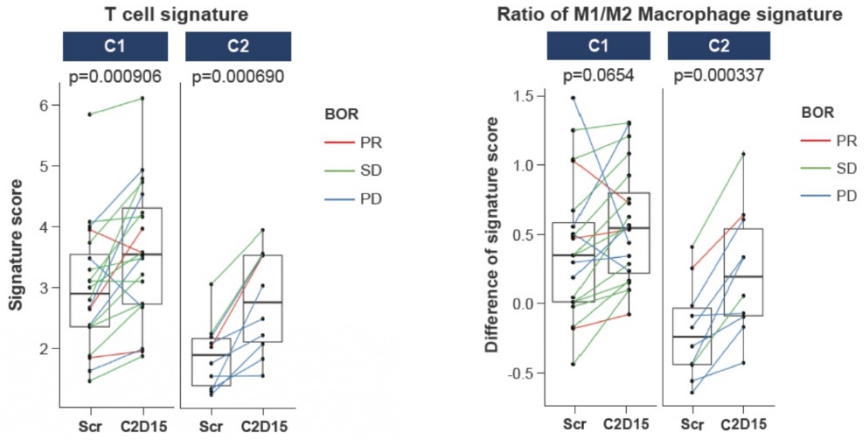
In Part C, tumor biopsies were performed before and after administration of the investigational treatment. With the cooperation of the patient, we collected and evaluated tumors before and after administration. We studied the impact of the combination of ONO-4578 and Opdivo at the molecular level.

This is the biomarker evaluation item.

I am very sorry, but what was measured it is not disclosed. Regarding the results obtained, we conducted a pooled analysis of clinical data such as efficacy and safety, and as shown on the right, for example, efficacy predictors, or to examine which items are most effective for patients with high scores, as well as to examine the mechanism of action in the first place.

Results of Biomarker Analysis

T-cell Gene Signature and M1/M2 Macrophage Gene Signature in Tumor Biopsies



Signature score was calculated as mean of log-transformed expression value BOR, best overall response; PD, progressive disease; PR, partial response; SD, stable disease
Scr, Screening period; C2D15, cycle 2 day 15

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In fact, here is the data presented at the conference.

These are some of the results of biomarker analysis. The figure shows the changes in gene expression in tumor tissue before and after administration.

As I mentioned at the beginning, ONO-4578 suppresses the so-called "bad" macrophage cell group, but the right side shows that the number of bad cells has decreased, and the number of good cells has increased.

On the other hand, when combined with ONO-4578 and Opdivo, the concept is to increase T cell activation with Opdivo while suppressing suppressive cells with ONO-4578, and as a result, activation of T cells has also been observed.

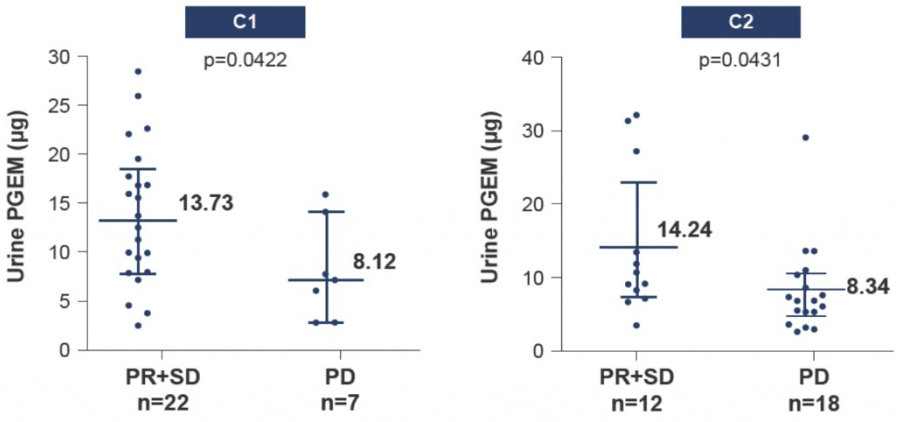
We believe that the preclinical results of activation of CD8-positive T cells while suppressing the bad cells have been reproducibly confirmed in the clinical setting.

In other words, our concept of combining Opdivo and ONO-4578 is supported at least by the results of Part C1.

Results of Biomarker Analysis

- Baseline urine PGEM, the potential surrogate marker of tumor PGE2, was found to be higher in patients with partial response or stable disease than in patients with progressive disease

Baseline Urine PGEM Levels



PD, progressive disease; PGEM, prostaglandin E2 metabolites; PR, partial response; SD, stable disease

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Here are the results of the quantitative measurement of PGE2 metabolites in urine.

As shown in C1 and C2, it can be seen that the amount of PGE2 metabolites in urine was higher in the group of patients who had an anti-tumor effect of SD or higher compared to the group of patients who had a PD.

Although this is only a backward-looking observation, we believe that the combination therapy of ONO-4578 and Opdivo may be particularly effective in patients with relatively high PGE2 levels.

Safety Results

n (%)	C1 (n=30)		C2 (n=30)		C3 (n=6)	
	Any grade	Grade 3-4	Any grade	Grade 3-4	Any grade	Grade 3-4
AEs	28 (93.3)	15 (50.0)	27 (90.0)	11 (36.7)	6 (100.0)	4 (66.7)
Drug-related AEs	24 (80.0)	10 (33.3)	18 (60.0)	3 (10.0)	4 (66.7)	4 (66.7)
Drug-related SAEs	4 (13.3)	3 (10.0)	2 (6.7)	2 (6.7)	3 (50.0)	3 (50.0)
Drug-related AEs leading to discontinuation of study treatment	3 (10.0)	2 (6.7)	2 (6.7)	2 (6.7)	3 (50.0)	3 (50.0)
Drug-related AEs leading to dose delay	12 (40.0)	7 (23.3)	7 (23.3)	1 (3.3)	2 (33.3)	2 (33.3)

AE, adverse events; SAE, serious adverse events

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This shows safety results.

The study is for patients with advanced recurrent gastric cancer. We believe that this combination therapy has demonstrated a manageable safety profile.

So far, I have presented the results of the Part C clinical trial itself. I am afraid that this is a projection-only document.

As you know, we have conducted a large number of clinical trials with Opdivo, and naturally we have a huge amount of data from those clinical trials, including data on individual patients. We believe that our strength lies in our ability to utilize this data for future development, and today we are presenting an example of this.

Here is a comparison of the results of Part C and Part C1 with the results of our previous clinical trials in gastric cancer.

I hope you will forgive me for the blurriness of the slide. First, the basic premise is that this is a comparison between different tests, so the data is only for internal review. Therefore, we need to be careful in interpreting the results, so we have added this blurring.

We can extract patients from previous clinical trials who have almost the same background information as our Part C1 patients. Therefore, by comparing the results of these trials, and taking into consideration not only the clinical data from Part C1 but also the changes in biomarkers and other factors, we came to the conclusion that the combination of ONO-4578 and Opdivo could be an effective treatment for gastric cancer, and as I mentioned earlier, we have started a phase II trial for the first-line treatment.

ONO-4578-01 Part D Results

Safety And Efficacy Of ONO-4578 Plus Nivolumab In Metastatic Colorectal Cancer

Akihito Kawazoe[1], Atsuo Takashima[2], Hiroshi Matsuoka[3], Yasuo Hamamoto[4], Tatsuya Okuno[5], Tetsuya Hamaguchi[6], Kensei Yamaguchi[7], Eiji Oki[8], Naotoshi Sugimoto[9], Yasushi Tsuji[10], Shogen Boku[11], Tomohiro Nishina[12]

1National Cancer Center Hospital East, Kashiwa, Japan; 2National Cancer Center Hospital, Chuo City, Japan; 3Fujita Health University, Toyoake, Japan; 4Keio University School of Medicine, Tokyo, Japan; 5Osaka Rosai Hospital, Sakai-Shi Kita-Ku, Japan; 6Saitama Medical University International Medical Center, Saitama, Japan; 7Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; 8Kyushu University, Fukuoka, Japan; 9Osaka International Cancer Institute, Osaka, Japan; 10Tonan Hospital, Sapporo, Japan; 11Cancer Treatment Center, Kansai Medical University Hospital, Hirakata, Japan; 12National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

These are the results of Part D of the Phase I trial of the combination of Opdivo and ONO-4578, which was presented at ASCO-GI in January this year for the treatment of colorectal cancer after the third line of treatment.

METHODS

Study Design

- Part D (CRC cohort) of the ONO-4578-01 phase 1 study (NCT03155061) was an open-label, uncontrolled study, conducted at 12 sites in Japan
- Key eligibility criteria were as follows
  - Age ≥20 years
  - Unresectable and metastatic CRC that progressed on/after standard treatment or could not tolerate it
  - ECOG performance status score of 0 or 1
- Patients with microsatellite-instability-high, deficient mismatch repair, or *BRAF* mutations (by local testing) were excluded
- All subgroups received 40 mg of ONO-4578 orally every day and 240 mg NIV intravenously every two weeks; one cycle consisted of 4 weeks (28 days)
- Study treatment was continued until any of the discontinuation criteria were met

Study Endpoints

- Primary endpoint: Safety
- Exploratory efficacy endpoints: Investigator-assessed overall response rate (ORR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS)

Study Assessments

- Tumor diameters were measured at various time points using CT and/or MRI images
- Antitumor effects are assessed using the same procedures throughout the study in accordance with the RECIST Guidelines version 1.1.

I am afraid we do not have a figure here, but 51 patients with colorectal cancer after the third line of treatment were enrolled in the study.

Efficacy Results

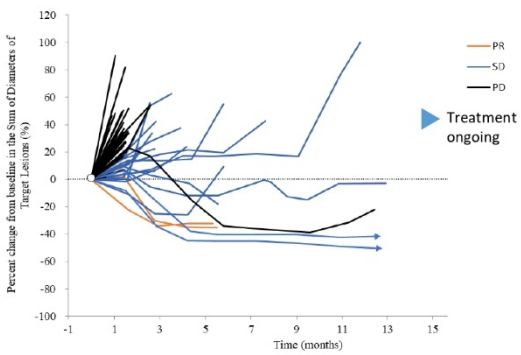
Best Overall Response (BOR)	n (%)	[90% CI]
CR	0 (0.0)	[0.0–5.7]
PR	2 (3.9)	[0.7–11.8]
SD	18 (35.3)	[24.2– 47.7]
PD	30 (58.8)	
NE	1 (2.0)	
ORR (CR+PR)	2 (3.9)	[0.7–11.8]
DCR (CR+PR+SD)	20 (39.2)	[27.7–51.7]

CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

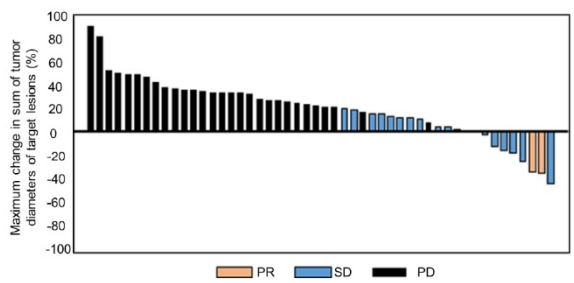
This slide shows efficacy results. The response rate, or ORR, was 3.9%, and the disease control rate, DCR, was 39.2%.

Efficacy Results

Spider Plot for Best Overall Response



Waterfall Plot by Best Overall Response



Best overall response follows RECIST guidelines version 1.1
PD, progressive disease; PR, partial response; SD, stable disease

The spider plot is shown on the left and the waterfall plot on the right.

At the cutoff, two patients were still on investigational treatment.

Results of studies in colorectal cancer

試験	ORR, DCR(%)	PFS(month)	OS(month)
CORRECT, CRC 3L, P3 [1] Regorafenib vs Placebo	ORR: 1.0 vs 0.4 DCR: 41 vs 15	Median: 1.9 vs 1.7 HR: 0.49	Median: 6.4 vs 5.0 HR: 0.77
RECOURSE, CRC 3L, P3 [2] TAS102 vs Placebo	ORR: 1.6 vs 0.4 DCR: 44 vs 16	Median: 2.0 vs 1.7 HR: 0.48	Median: 7.1 vs 5.3 HR: 0.68
Imblaze 370, CRC 3L, P3 [3] Atezolizumab+Cobimetinib vs Regorafenib	ORR: 3 vs 2 DCR: 26 vs 34	Median:1.91 vs 2.00 HR: 1.25	Median:8.87 vs 8.51 HR: 1.00
Imblaze 370, CRC 3L, P3 [3] Atezolizumab vs Regorafenib	ORR: 2 vs 2 DCR: 21 vs 34	Median:1.94 vs 2.00 HR: 1.39	Median:7.10 vs 8.51 HR: 1.19
LEAP 005, CRC 3L, P3 [4] Pembrolizumab + Lenvatinib	ORR: 10.4 DCR: 63.1	Median: 3.8 vs 3.3 HR: 0.69	Median: 9.8 vs 9.3 HR: 0.83
CRC 3L, P2 [5] Pembrolizumab + Favezelimab	ORR: 6.3 (All comer) ORR: 11.1 (CPS≧1) DCR: 25.4 (All comer) DCR: 36.1 (CPS≧1)	Median:2.1 (All comer) Median: 2.2 (CPS≧1)	Median: 8.3 (All comer) Median: 12.7 (CPS≧1)
SUNLIGHT, CRC 3L, P3 [6] TAS102+Bev vs TAS102	ORR: 6.3 vs 0.9 DCR: 76.6 vs 47.0	Median: 5.6 vs 2.4 HR: 0.44	Median: 10.8 vs 7.5 HR: 0.61
FRESCO-2, CRC 4L, P3 [7] Fruquintinib vs Placebo	ORR: 1.5 vs 0 DCR: 55.5 vs 16.1	Median: 3.7 vs 1.8 HR: 0.321	Median: 7.4 vs 4.8 HR: 0.662
CRC 3L or later, P1 [8] Nivo+ONO-4578	ORR: 3.9 DCR: 39.2	Median: 1.54	Median: 10.68

1) Lancet. 2013 Jan 26;381(9863):303-12.
2) N Engl J Med 2015;372:1909-19.
3) Lancet Oncol. 2019 Jun;20(6):849-861.
4) ESMO 2023. Abstract LBA-5.
5) ESMO Open. 2022;7(6):100639
6) N Engl J Med 2023;388:1657-67.
7) ASCO GI 2023 Abstract 4.
8) Lancet. 2023;402(10395):41-53.
9) J Clin Oncol. 2024;42. Abstract 93.

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This list summarizes the results of Part D introduced so far, as well as the results of other clinical trials that have already been reported in previous reports and papers.

Looking at the 3.9% response rate for Part D that I mentioned earlier, some of you here may have the impression that it may not be working very well.

However, we believe that it is very difficult to obtain tumor shrinkage in colorectal cancer after the third line of treatment. In fact, the response rates for the above treatments, Regorafenib, which is one of the standard treatments, and TAS102, are all in the 1% range. While it is difficult to see tumor shrinkage in the third-line treatment of colorectal cancer, we believe that a response rate of 3.9% is not bad.

Efficacy Results

Subgroup Analysis by PD-L1 (CPS)

	PD-L1 CPS=0 (n=22)		PD-L1 CPS≥1 (n=25)	
	n (%)	[90% CI]	n (%)	[90% CI]
ORR (CR+PR)	1 (4.5)	[0.2–19.8]	1 (4.0)	[0.2–17.6]
DCR (CR+PR+SD)	8 (36.4)	[19.6–56.1]	12 (48.0)	[30.5–65.9]

CPS, combined positive score; CR, Complete Response; DCR, Disease Control Rate; ORR, Objective Response Rate; PD, Progressive Disease; PD-L1, programmed death ligand-1; PR, Partial Response; SD, Stable Disease

Here are the results of the subgroup analysis.

We believe that ONO-4578 is unique in that it enhances the efficacy of PD-1 antibodies through a different mechanism of action. It is generally known that PD-1 antibodies, including PD-L1 antibodies, are more effective when the number of PD-L1-positive cells in the target cancer cells is high.

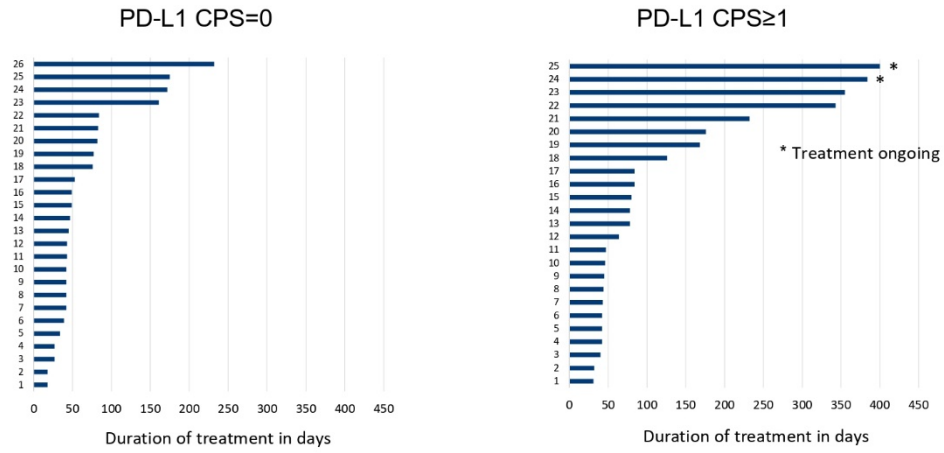
This slide shows the results of stratified analysis in the CPS, in which PD-L1 expression was evaluated in tumor cells and immune cells.

The PD-L1-positive group had a 4% response rate and a 48% disease control rate. On the other hand, the response rate for PD-L1 negative was 4.5%, but the disease control rate was 36.4%, indicating that the disease control rate was better in the PD-L1 positive group.

Efficacy Results

Duration of Treatment by PD-L1 Status

- The proportion of patients continuing treatment for 6 months was 4.5% (1/22) in those with CPS of 0 vs 20% (5/25) in those with CPS ≥1



PD-L1, programmed death ligand-1; CPS, combined positive score

ASCO-GI 2024: Poster #93 24/63

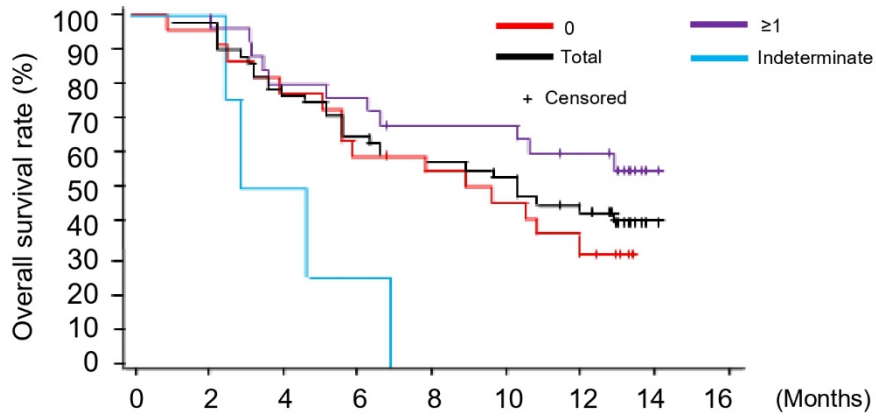
This is a swimmer plot, a plot that shows the duration of the administration.

This is a visualization of the duration of time that the combination of Opdivo and ONO-4578 could be continued. As you can see, the duration of treatment is clearly longer in the CPS-positive group on the right.

Efficacy Results

Kaplan-Meier Plot for Overall Survival, Overall and by PD-L1 Status

- The overall survival rate at 12 months was numerically better in those with CPS ≥1 (59.5%) than those with CPS of 0 (36.4%)
- Specifically, median (90% CI) overall survival was 9.4 months (5.65–12.06) in those with CPS of 0 and NR (10.41–NR) in those with CPS ≥1



ASCO-GI 2024: Poster #93 25/63

Here is the Kaplan-Meier curve of OS by PD-L1 expression status.

Purple, the top one, is positive. As you can see, the PD-L1-positive group had better survival than the negative group.

The overall survival rate at 12 months was 59.5% in the PD-L1-positive group and 36.4% in the PD-L1-negative group. Additionally, the OS of the PD-L1 positive group had not reached the median at this cutoff point.

Given that this is a small, single-arm study, we naturally need to be cautious in interpreting the results. However, the OS results of the PD-L1-positive group are numerically better than those of other trials including similar drugs, as I have just shown you a list. We are now in the process of positively considering the next development for colorectal cancer as well as gastric cancer.

Safety Results

Type of Event	Any Grade	Grade 3–4
AEs	48 (94.1)	23 (45.1)
SAEs	11 (21.6)	9 (17.6)
AEs leading to discontinuation of treatment	6 (11.8)	6 (11.8)
AEs leading to dose delay	29 (56.9)	13 (25.5)
AEs leading to death	0	0
Drug-related AEs	36 (70.6)	13 (25.5)
Drug-related SAEs	6 (11.8)	5 (9.8)
Drug-related AEs leading to discontinuation of treatment	5 (9.8)	5 (9.8)
Drug-related AEs leading to dose delay	22 (43.1)	9 (17.6)
Drug-related AEs leading to death	0	0

Data presented as n (%), n is the number of subjects; AE, adverse events; SAE, serious adverse events

This is a safety result.

As in Part C for gastric cancer, the combination therapy, Opdivo and ONO-4578, showed a manageable safety profile in patients with colorectal cancer in this treatment line.

Summary

- ✓ **The results were presented here, the domestic phase I study (ONO-4578-01, Part C and Part D) of combination therapy with ONO-4578 and nivolumab in patients with gastric cancer or colorectal cancer that was refractory or intolerant to standard therapy. These are excerpts of the contents reported at academic conferences.**
- ✓ **The results of the efficacy and BM analyses obtained in Part C suggested the certainty of the ONO-4578 and nivolumab combination concept.**
- ✓ **ONO-4578 may contribute to the efficacy of PD-1 antibodies in colorectal cancers in which the PD-1/PD-L1 antibody monotherapy is not effective.**
- ✓ **A global phase II study in 1L gastric cancer (ONO-4578-08, jRCT2031230389) has been initiated based on the results of Part C and other clinical studies.**

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Here is a summary.

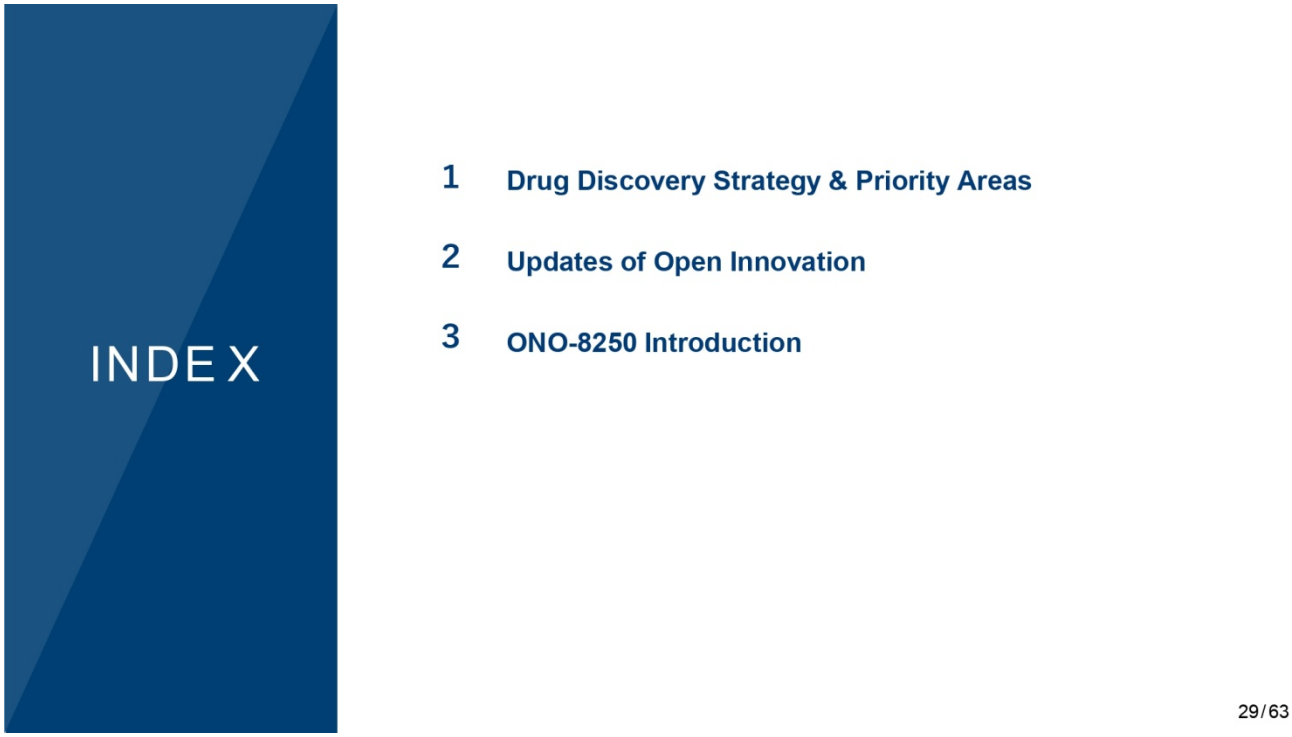
The results of Part C and Part D of the ONO-4578-01 study, a Japanese Phase I trial of ONO-4578 in combination with nivolumab for gastric cancer and colorectal cancer that has failed or not tolerated standard therapy, were presented in excerpts from the conference report.

We believe that the results of the efficacy and biomarker analyses obtained in Part C are encouraging and suggest that the concept of combination therapy with ONO-4578 and nivolumab is sound.

In colorectal cancer, where PD-1/PD-L1 antibody alone is not effective or has poor efficacy, ONO-4578 has been seen as an effective expression of PD-1 antibody drug, where PD-1 antibody was originally supposed to work, but the inhibitory cell population was disturbed by ONO-4578 acts and suggested that it may contribute to the expression of its effect.

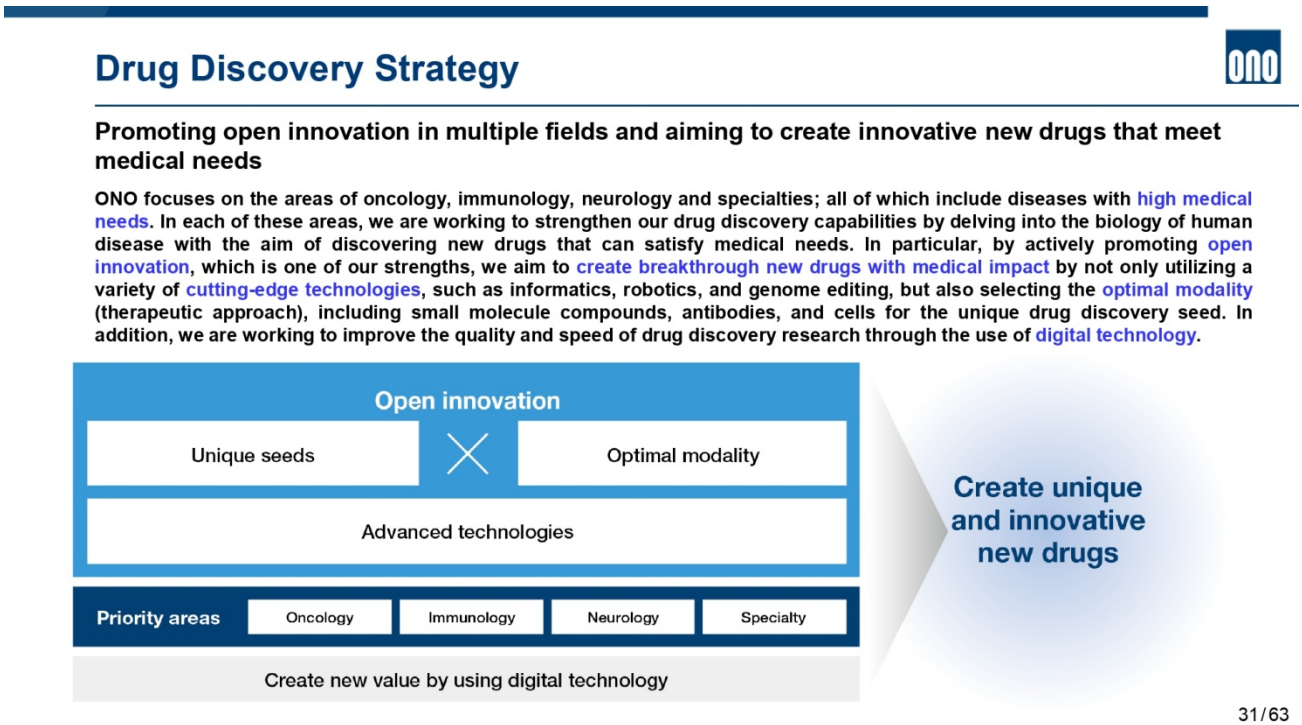
Based on the results of Part C and other clinical trials, we have initiated a global Phase II trial, ONO-4578-08, for first-line gastric cancer.

Imura: Next, Dr. Takino, Executive Director of Discovery & Research, will introduce the progress of Open Innovation and ONO-8250.



Takino: I would like to update on research.

In the first half, I would like to outline the direction of the research as I update Open Innovation again. In the latter half, I would like to introduce the ONO-8250, which has emerged from such an open innovation.

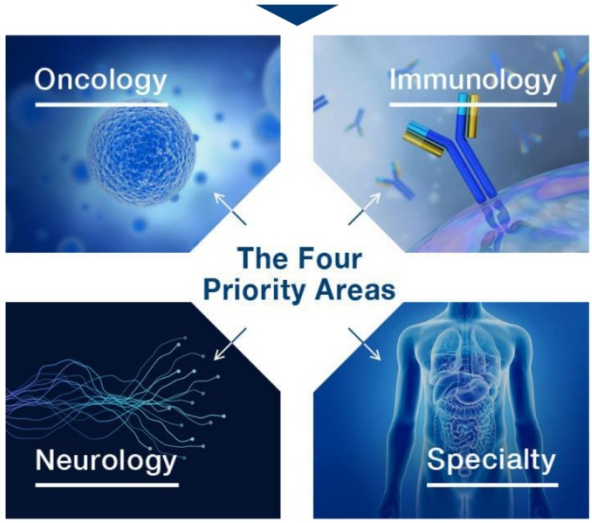


But first, I would like to introduce our drug discovery policy and areas of focus.

Our drug discovery is all about open innovation. This is an initiative to create new drugs with original medical impact by combining unique seeds with optimal modalities using the latest technology.

Priority Areas of Drug Discovery Research

"developing original and innovative new drugs."



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We have four main areas of focus: oncology, immunology, neurology, and specialties. As I don't have to tell you, the unmet needs of these areas are still high, and patients are still waiting for the next step. Specialty is an area that we will work on if unmet needs are high in addition to these three.

Updates of Open Innovation (2021～)

2021

Month	Partner
Feb	Lab Central / MBC biolabs
Mar	PeptiDream
Mar	UCDDC
Aug	healx
Aug	MiraBiologics
Dec	Vanderbilt Univ.

explained at the R & D Day on Feb 24th, 2023

2022

Month	Partner
Jan	neurimmune
Mar	IKTOS
Apr	Domain Therapeutics / Université de Montréal
Jun	Fate Therapeutics
Aug	knowledge palette
Nov	MEMO Therapeutics AG
Nov	Captor Therapeutics
Dec	precisionLife

2023

Month	Partner	Keywords	Tx Area
Jan	MONASH University	Anti-GPCR Antibodies (Abs)	Immunology
Jan	KSQ	DNA Damage Response (DDR)	Oncology
Feb	CUE	Modified Cytokine	Immunology
Mar	MOLCURE	AI-Antibody	undisclosed
Mar	PeptiDream	PDPS (cyclic peptide)	undisclosed
Mar	macomics	Macrophage modulating Ab	Oncology
Aug	TWIST	Functional Abs	Immunology
NEW	ADIMAB	Bispecific Abs	Oncology
Oct	turbine	Target ID & Validation	Oncology
Dec	EVQLV	Generative AI for Antibody	undisclosed
Dec	UK Dementia Research Institute	Research Collaboration for Dementia	Neurology
Dec	BioMedX	Cancer Immunotherapy by targeting Neutrophil	Oncology

2024

Month	Partner	Keywords	Tx Area
Feb	NUMAB	Multispecific Macrophage Engager	Oncology
Feb	SHATTUCK	Bifunctional Fusion Proteins	Immunology
Feb	Inveni AI	AI-Target ID	undisclosed
Feb	EMB	VHH Abs	undisclosed

NEW

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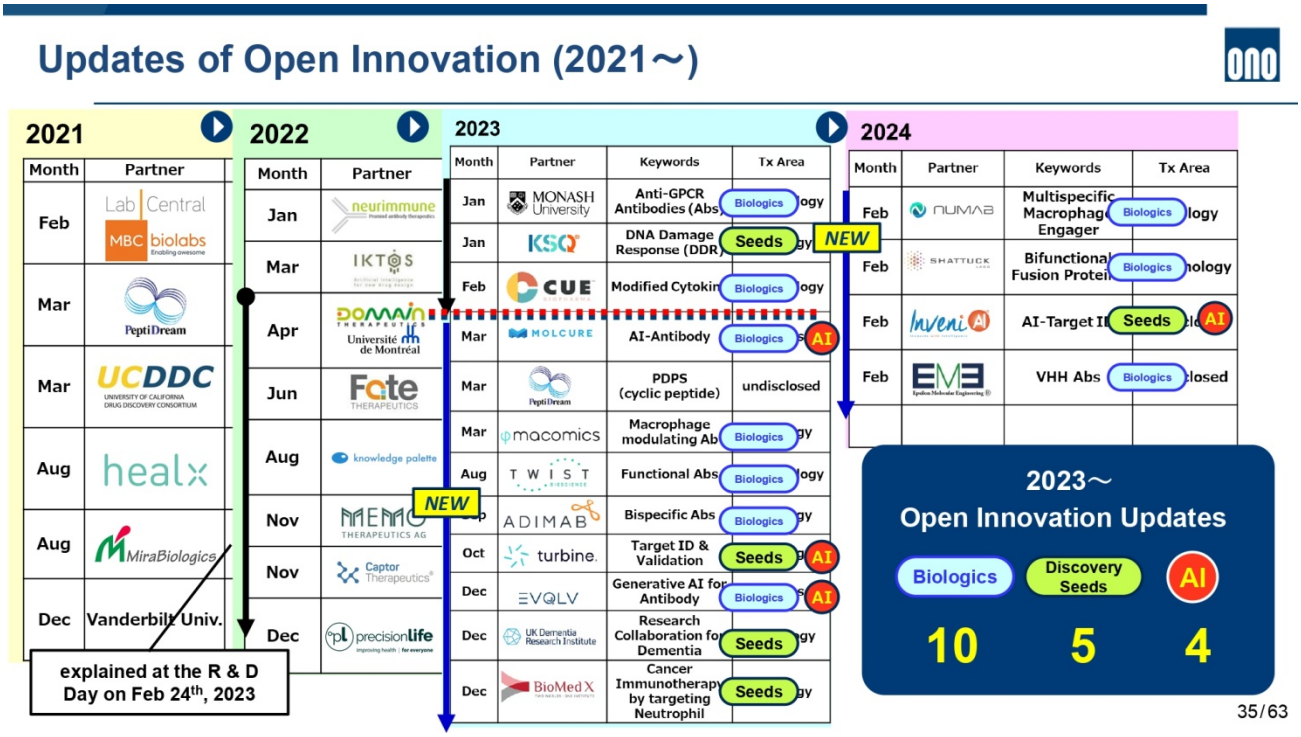
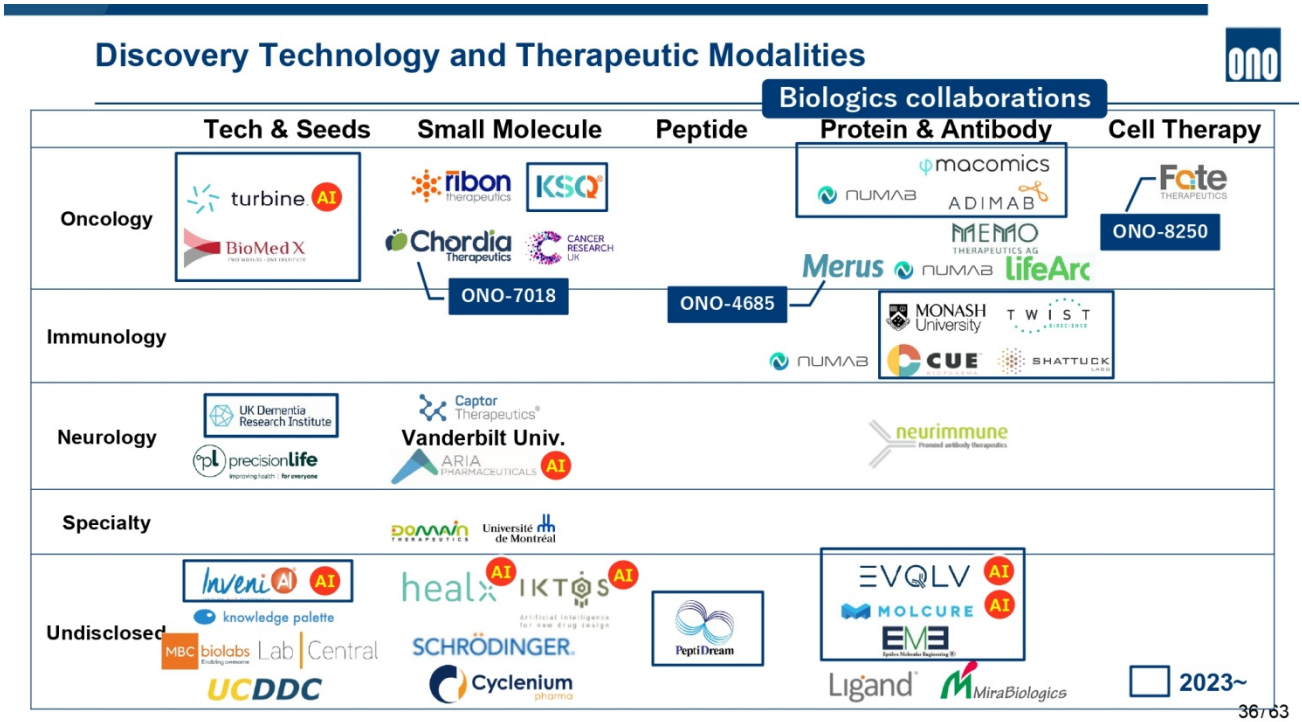
Here is a recent update on Open Innovation.

It is summarized in a chronological table, but from last year's R&D meeting session, we have summarized the entire year in NEW.



As you can see, we are working very hard on the light blue section, biologics. We are also actively working on the use of digital AI, as indicated by the orange circle, on a trial basis.

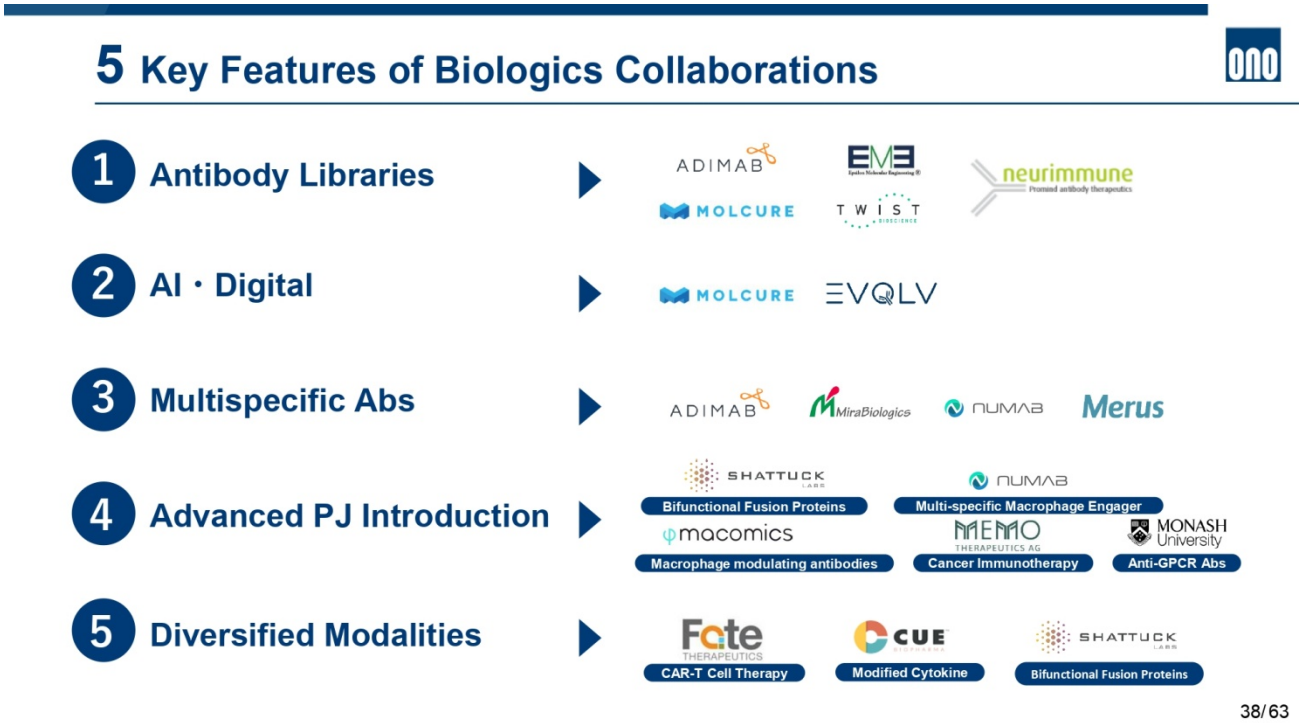


This just changed that sequence we just reviewed.

The left side shows the disease areas vertically, and the upper right side shows from seeds to modality. The squares indicate the initiatives that have been undertaken over the past year.

One of the first initiatives this year is a commitment to antibodies. As for AI, of course, we are using AI to search for seeds and drug targets. Especially for generating small molecule drugs, AI is being used in order to improve the efficiency of drug discovery. In addition to that, we are working to make a strong use of AI in our biologic's efforts

Also, the white letters in the blue boxes show initiatives of ONO-7018 from Chordia, ONO-4685 from Merus, and ONO-8250 from Fate, which I will mention later. Open innovation, of course, takes time, but I feel that this type of open innovation is leading to the strengthening of the clinical pipeline.

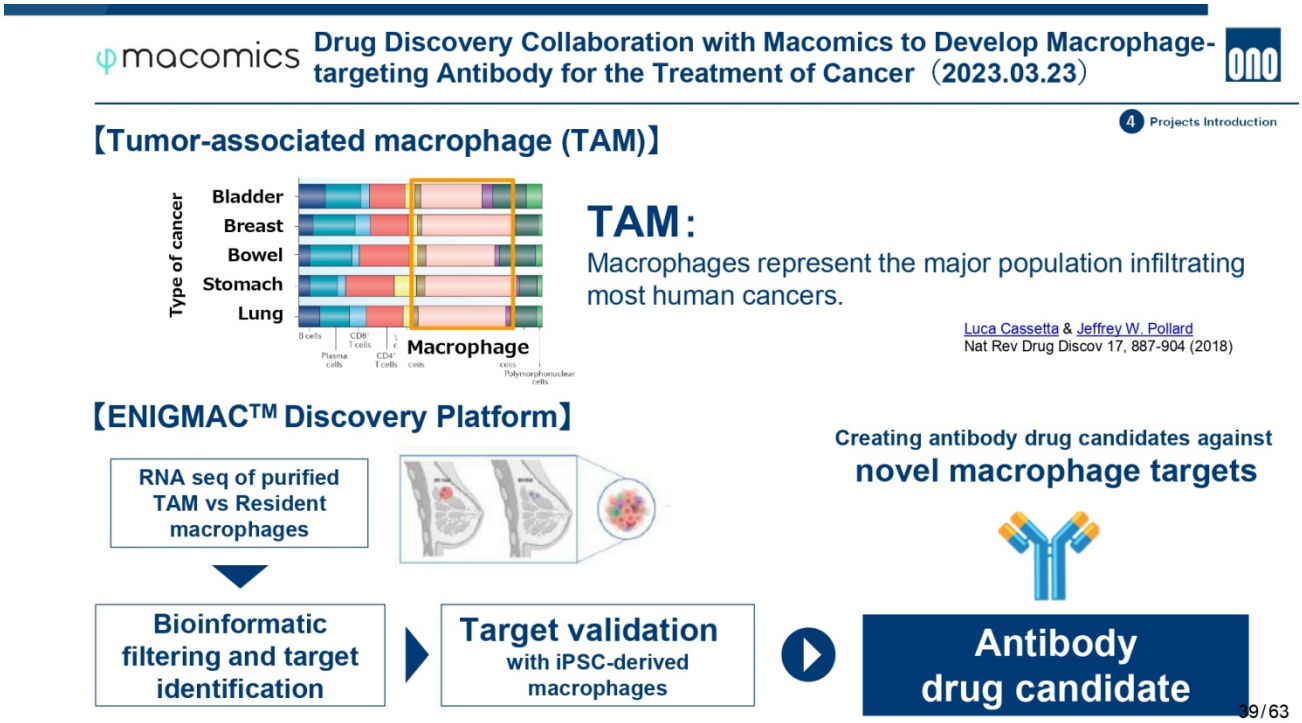


Next, I would like to provide a small summary of our biologic's initiatives.

As you already know, the main focus has been on small molecules from PG, but considering the current trends in the world, we are also making efforts to achieve a good balance between success probability and portfolio by engaging in biologics centering on antibodies.

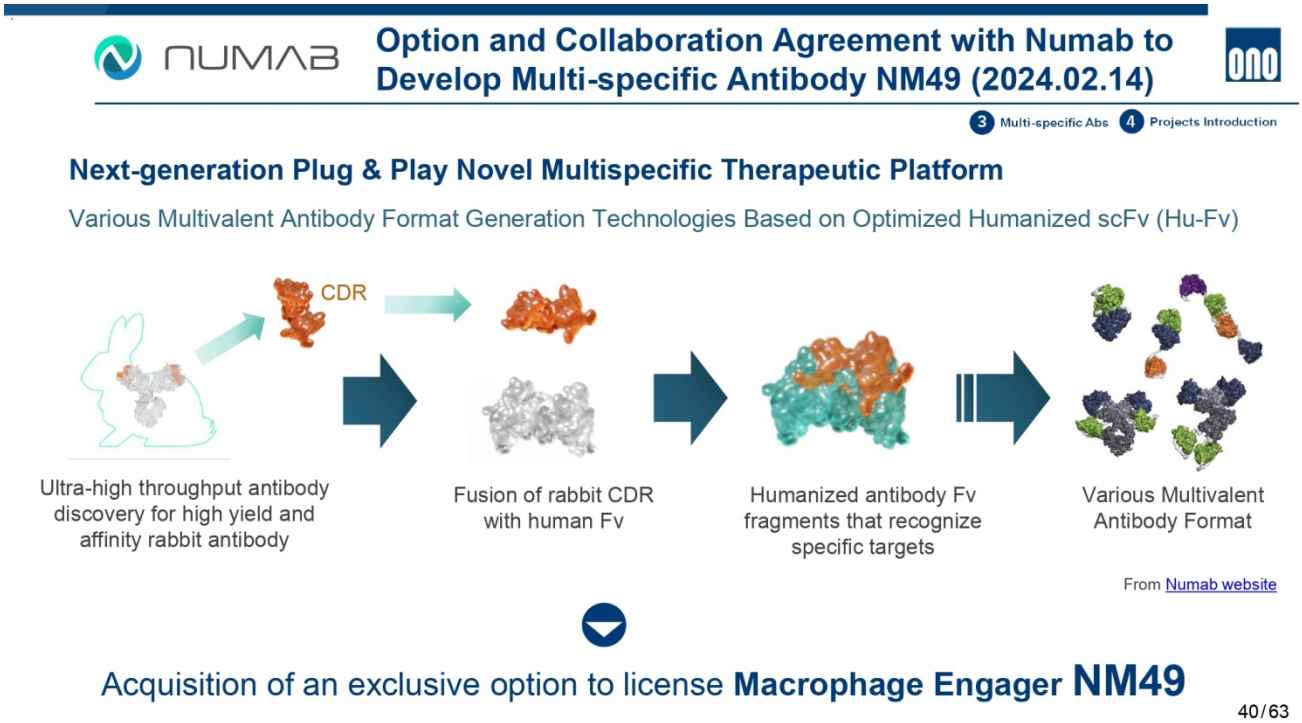
In doing so, we will first utilize antibody libraries, digital and AI, and also work on the technological evolution of multi-specific antibodies. We are not only working on drug discovery from the "seed" stage, but also introducing research themes even from the "seedling" stage.

We are also working with Fate on cells and modified cytokines amidst the diversity of modalities.



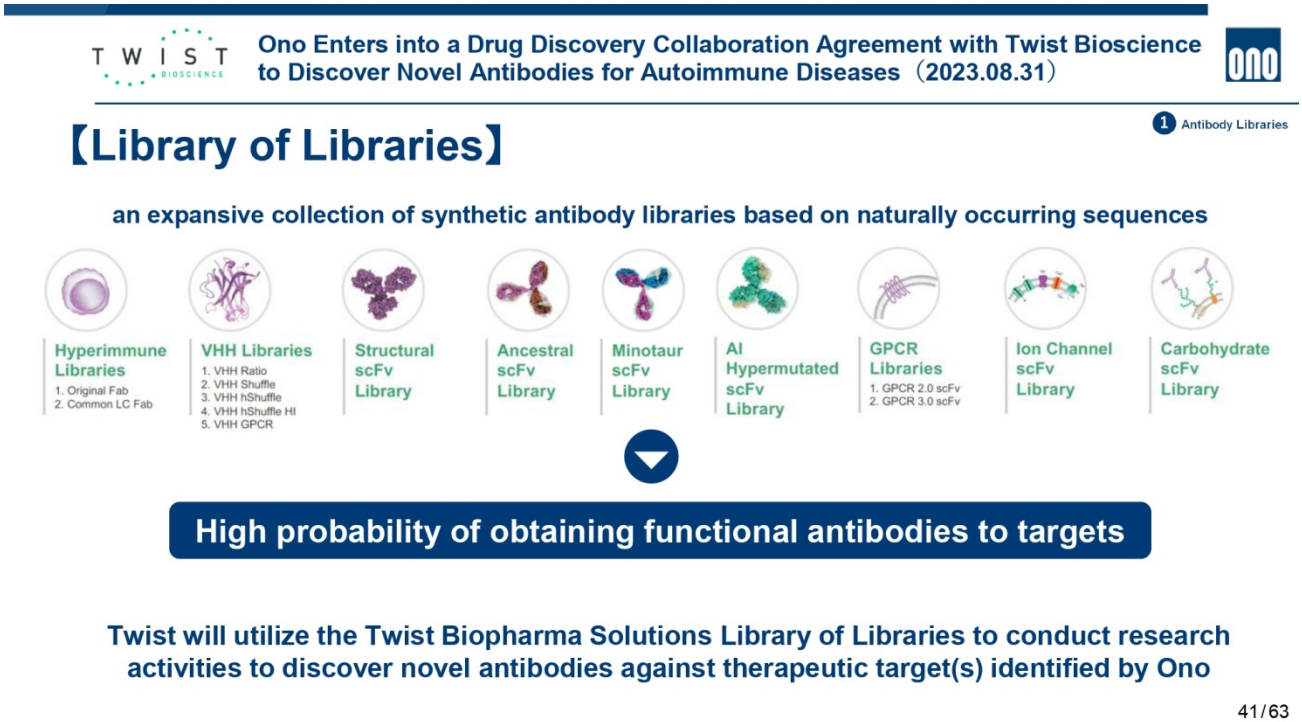
First, this is one of the research themes introduced in the field of oncology from a British venture called Macomics. As we explained in the clinical development session, Macomics is a company that deals with tumor-associated macrophages TAMs, and it was created by Professor Pollard of the University of Edinburgh, who was a leading researcher in this field. In the tumor microenvironment, the presence of TAMs is not negligible, as shown in the upper left figure. After identifying and verifying their new drug discovery, we set out to discover new drug discovery targets for macrophages.

In cancers where PD-1 is not effective and T-cell infiltration is not sufficient, we are trying to make better use of macrophages.

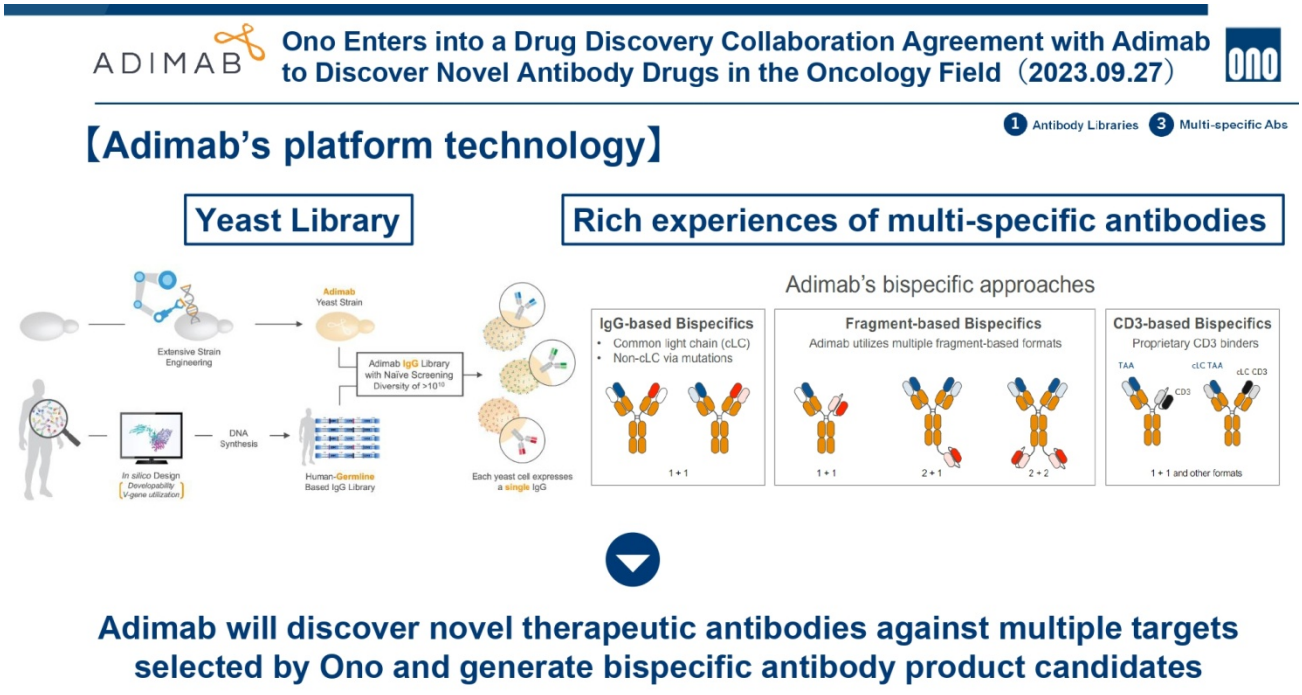


Another macrophage initiative, which we announced last week, is Numab, a Swiss company that is quite advanced in the engineering of antibodies.

We have already experienced this in our drug discovery partnerships since 2017. The company is working on a macrophage engager using a multi-specific antibody called NM49, an approach that forces macrophages to attach to cancer cells, although it is still in its early stages. This is one of the themes we have introduced, and we are working to make it one of our future pipelines.

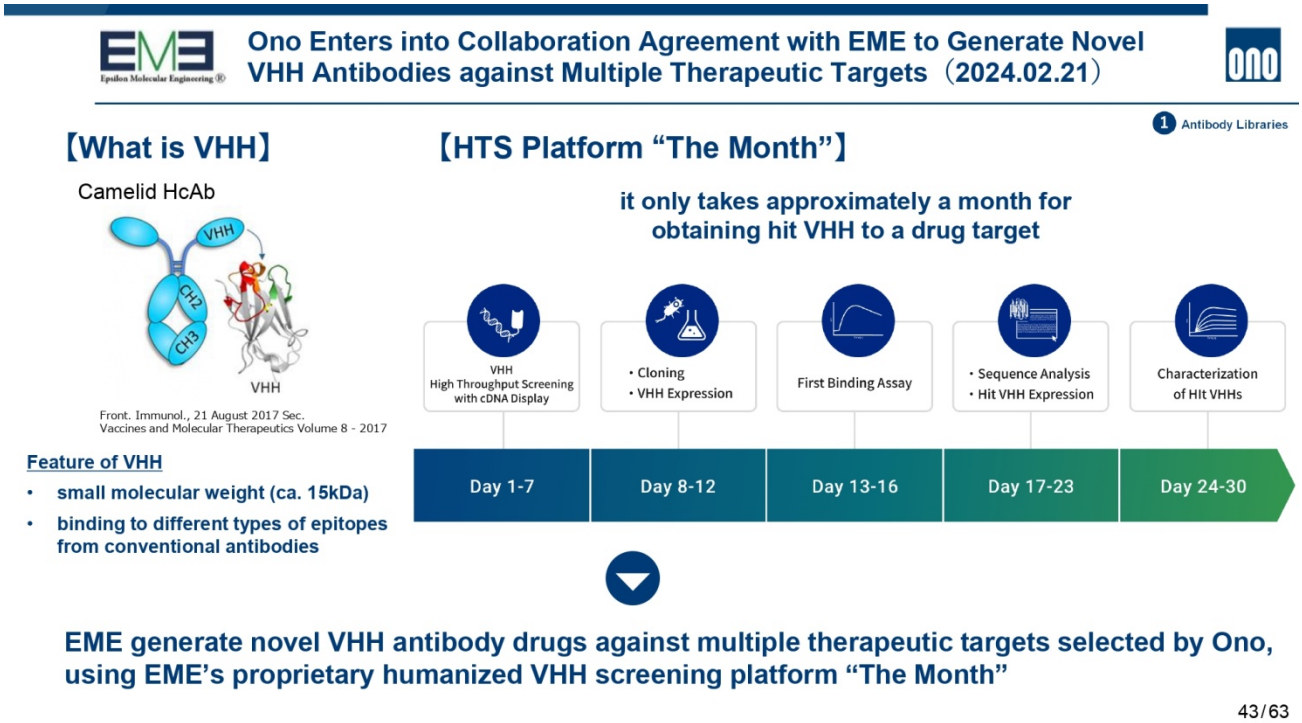


In addition to introducing themes, we are also working on more basic targets that we would like to work on, partnering with well-established or highly skilled companies in the field of antibodies. One is Twist. They also have an extensive library of antibodies, so we are working together with them to generate antibodies that we are unable to generate alone.



Another company is Adimab.

The company has a rich format and experience and track record in the field of multi-specific antibodies, and we are working to increase our pipeline of bispecific antibodies.



We also decided to partner with EME, a domestic venture company. This is a VHH with a small molecular weight. For targets that are difficult to obtain antibodies for, there are targets that can be obtained with VHH due to its characteristics, so we decided the collaboration to make the most of the characteristics of VHH.

A Collaboration and Option Agreement with Shattuck Labs for Bifunctional Fusion Protein（2024.02.13）

4 Projects Introduction 5 Diversified Modalities

Agonist Redirected Checkpoint (ARC) Platform

- **Shattuck Labs has proprietary technology for creating modified proteins, enabling the development of functional proteins for previously challenging therapeutic targets.**
- **Shattuck Labs has generated bifunctional fusion proteins demonstrating immunomodulatory effects in animal models and are expected to be effective across a wide range of autoimmune and inflammatory diseases.**

We will use Shattuck's "ARC Platform" to develop Bifunctional Fusion Proteins for treating autoimmune and inflammatory diseases.

https://www.shattucklabs.com/wp-content/uploads/2020/06/2018_SITC_TIM3.pdf (modified) 44/63

In terms of areas other than antibodies, we collaborated with Shattuck to incorporate recent technological advances in engineered cytokines.

We would like to work on a project in the area of autoimmunity, because the company has a technology that enables the creation of proteins that have two actions with a single molecule.

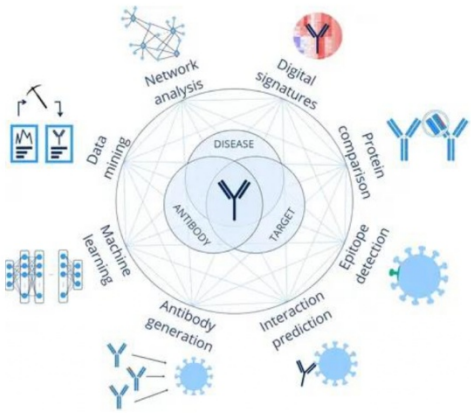
These are the biologics-related updates.

Ono Enters into Collaboration Agreement with EVQLV to Generate Novel Antibodies against Multiple Targets Utilizing EVQLV's AI-powered Antibody Design Engine for Development of Innovative Antibody Drugs（2023.12.19）

2 AI・Digital

【EVQLV Platform】

AI-powered Antibody Design Engine



The platform

designs and **modifies antibodies while retaining conformational** and **functional integrity** using **AI**

create novel antibody candidates more promptly and effectively

EVQLV will generate therapeutic antibody designs using EVQLV's proprietary Artificial Intelligence (AI)-powered Antibody Design Engine

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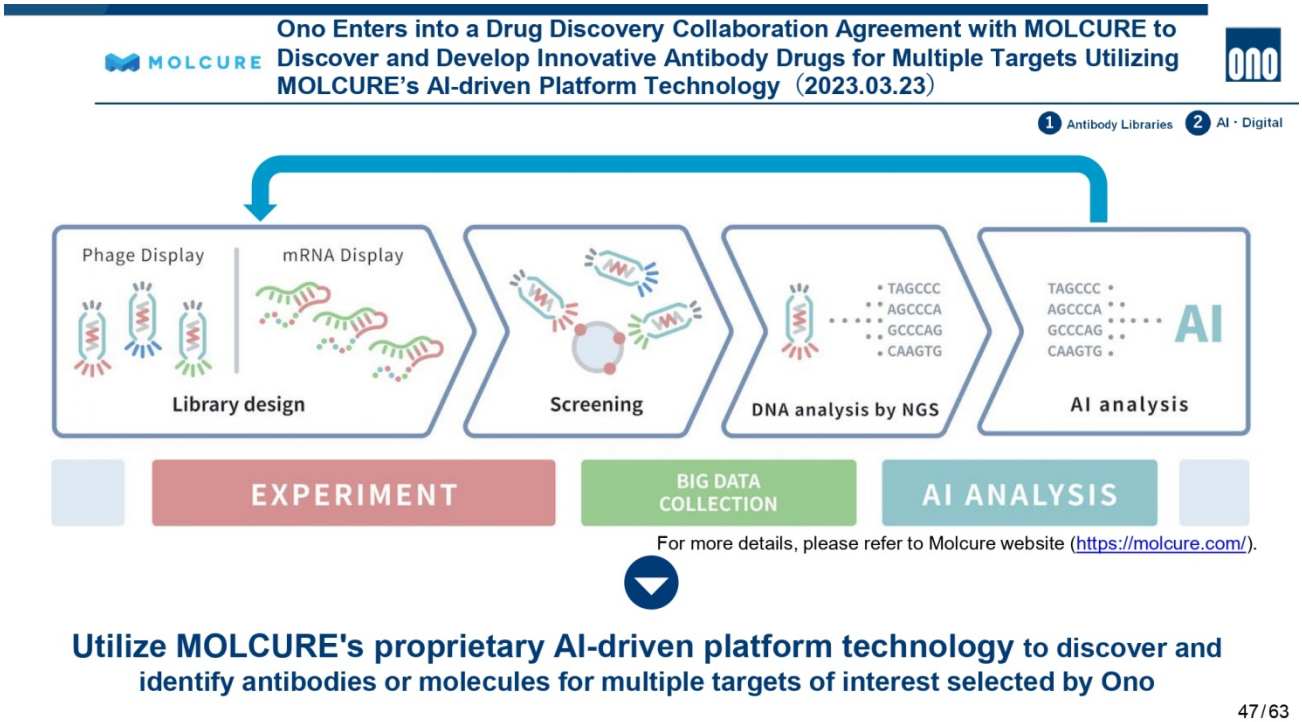
Next, let me touch on the initiative in the AI/digital area.

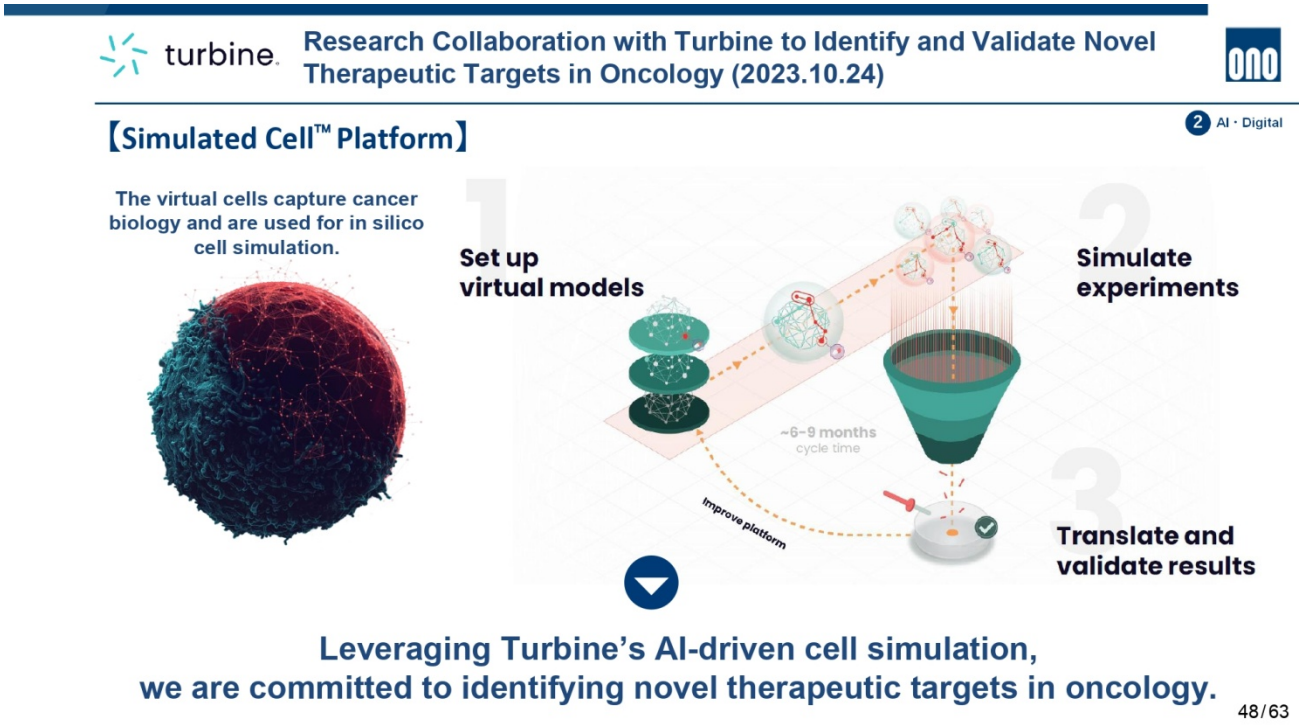
First, I would like to talk about the application to biologics.

This is a drug discovery partnership with EVQLV. This is entirely in silico, using a protein language model and natural language processing, to activate antibody sequences from antigens from scratch. This is cutting edge technology. We are now in the process of trying to see the possibility of dramatically accelerating the speed of antibody design.



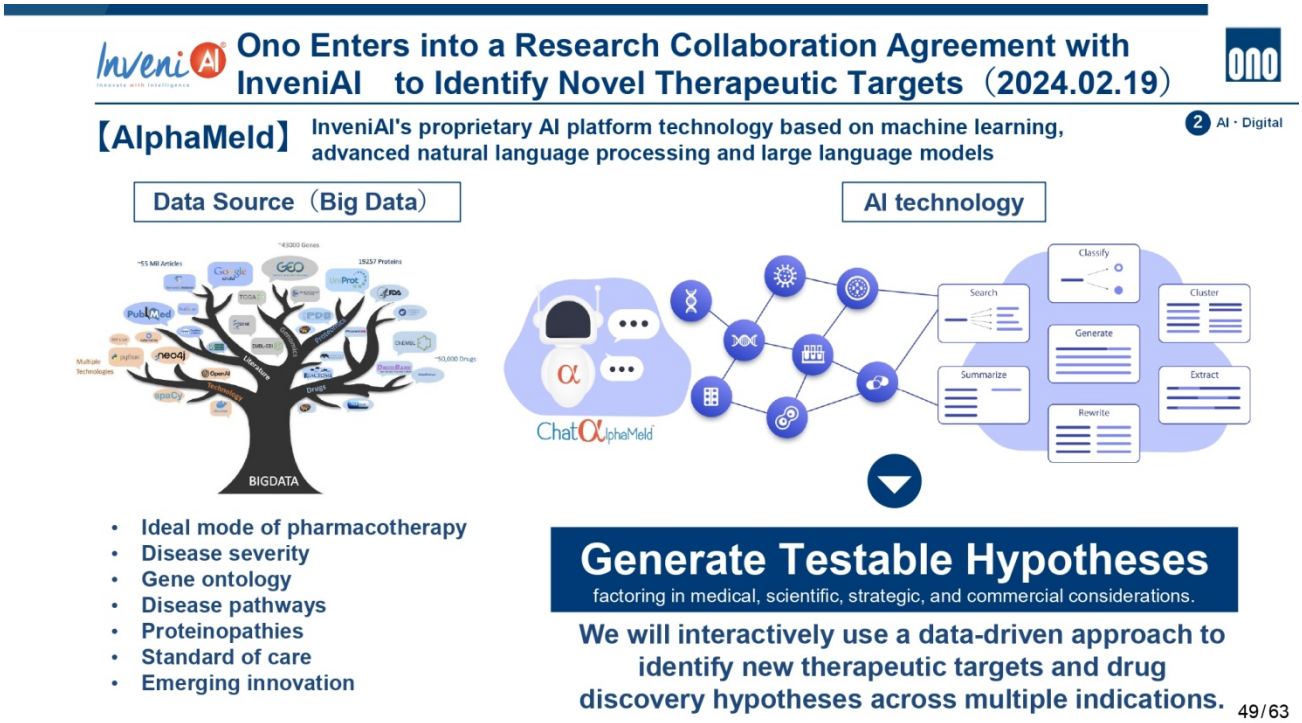
This is a domestic venture company MOLCURE.

We are also working on using AI to learn more about the various characteristics of biopharmaceuticals through machine learning, which we believe will make it possible to create antibodies that have been difficult to create in the past.

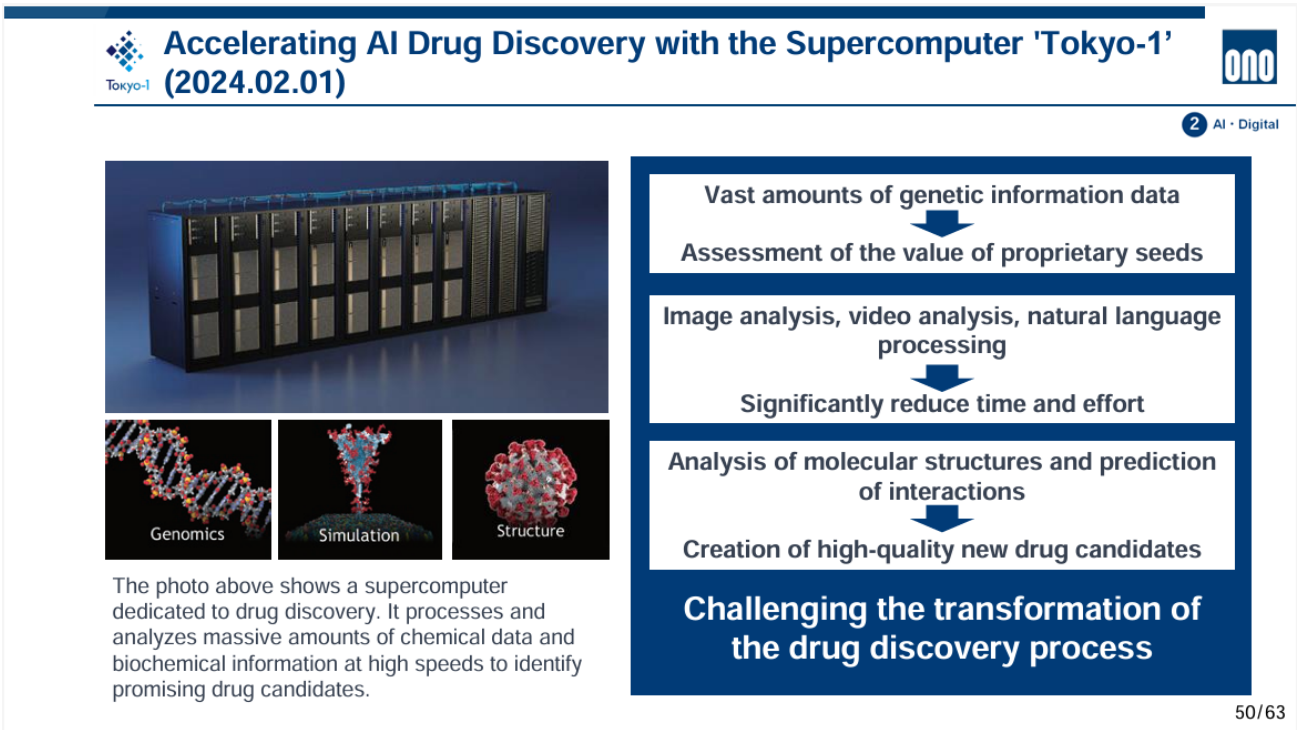


Let me also mention a few examples of AI outside of biology.

This is Turbine, a British company. The company owns simulation technology using cancer cells on a computer. This is a method to collect information on cancer-specific biology, and to find new therapeutic targets based on the information by calculation. This is one of the partnerships that we are looking forward to, as it will hopefully lead to groundbreaking breakthroughs.

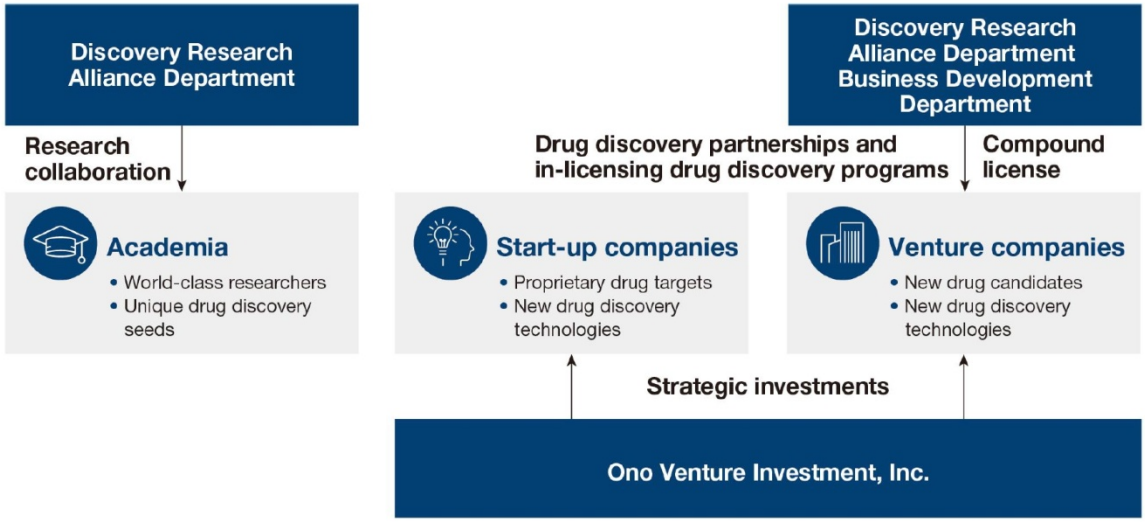


This was also in the press release this week, but we will use their proprietary natural language processing and AI drug discovery platform technologies, including the latest technologies such as generative AI, and we will work interactively with them to discover possibilities for data-driven drug discovery.



This is the last of the digital. This is not a venture, but a Tokyo-1 project, which is supercomputer for drug discovery being developed by the NVIDIA. We are currently starting to explore the possibility of dramatically changing value judgments and design predictions by processing extremely large amounts of data at high speeds that have not been possible before.

Open Innovation That Supports Drug Discovery



https://www.ono-pharma.com/en/company/rd/open_innovation.html

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That's all for open innovation, but I will update you a little bit about other forms of open innovation.

The first will be OVI, which is our CVC. Based in the West Coast in the US, we started with USD100 million, but have now scaled up to USD200 million and are making investments with the strategic return of acquiring information on innovation.

Investment in the start-up Bio-Ventures

Company	Location	Notes
Mediar Therapeutics	Boston, MA, USA	Bio-Venture for development of new drugs for the treatment of fibrosis
Curreio	Tokyo, Japan	Bio-Venture for drug discovery based on detailed protein structure information by cryo-electron microscopy
Immunitas Therapeutics	Waltham, MA, USA	Bio-Venture committed to the creation and development of novel therapies for cancer patients
arbor	Cambridge, MA, USA	Bio-Venture for new gene editing therapy with a unique DNA/RNA degrading enzyme
CASMA Therapeutics	Cambridge, MA, USA	Bio-Venture for aiming to reprogram autophagy to eliminate diseases that current drugs have failed to target

Company	Location	Notes
SWITCH THERAPEUTICS	South San Francisco, CA, USA	Bio-Venture for developing innovative genetic medicines to transform the treatment of CNS diseases
VIOLET Therapeutics	Cambridge, MA, USA	Bio-Venture for leveraging its proprietary cell to cell engine to develop a pipeline of the CNS therapeutics
MOZART THERAPEUTICS	Seattle, WA, USA	Bio-Venture for developing CD8 Treg modulators for the treatment of autoimmune and inflammatory diseases
Photys	Waltham, MA, USA	Bio-Venture for developing phosphorylation-inducing chimeric small molecule medicines(PHICS) to treat a range of diseases

ONO VENTURE INVESTMENT, INC.

https://www.onoventure.com/news

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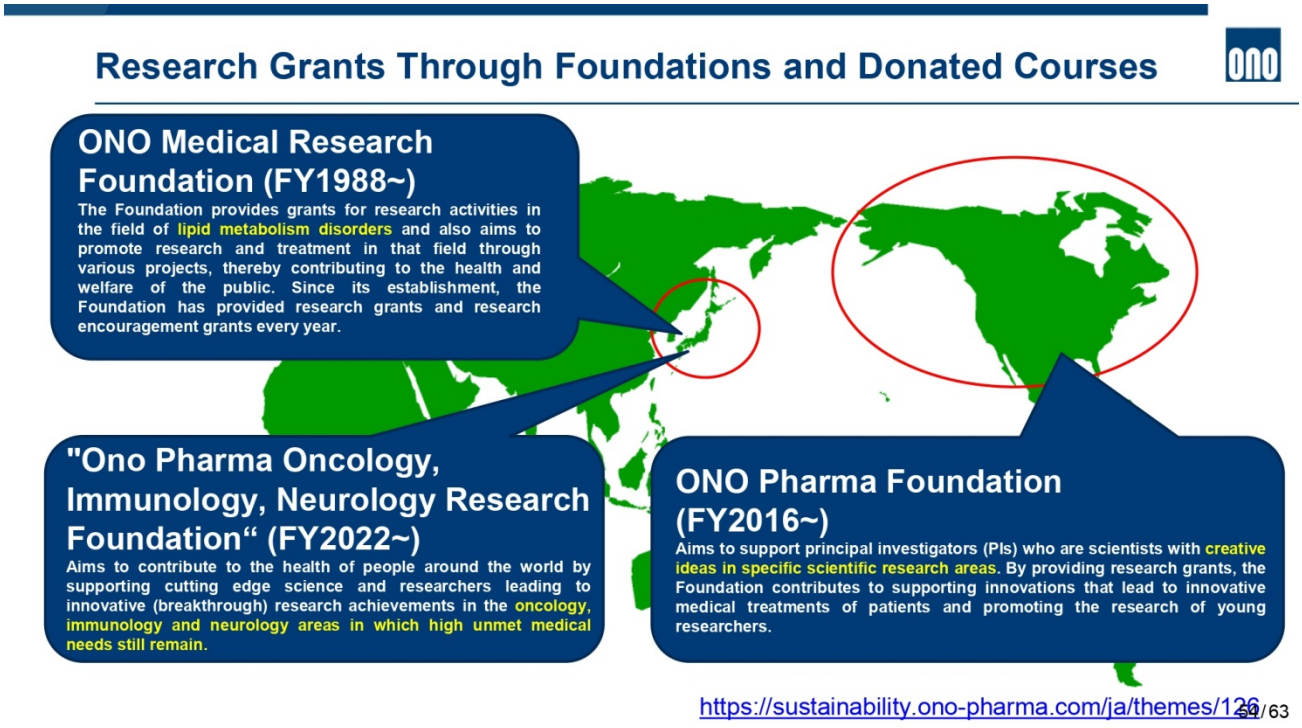
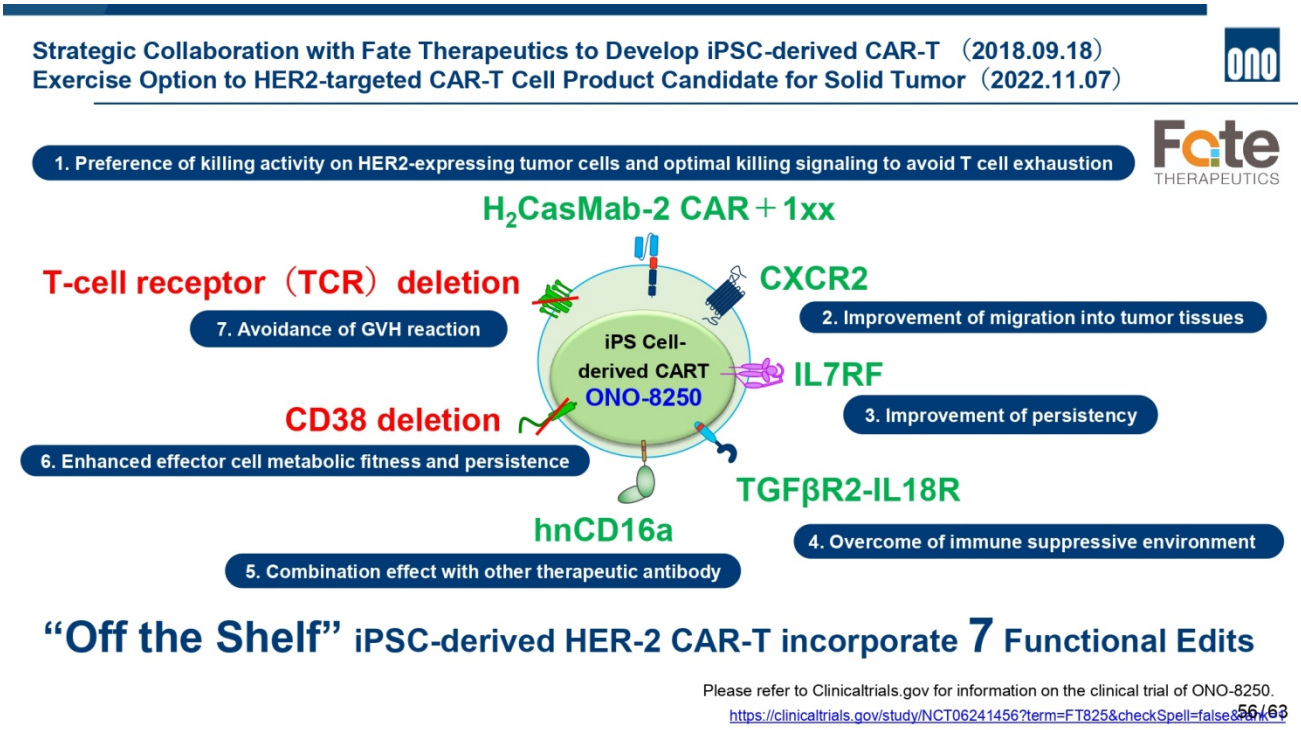
I won't mention one of each, but you can see listed here, we are investing in technologies and innovations that will contribute to building our pipeline in the future. We are planning to expand this investment more and more.



On the other hand, this is a way of giving back to academia, we have established a foundation that provides research grants to researchers in academia, both in Japan and overseas.

The top left corner is the foundation for research, which is independently operate. It is called Ono Medical Research Foundation. Since 2022, the foundation is for cancer, immunology, and neurology. We want to support researchers who are working on research in areas where there is still a lot of unmet needs.

The ONO Pharma Foundation, shown on the right, is a foundation that is working to fund for cutting-edge research in the US West Coast, Cambridge, and Boston, which are at the forefront of science.



Next, I would like to introduce ONO-8250 in a few pages.

As you know, this is also a drug discovery collaboration with Fate, which itself is working to create CAR-T using IPS-derived cells. Their iPS gene editing technology is top of the line in the world, and they have the technology to differentiate it into immune cells. This is a CAR-T that is coming out of the Fete drug discovery alliance, and it is ONO-8250, which is a highly armed HER2-directed iPS-derived CAR-T, with seven gene edits.

iPS-derived cells are different from the autologous process, in which blood samples are obtained from patients and prepared on site. A large amount can be prepared and quality can be made uniform. Although refrigeration will be necessary, it is expected to have the potential to become a product in the form of an off-the-shelf, truly product-like product.

In the case of the autologous CAR-T, medical institutions and patients are burdened with time, cost, and effort, but with this iPS-derived CAR-T, we can expect great benefits.

We issued a press release that P1 of ONO-8250, targeting patients with HER2-positive solid tumors, has started in the United States.

Novel binder incorporated into ONO-8250

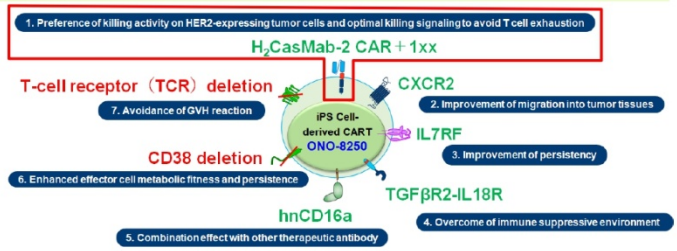
Jan 08 2024

Fate Therapeutics Announces Initiation of Phase 1 Clinical Trial for FT825 / ONO-8250 in Patients with HER2-expressing Advanced Solid Tumors

iPSC-derived CAR T-cell Product Candidate Incorporates Seven Synthetic Controls of Cell Function including a Novel HER2-targeted Antigen Binding Domain

Phase 1 Study is Being Conducted in Collaboration with Ono Pharmaceutical

"The preclinical data for FT825 / ONO-8250 indicate a highly-differentiated therapeutic profile across a broad range of solid tumors, with **the novel HER2-targeted antigen binding domain demonstrating selective targeting of cancer cells expressing HER2** including those with low expression. We are excited to initiate the Phase 1 study in collaboration with Ono and assess the potential to benefit patients with hard-to-treat advanced solid tumors who currently have limited treatment options."



https://ir.fatetherapeutics.com/news-releases/news-release-details/fate-therapeutics-announces-initiation-phase-1-clinical-trial

2024年01月09日

研究成果

HER2に対するがん特異的抗体を導入したCART細胞の第I相臨床試験を米国にて開始

東北大学大学院医学系研究科 分子薬理学分野の加藤幸成教授の研究グループは、がん細胞を特異的に攻撃する抗体医薬（CasMab；キャスマブ）の開発を行ってきました。近年、AMED先端的バイオ創薬等基盤技術開発事業において、ヒト上皮細胞増殖因子受容体2（HER2）を標的とする抗HER2-CasMab（H2Mab-250/H2CasMab-2）を作製し、令和2年に小野薬品工業株式会社と実施許諾契約を締結しました。

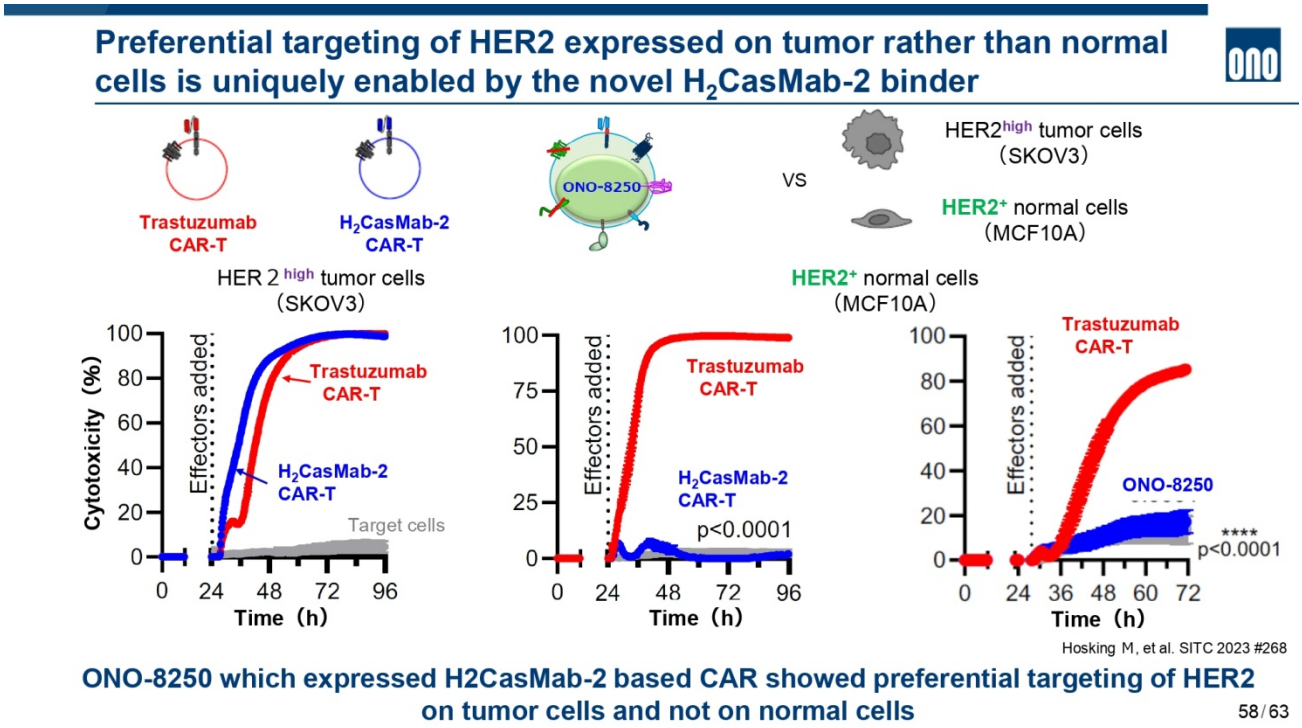
令和6年1月8日、小野薬品工業株式会社の提携企業であるFate Therapeutics社（米国カリフォルニア州サンディエゴ）は、H2CasMab-2の遺伝子を導入した多重遺伝子編集キメラ抗原受容体（CAR）T細胞製品候補であるFT825/ONO-8250の第I相臨床試験において、患者登録を開始したことを発表しました（https://ir.fatetherapeutics.com/news-releases/news-release-details/fate-therapeutics-announces-initiation-phase-1-clinical-trial）。

本試験では、治療歴を有する進行固形がんの患者を対象に、FT825/ONO-8250の単剤療法およびモノクローナル抗体療法との併用療法として、FT825/ONO-8250の単回投与が評価されます。本試験の用量漸増パートおよび用量拡大パートでは、安全性、忍容性および薬物動態、並びに奏効率、奏効期間と病勢コントロール率による抗腫瘍活性が評価されます。

なお、H2Mab-250/H2CasMab-2の作製については、プレプリント（https://www.preprints.org/manuscript/202309.0906/v5）で公表されています。

The above description is referred from Tohoku University. For more details, please visit the website (https://www.med.tohoku.ac.jp/5565/)

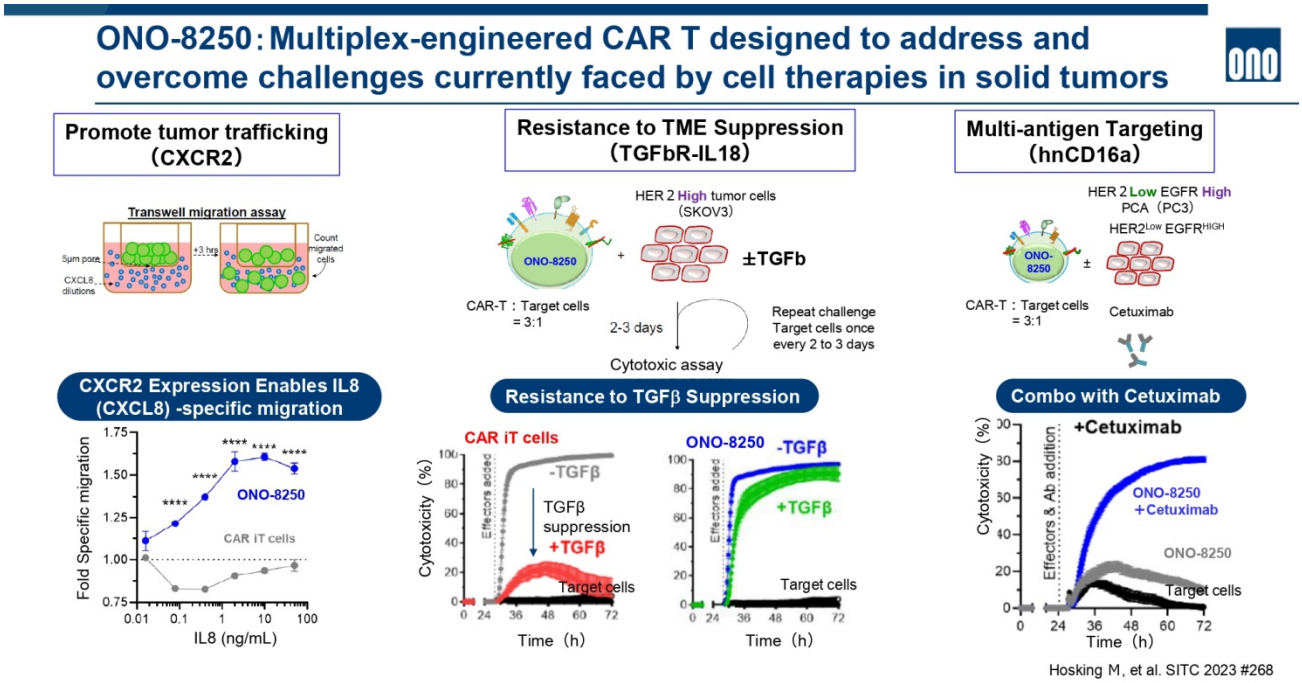
The first of these seven gene editing is a HER2 antibody used for CAR-T. It uses a CAR based on H2CasMab, a HER2 antibody superior in cancer selectivity, acquired by Dr. Kato of Tohoku University.



Here is the data that shows the actual extent of its cancer selectivity. This red marker is trastuzumab, which is commonly used HER2 antibody. In contrast, the one shown in blue is ONO-8250, which uses H2CasMab as the CAR.

On the far left is a HER2-expressing cancer cell line, although this one will show cell-killing effects with either CAR. In terms of normal cells expressing HER2, CAR with trastuzumab CAR has a cell-killing effect, but basic data suggest that our ONO-8250 has a low injury potential to normal cells, due to its superior cancer selectivity.

We will not know the magnitude of this until we see a clinical trial, but we are taking this as a signal to look forward to.



Let me explain a few other features of ONO-8250.

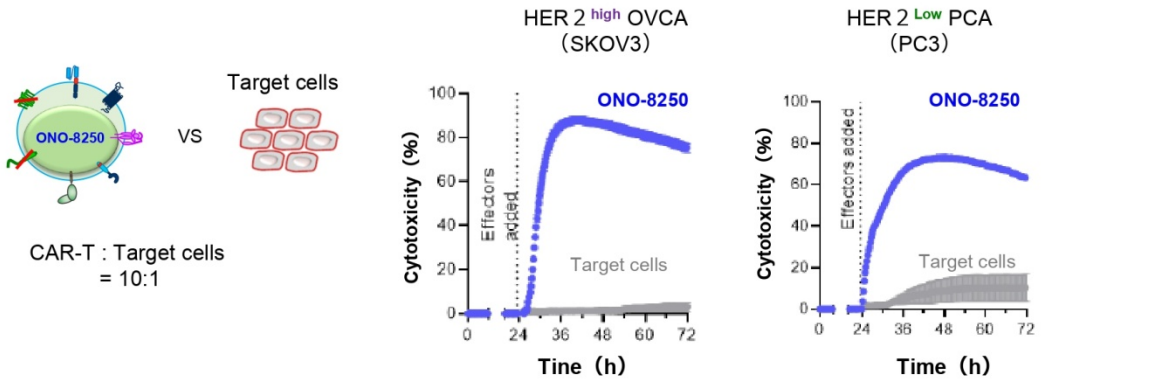
First, we intend to target solid tumors among cancers. In such cases, there are various barriers, first, the migration of tumor tissue is an issue. The CXCR2 gene has been gene-edited, and since the production of IL8 is increased in cancer tissues, the IL8 makes it easier for 8250 to migrate toward the cancer cells.

And then there is the middle one. As Mr. Okamoto explained earlier, this cancer microenvironment is an environment that makes it difficult for the immune system to function properly and TGFβ controls the immunosuppressive environment. As shown in red, if TGFβ is introduced, cytotoxicity is greatly suppressed. On the other hand, by inserting the fusion gene of TGFβ receptor and IL18 receptor, as shown in the green curve on the right, it clearly shows cytotoxicity.

We have added one more thing to arm, CD16 gene is included as shown in the far right. It has also been reported in oncology that the expression of the target can become heterogeneous due to the cancer's escape behavior, in which the cancer eventually loses the expression of HER2.

Therefore, by inserting CD16 gene, ONO-8250 shows cytotoxic activity even in cancer cells that have lost HER2 expression, when used in combination with other cancer antigens.

ONO-8250：Robust HER2 Targeting Across a Wide Range of Antigen Expression Density



Hosking M, et al. SITC 2023 #268

ONO-8250 is capable of killing tumor cells with a range of expression from HER2 high to HER2 low targets.

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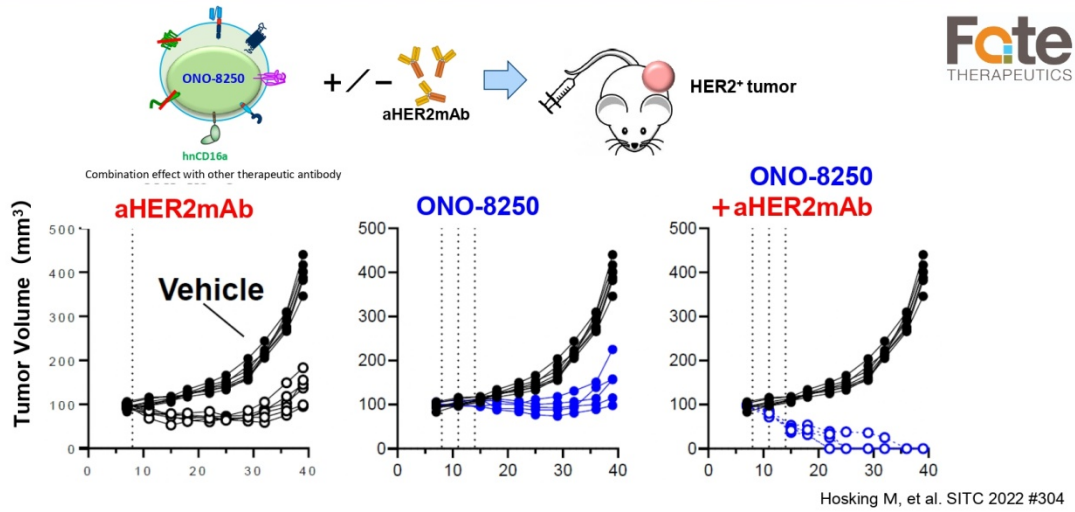
We believe that this may be due to the CAR, which is highly selective for cancer, but it has been confirmed the cell-killing effect of ONO-8250 on cancer cells with low HER2 expression.

his is only a signal at the basic stage and will be confirmed in clinical trials.

ONO-8250: Anti-tumor effect on HER2+ tumor bearing model



Hosking M, et al. SITC 2022 #304

ONO-8250 showed anti-tumor effect in HER2+ tumor bearing model.
Combo with anti-HER2 mAb enhanced anti-tumor effect by hnCD16a activation

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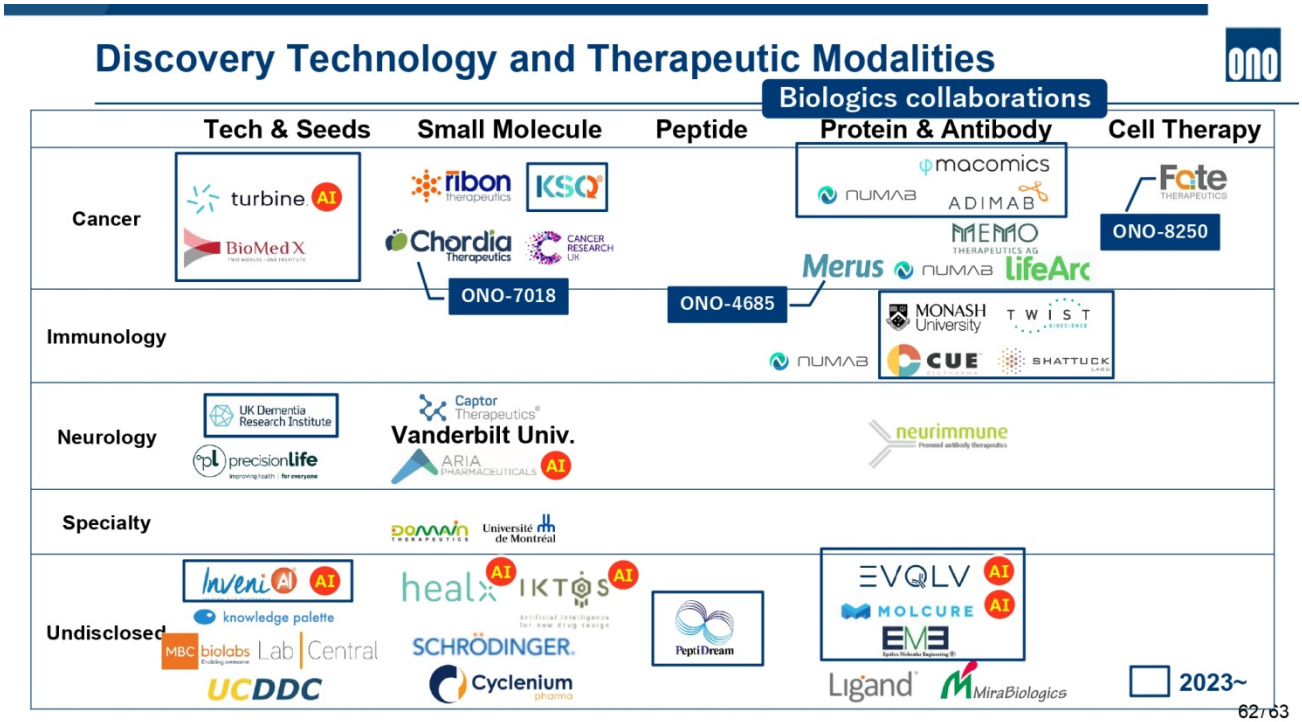
This is the last data regarding 8250.

In HER2-positive cancer cells and tumor-bearing models, basic data have emerged suggesting that ONO-8250, when used in combination with other antibodies, may enhance the anti-tumor effect.

As described above, the possibilities of iPS derived CAR-T, at least at this point, are very promising through various kinds of armed gene editing that cannot be conceived of in the conventional drug generating process. We look forward to future clinical signals.



This is a reposted content. We will continue to increase the number of partnerships in our priority areas, from seed discovery to small molecules and biotechnology, and we consider that we would like to apply AI and digital technology to various areas.

We would also like to speed up drug discovery, improve the probability of drug discovery, and strengthen our innovative pipeline by working in these areas.

Main Status of Development Pipelines

Therapy Area	Development Code	Area	Phase	Target Indication
Oncology	ONO-4578	Japan	I	Solid Tumor, Gastric Cancer, Pancreatic Cancer, Colorectal cancer, non-small cell lung cancer, Hormone receptor-positive, HER2-negative breast cancer
	ONO-7475	Japan	I	Solid Tumor, EGFR mutation-positive non-small cell lung cancer
	ONO-7914	Japan	I	Solid Tumor
	ONO-4685	Japan USA	I	T-cell lymphoma
	ONO-8250	USA	I	Solid Tumor
	ONO-7018	USA	I	Non-Hodgkin's lymphoma, Chronic lymphocytic leukemia
Immunology	ONO-4685	Japan Europe	I	Autoimmune diseases
Neurology	ONO-2910	Japan	II	Diabetic polyneuropathy, Chemotherapy-induced peripheral neuropathy
	ONO-2808	USA	II	multiple system atrophy
	ONO-1110	Japan	I	Pain
	ONO-2020	USA	I	Neurodegenerative disease

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This will be the last one. This is the current pipeline under development. We would like to produce clinical signals, and we need to further enrich this pipeline itself and make it stronger, which is what we are currently doing. We are fully aware that this is an issue that must be addressed and are doing our best to address it.

Question & Answer

Imura: First, Mr. Yamaguchi from Citigroup Global Markets Japan Inc., please go ahead.

Yamaguchi: I will ask you two questions briefly regarding the first ONO-4578.

There was a blurry diagram, but if we look at it, we can't see it clearly, but the green one is the combo one, and if you compare them properly, did you suggest that the OS is going to show quite well?

Okamoto: You are right, and as I mentioned earlier in my explanation, the blue one is Part C1, and the red one is the matched data.

In the Opdivo trial, the drug was allowed to continue to be administered if patients re-consent even after PD in many of the clinical trials because of the phenomenon of pseudo-progression, and apparently PD despite being effective, which is common in tumor immunotherapy drugs and is called "Beyond PD".

Therefore, although it may be hypothetical, we have extracted data from patients who were continuously treated with Opdivo after PD, which we believe can be compared with Part C1, and compared them with each other in terms of inter-trial comparison.

Yamaguchi: Is it correct that you are aiming for Phase II because the green area might start up at the top, so this can go, including that?

Okamoto: Yes. The range indicates the width of the confidence interval. Although the judgment here will vary depending on the viewer, we feel a certain degree of certainty from the fact that at least the confidence intervals do not overlap much.

Yamaguchi: On the other hand, you have shown us various charts and graphs on the CRC. It's true that the absolute ORR at first glance is very low, and I think the PFS is probably quite low as well, but I've been looking at the OS for a little longer now.

II understand that it's not bad, but there are quite a few drugs out there, so unless they're really good, I think it would be difficult to get in later and push others out. If you have a strategy to increase the odds of winning, or something like that, please let me know. It looks pretty tough if you go into as is, but what are your thoughts on that?

Okamoto: Thank you very much. Can we show the slide for colorectal cancer? Part D Results.

Yamaguchi: Are you talking about the CRC data for reference?

Okamoto: Thank you. As you pointed out, we are not necessarily thinking of continuing the development of Part C1 for gastric cancer and Part D for colorectal cancer in the same therapeutic line.

Since Part C and Part D are both from the early stages of Phase I, it was more of a test to see if the drug was working as intended, including at the molecular level. So, you are right in pointing out that it would be a bit tough to use the combination of Opdivo and ONO-4578 alone as a drug after the third-line treatment, for example, with this result. On the other hand, as I indicated in the list of trials, ONO-4578 is also being tested in combination with chemotherapy for the first-line treatment of colorectal cancer, so I am sorry to go into too many details, but we are considering the future development of this compound in a combined manner.

Yamaguchi: In the first place, Opdivo doesn't work very well, so I'm not sure how it would work even if you added something on that.

Okamoto: You are right. In addition, as I have said earlier, obtaining tumor shrinkage in the later line of colorectal cancer is quite challenging. On the other hand, it is generally true that the earlier the treatment line, the higher the response rate for any type of cancer. We are considering that as well.

Yamaguchi: So, there is a way to put them on TAS, for example.

Okamoto: I'm sorry, but I will refrain from giving details.

Yamaguchi: I understand. Lastly, I understand that you have introduced a lot of technology, but I am not sure how many of your people understand and can use it properly internally.

What about an allowance for such personnel? I hate to say this, but I bet there are a lot of technologies that old-timer researchers have no idea what those technologies are about. I think it will be difficult to lead to drug discovery even with the new technologies unless deals with a considerable amount of human resource issues, such as bringing in people from outside who can understand them. So, I would like to know your thoughts in terms of the allowance for those people?

Takino: As you point out, it is true that nowadays people who understand those technologies are really the drivers in determining how this should be incorporated.

Therefore, it is not that we force to incorporate those technologies into our projects. In this sense, we introduce technologies as we need them, and I do not think there is any need to worry about the technology being left in limbo.

Yamaguchi: Do you use a lot of young people who do not do wet work anymore, or do you deploy a lot of people who specialize in digital work?

Takino: We are aware of the possibility that people who only use dry may not fully understand biology. We believe that we need someone who is half-wet and half-dry, but we have input into acquiring such a person and are working on drug discovery that takes advantage of advances in dry technology.

Imura: Now, Mr. Sakai from UBS Securities Japan Co., Ltd., please go ahead.

Sakai: Regarding the table on page 12. Both C1 and C2, studied only 30 patients each, so I don't think you have solid statistics yet. This means that C1 is the one with PD-L1 and C2 is the naive one. So, which is more effective in this case? I think this is Opdivo, but I am not sure whether Opdivo or ONO-4578 works. Has any verification been done in this regard?

Okamoto: Thank you. Although we have not disclosed it, regarding the acquisition of the biomarkers that I mentioned earlier, besides comparing the clinical data with past data, we are also internally studying the difference in biomarker movements between the biomarkers obtained when Opdivo is used as a single-agent and when it is combined with ONO-4578. Therefore, including all the results, we interpret that there is a certain degree of contribution of ONO-4578.

Sakai: Then that will have to be verified in Phase III. Does this mean that the trials that are being conducted now will be validated in Phase II?

Okamoto: Yes. In Phase II, we are going to confirm whether or not this will be a real PoC establishment in the true sense.

Sakai: I understand. I have a question regarding ONO-8250. How will this be delivered? I believe it will be an intravenous injection. For example, you may not yet know the number of doses or the dosage, but please let us know if you have any information regarding that.

Okamoto: Thank you. First, the method of administration is intravenous. As for the frequency of administration and dosage, the first-in-human study has just started in the US, and the dosage escalation process is the same as for small molecules or antibodies, so the currently it is not yet determined. However, in general, there are CAR-T therapies that have already been approved in the field of blood cancers, and I believe that they will be administered in a pattern similar to that of increasing doses.

Sakai: So, you are saying that this is effective against solid tumors because of the characteristics of the substance itself or the antibody itself?

Okamoto: As you just pointed out, I think one of the reasons why CAR-T therapy and cell therapy are not effective against solid tumors is whether they migrate to the local tumor. As Dr. Takino explained earlier, the mechanism is that it is induced by cytokines released by tumors, so I think it will work in theory, but I think it is necessary to confirm in clinical practice whether it actually works.

Sakai: I see. Thank you.

Imura: Now, Mr. Hashiguchi from Daiwa Securities, please go ahead.

Hashiguchi: I too have a question about ONO-4578 and ONO-8250, one each.

Regarding ONO-4578, why is the Phase II trial a first line development? The C1 cohort is practically the first line and C2 is practically the third line. Considering that the patient backgrounds are different in that sense, C1 seems to work somewhat better.

Then, it seems to me that the change in the tumor microenvironment after the previous treatment with Opdivo seems to have elicited the effect of ONO-4578. How should we understand Phase II is for the first line?

Okamoto: First of all, we are currently conducting P2 and randomized P2. The control group is combination therapy with Opdivo and chemotherapy. In other words, it is the current global standard of care.

Therefore, the study design that can most clearly clarify the feasibility of the study and whether ONO-4578 is really contributing is to put ONO-4578 on top of Opdivo and ONO-4578 as the standard of care. This design is possible for the first-line treatment.

Another is that we are conducting exploratory studies in combination with chemotherapy for first-line treatment of colorectal and pancreatic cancer, for example, and we believe that chemotherapy for first-line treatment of gastric cancer is relatively compatible with immunotherapy. We think this is mainly due to the inclusion of oxaliplatin.

Therefore, it is true that there is a point to be made that the results obtained now may work well if only a group that has acquired resistance is selected, but in terms of how much anti-tumor immunity can be strengthened in total, we believe that there is a good chance for first-line treatment. Therefore, we would like to take on the challenge of treating gastric cancer as a first-line treatment, considering its marketability.

Hashiguchi: Regarding ONO-8250, there seems to be a lot of views on the issue of secondary tumors, which has recently become a hot topic in CAR-T therapy. There seems to be an opinion that Off the Shelf CAR-T may be have higher risk than autologous CAR-T, but what are your thoughts on this?

Takino: At present, this is just a speculation, but there is a concept that unnecessary gene editing is included in Off the Shelf CAR-T, leading to a risk. In this context, in the case of iPS gene editing, the uniformity of quality can be fully assumed, so we assume that the risk may be quite different and lower.

Hashiguchi: Does that mean that the gene editing mistakes that would cause secondary tumors to have been identified and can be checked in advance before shipment?

Takino: That's right. Since iPS cells with gene editing will be differentiated and produced, we expect that this will be an advantage of iPS.

Hashiguchi: I understand very well. Thank you.

Imura: Mr. Muraoka of Morgan Stanley MUFG Securities. Please go ahead.

Muraoka: Regarding ONO-4578, I think it's fine for Japan when a patient with gastric cancer is successfully treated for the first line using ONO-4578 and can see a path forward, but will the rest of the world be able to continue as is?

Okamoto: Thank you very much. When you say, "as is", what do you mean?

Muraoka: In other words, the data from these studies could be used, for example, for an application in the US.

Okamoto: Thank you. Since this is a Phase II trial, the ultimate goal would be to conduct an international Phase III trial including the US after the results of this trial are obtained. Therefore, we are not currently considering applying for approval based on this study.

Muraoka: I think there is a general background that gastric cancer is very different between Asia and the US. If you do well there, you should be able to go after Phase II in one test without too many problems, I guess?

Okamoto: As you mentioned, there are certainly epidemiological differences between Western and Asian regions, but at least the combination of Opdivo and chemotherapy is one of the first-line treatments for gastric cancer worldwide, so I do not see any particular difficulty in conducting the study.

Muraoka: I see. Thank you. On page four, where you talk about growth strategies, you also mentioned at the beginning that you will launch Velexbru in FY2026. I have a feeling that the results of the clinical trials will begin to appear later this year or so if we look at ClinicalTrials.gov. The point is, I'm asking, is there any way to get the application approved one year earlier? Is that a rather unreasonable story?

Okamoto: Thank you. I am sorry, but we have been refraining from giving you an answer on the progress of the clinical trials that we have been conducting. As President Sagara mentioned at the beginning of this presentation, the test itself is going well. The clinical trial is now in a state where we can apply according to the timeline we have always communicated.

Muraoka: The range of application periods is very wide in the chart, but which side is it?

Okamoto: I hope you will excuse me from answering that today. I'm sorry. Since we have received a high level of interest in Velexbru from everyone, it is natural that we will be updating the progress of the clinical trial, specifically through public databases, etc., in the not-too-distant future. That's all I can say today.

Muraoka: I understand. Thank you.

Imura: The next question is from Mr. Akahane of Tokai Tokyo Research Center.

Akahane: I understand what you are saying about ONO-4578 and ONO-8250. This ONO-4578, in the material you gave us, is a prostaglandin receptor, and it is already in Phase II for gastric cancer, colorectal cancer. When I first started covering your company, we were told that your company was a compound- oriented company,

specializing in prostaglandins and enzyme inhibitors, and you didn't know what you were going to get. Does that mean that the research team is now focusing on drug efficacy, such as cancer and immunity, as you mentioned on the last page, after Opdivo?

ONO-4578 is for solid tumors, stomach cancer, etc., but is it correct to think that there are still many prostaglandin-related seeds that can be developed in this way for cancer?

Takino: In the first half for your question, we are certainly shifting to a policy of understanding the biology of diseases in the area, but this does not necessarily create a barrier between cancer and immunology, or between immunology and the central nervous system.

In fact, I believe that the conventional trend of maximizing the value of the specialty, including the back pocket of the specialty, remains. Regarding the latter half of your question, I interpreted your question as asking whether more PG or PG-related projects will be applied to cancer, but I am not sure that we can expect to see that many projects at this time.

Akahane: I understand very well. Thank you.

Imura: Thank you for your patience. Mr. Sawada of JP Morgan, please go ahead.

Sawada: I would like to ask four questions about ONO-8250.

One is gene editing. If you were to use CRISPR-Cas9, I think it would cost a certain amount of money. The question is whether the burden of that cost is particularly problematic.

Secondly, I think that TCR is deleted to prevent so-called GVHD, but is this TCR deletion alone enough to prevent it? I think that CD52, or something like that, is deleted together with some of the other existing products, and I'm not sure if this TCR deletion will be sufficient.

The third point is ensuring the quality of iPS cells. I haven't heard from the industry that quality control of Fate iPS is necessarily high. In that respect, I think it is said in this industry that the effects are completely different depending on the quality of Fate's iPS cells, especially the quality. Therefore, I wonder, in that respect, how is the quality?

Finally, Phase I. Now, I think it is a combination regimen with chemotherapy, why are you putting chemotherapy in the course together? If you are looking at the effectiveness of this product itself, I think it would be clearer to look at it as a purely administered course. That's all from me.

Takino: Thank you for asking all the questions.

As to the cost of gene editing, Fate has not separately disclosed or commented here, and we do not believe we are in a position to do so. However, I will only respond with the comment that over-all, we are at least hopeful about the possibility of an economic effect considering the current situation in autologous CAR-T products.

As for whether the measures for GVHD is sufficient, I do not know the answer. However, it is not realistic to say that we will continue to include dozens more edits of everything. If we are going to explore with reality somewhere, we interpret the specifications we are working with now as being at least a sufficient profile to conduct a clinical trial first.

As for ensuring the quality of iPS, of course, we are at the stage of entering clinical trials, and we have secured the quality. However, Fate is not conducting a trial of iPS-derived cells as a first-in-human, so in that sense, it

is not a pessimistic idea. This is the answer to the first three questions. Mr. Okamoto will answer the fourth question.

Okamoto: Thank you. I am aware that the dose is not being titrated in combination with chemotherapy. Generally, in all cell therapies of this type, lymphocyte depletion is done first for the administered cells to take root, and we do conduct that.

Since it is a first-in-human treatment that is combined with chemotherapy, it is necessary to confirm the tolerability of cell therapy alone, so we are currently at that stage, and we are not currently considering using it in conjunction with chemotherapy.

Imura: Now, Mr. Wada of SMBC Nikko Securities Inc., please ask your questions.

Wada: I would like to ask one question each on ONO-4578 and ONO-8250.

The first is ONO-4578. I believe that the reason why these cancer immunotherapy drugs, after Opdivo, have been slow to emerge is because, as your company is doing, they are biomarkers, so it is difficult to select the right patients.

I would like to ask one question here, since you have just shown us this biomarker on page 16. Are you saying that this can be done predicatively, or by measuring PGE2 in urine prior to administration, so that it is possible to select patients who will benefit from the drug?

Okamoto: Thank you. As I mentioned earlier during the presentation, retrospectively, when we separated patients with SD or higher from patients with PD, the fact that PGE metabolites were high in urine suggests that this is one of the proofs that ONO-4578 contributed.

On the contrary, this does not mean that we will continue to develop these biomarkers as predictors of efficacy and effectiveness.

In addition to us, other companies have also developed compounds that target EP4, and I recall that there have been reports in the past that the metabolites in urine may play some role in the efficacy of these compounds.

Wada: I understand. Thank you. Regarding ONO-8250, it is said that there are two reasons why CAR-T cannot be used or applied to solid tumors. Regarding tumor metastasis, CX and CR2 have been included, so I think this is what we are trying to deal with.

The other thing is that cancers that are heterogeneous and express antigens other than HER2 are unavoidably expressed heterogeneously with solid cancers, so if they remain, it is difficult to be effective. I think these two are reasons.

In the latter part of the article, on page 61, you use HER2 antibodies in combination with the HER2 antibody. Can you explain the reasoning for this again?

Takino: Thank you for your question. I am sure this can be interpreted in many ways.

The HER2 antibody trastuzumab may have a different epitope from the HER2 antibody that we use for CAR, and in such a case, the ability to bind to it in multiple points may be increased.

To be honest, we do not yet have enough insight to comment clearly on how this generalized or synergetic effect is occurring.

Wada: Does Fate's CAR-T alone have an added function of killing tumors that do not express HER2, or attracting such T cells?

Takino: Are you asking about tumor cells that do not express HER2? We do not expect to go that far at this time.

Wada: So, will you target that with another antibody?

Takino: That’s right. I hope I answered your question.

Wada: Yes. I understand very well. Thank you.

Imura: I would like to conclude the R&D meeting.

Thank you very much for your participation.