# R&D Meeting
# February 22, 2024

ONO PHARMA

# Cautionary Notes

Forecasts and other forward-looking statements included in this document are based on information currently available and certain assumptions that the Company deems reasonable.
Actual performance and other results may differ significantly due to various factors. Such factors include, but are not limited to:

- **( i ) failures in new product development**
- **( ii ) changes in general economic conditions due to reform of medical insurance system**
- **( iii ) failures in obtaining the expected results due to effects of competing products or generic drugs**
- **( iv ) infringements of the Company's intellectual property rights by third parties**
- **( v ) stagnation of product supply from the delay in production due to natural disasters, fires and so on**
- **( vi ) onset of new side effect of post-licensure medical product and,**
- **( vii ) currency exchange rate fluctuations and interest rate trend.**

Information about pharmaceutical products (including products currently in development) included in this document is not intended to constitute an advertisement of medical advice.

# Agenda

## Introduction（13:00-13:10）

President, Representative Director, and CEO **Gyo Sagara**

## ONO-4578 Development Status（13:10-13:30）

- ONO-4578-01 Part C
- ONO-4578-01 Part D

Corporate Officer /
Deputy Executive Director, Clinical Development **Tatsuya Okamoto**

## Updates of Open Innovation and ONO-8250 Introduction（13:30-13:50）

- Drug Discovery Strategy & Priority Areas
- Updates of Open Innovation
- ONO-8250 Introduction

Member of the Board of Directors, Senior Executive Officer /
Executive Director, Discovery & Research **Toichi Takino**

## Q&A session（13:50-14:30）

# 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 |

# Future growth strategies - Aggressively invest in R & D for growth -

## Investment allocation (FY 2022 to FY 2026)

| R & D investment 600 billion yen scale | Strategic investment 250 Billions yen | Shareholder Returns | Investment to increase corporate value |
|---|---|---|---|

**Leverages abundant R & D capabilities**
**Accelerate global business development**

**R & D expenses (billion yen)**


| | FY 2022 | FY 2023 | FY 2024 | FY 2025 | FY 2026 |
|---|---|---|---|---|---|
| **Filing/approval** | ・Opdivo 2 Approval | ・Opdivo 2 Approval | Opdivo 2 Approval(forecast) 5 Filing(forecast) BRAFTOVI/MEKTOVI 1 Approval(forecast) 1 Filing(forecast) | ・Application for tirabrutinib in the US (forecast) | |
| **Pipeline Stage transition** | • Opdivo 3 cases<br>• ONO-7018 P1 Start<br>• ONO-2020 P1 Start<br>• ONO-1110 P1 Start | • ONO-2910 P2 Start<br>• ONO-2808 P2 Start<br>• ONO-4578 P2 Start<br>• ONO-8250 P1 Start<br>• ONO-4538HSC P1 Start | | | |
| **Alliance** | ・Itrizumab, Exclusive Option and Asset Purchase Agreement<br>・Exercise option rights the drug discovery collaboration agreement with Fate<br>・12 Drug Discovery Alliance | ・9 Drug Discovery Alliance | ・Itrizumab Decision to exercise options (Forecast) | | |

As of Feb. 21, 2024

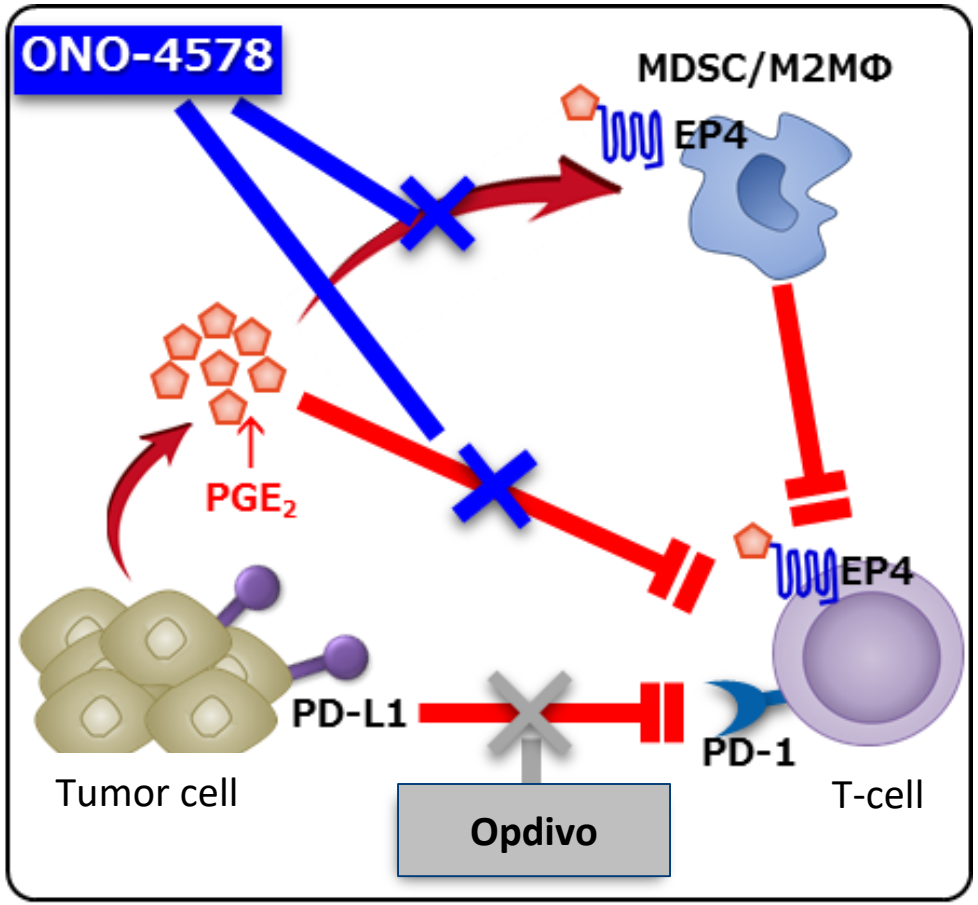
# ONO-4578 Development Status

# ONO-4578

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

# ONO-4578 Mechanism of Action

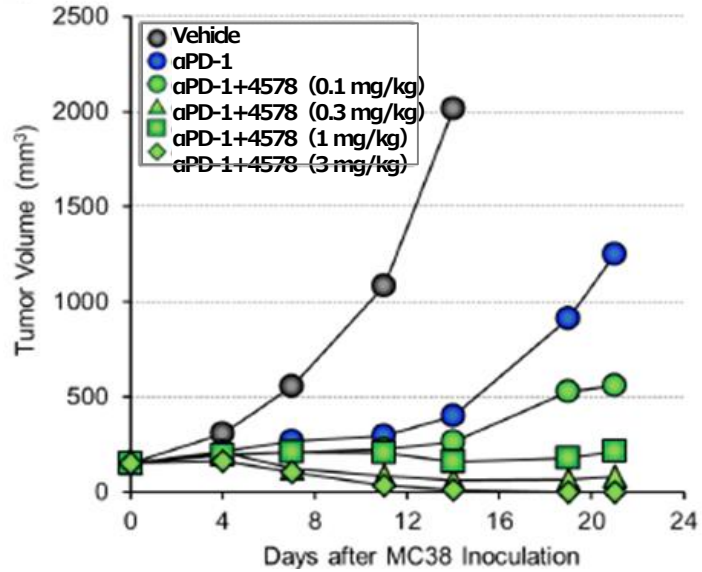
- **Prostaglandin $E_2$ ($PGE_2$) is produced from arachidonic acid through cyclooxygenase-2 (COX-2)**
- **COX-2 is overexpressed in solid cancer[1]. $PGE_2$ has been reported to induce myeloid-derived suppressor cells (MDSC) and M2 macrophages in the tumor microenvironment through one of its receptors, 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

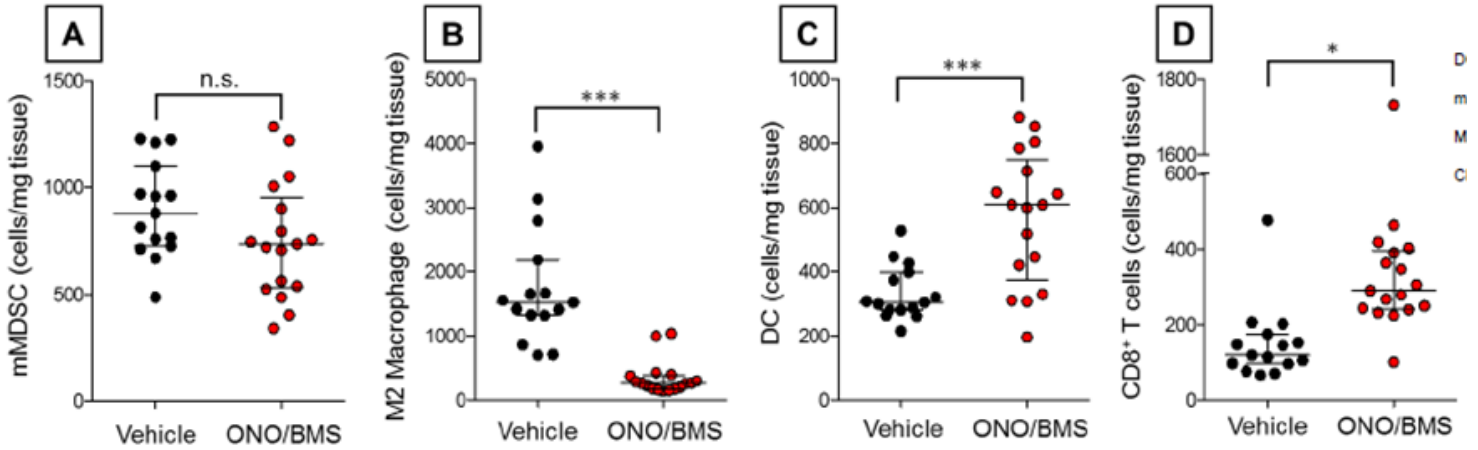
# ONO-4578 Non-clinical data

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



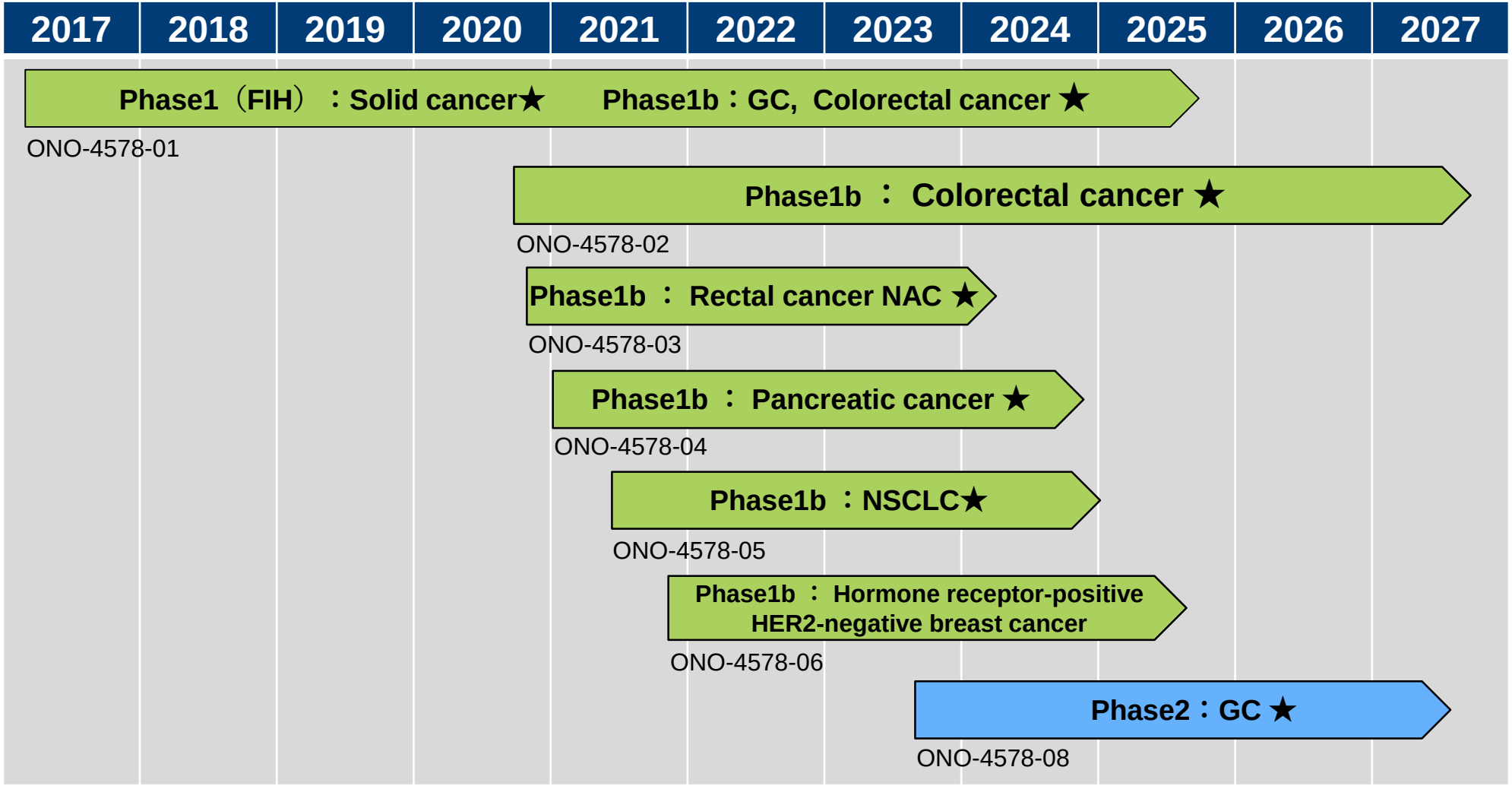

- **In syngeneic mouse tumor-bearing model, ONO-4578 improved immunosuppressive tumor microenvironment and showed antitumor effects (Figs. 1 and 2).**
- **Furthermore, ONO-4578 enhanced its antitumor effect by co-administration with anti-mouse PD-1 antibody (αPD-1) (Fig. 1).**

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

# ONO-4578　Development stage




★Combination with OPD

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

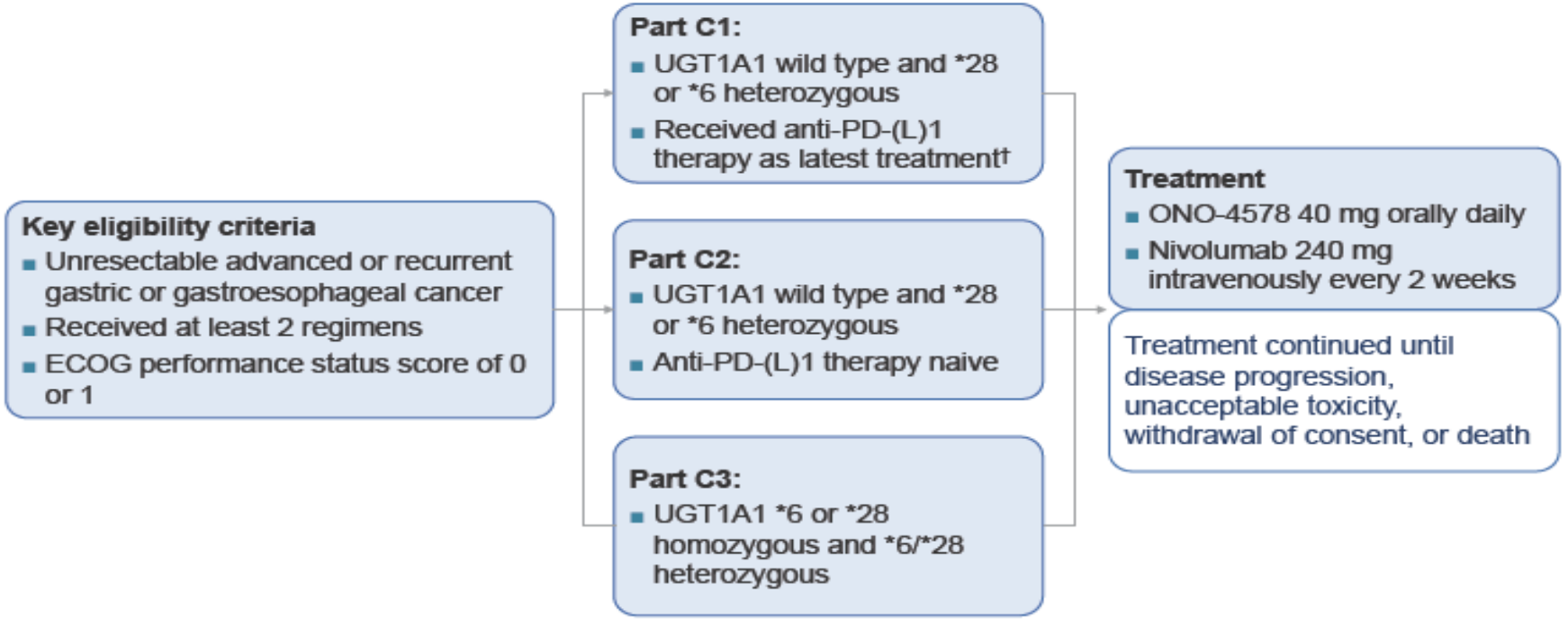
Hidekazu Hirano[1], Akihito Kawazoe[2], Kensei Yamaguchi[3], Tetsuya Hamaguchi[4], Yukiya Narita[5], Shogen Boku[6], Takashi Oshima[7], Hiroki Hara[8], Yasuo Hamamoto[9], Taito Esaki[10], Kenji Ishido[11]

[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

# 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

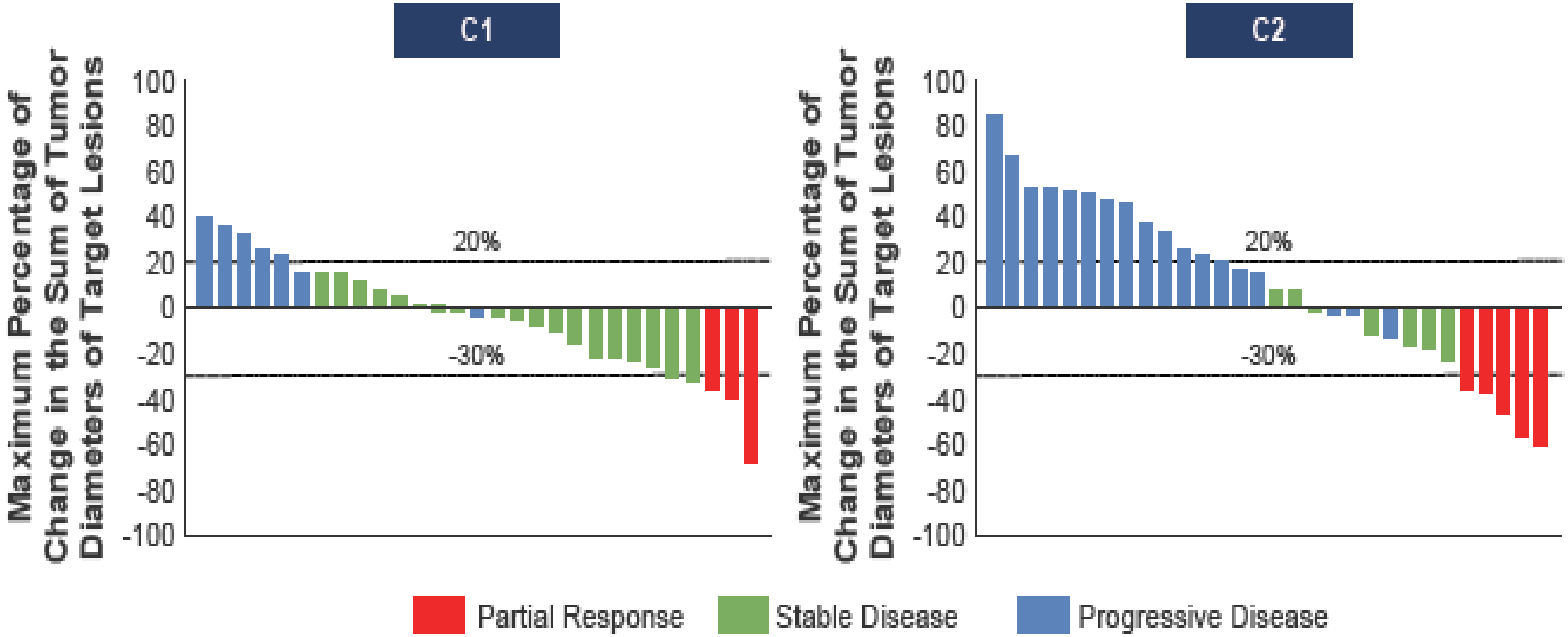
# Efficacy Results

| | 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] |

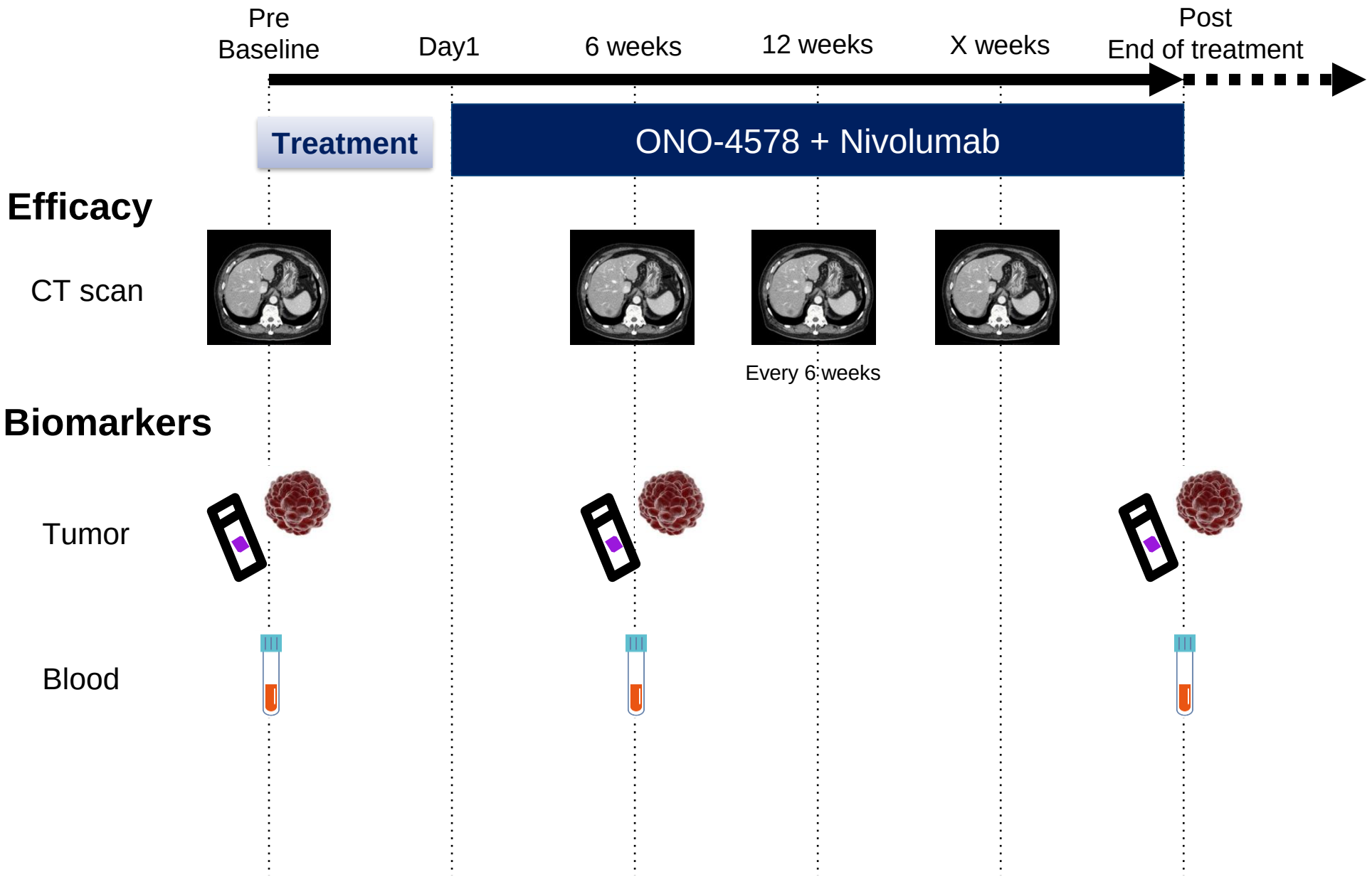
90% confidence intervals (CI) on both sides were calculated using the Clopper-Pearson method
[a]Analysis using Kaplan-Meier method

# Efficacy Results

## Waterfall Plot by Best Overall Response

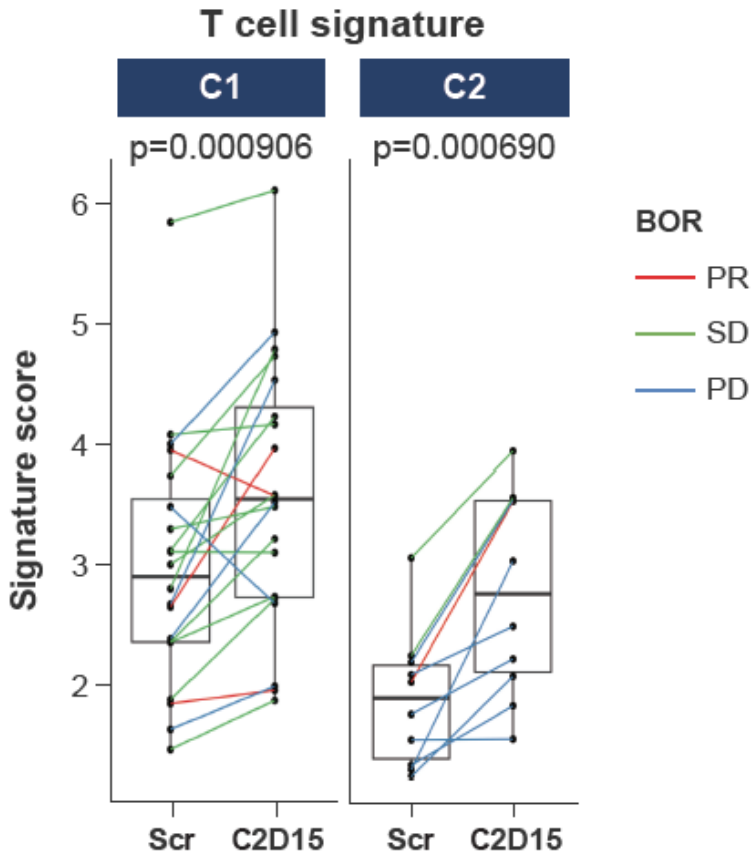


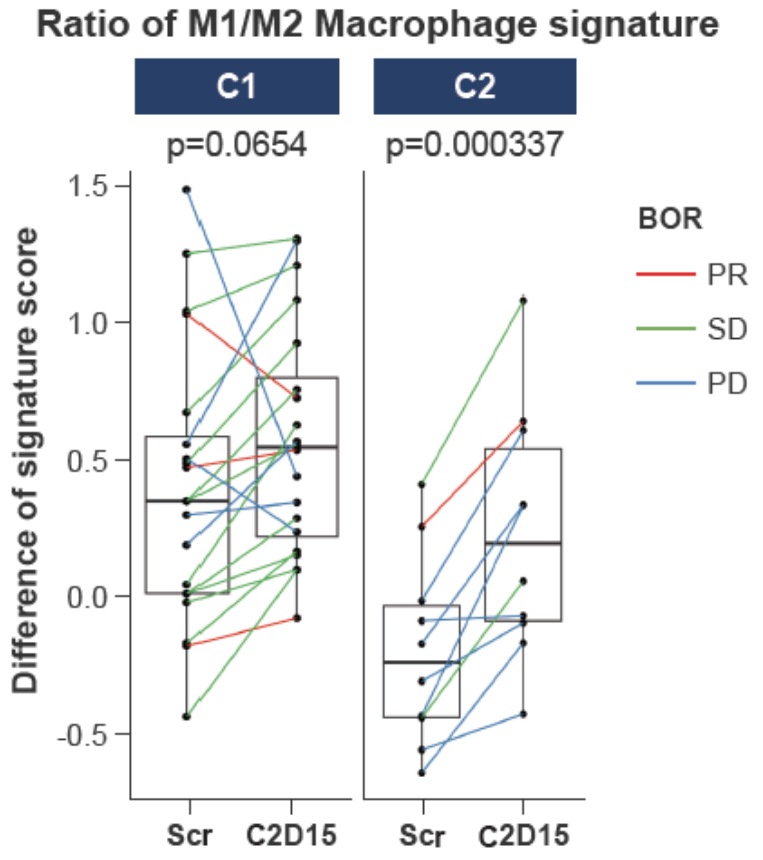
# Study schedule of ONO-4578-01 Part C (3rd or later line, GC)



# Results of Biomarker Analysis

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



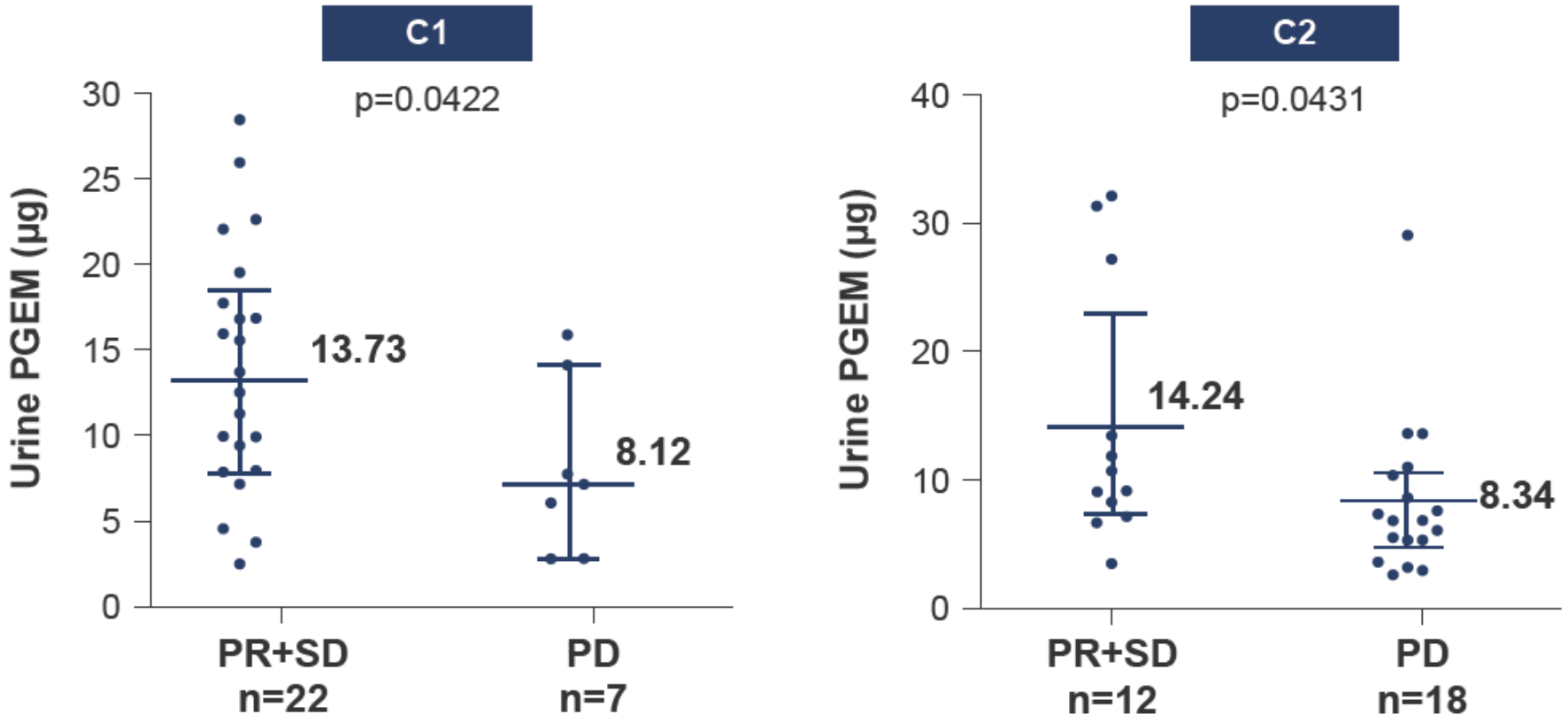




Signature score was calculated as mean of log-transformed expression value BOR, best overall response; PD, progressive disease; PR, partial response; SD, stable disease
Scr, Screening period; C2D15, cycle 2 day 15

# 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

# 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

# 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

# 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.

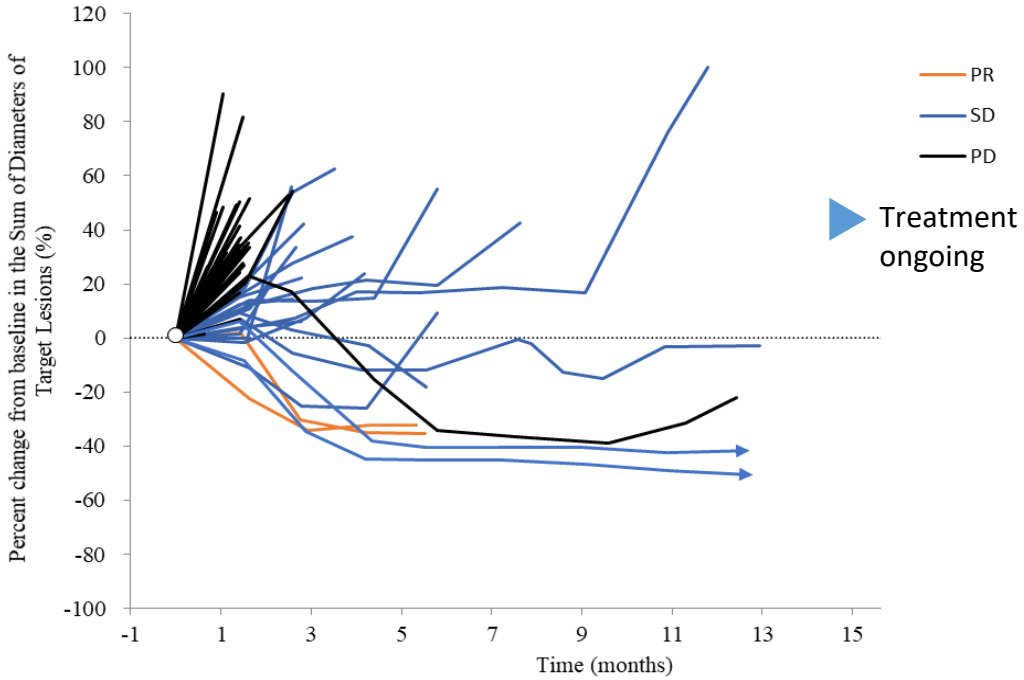
# Efficacy Results

| 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] |

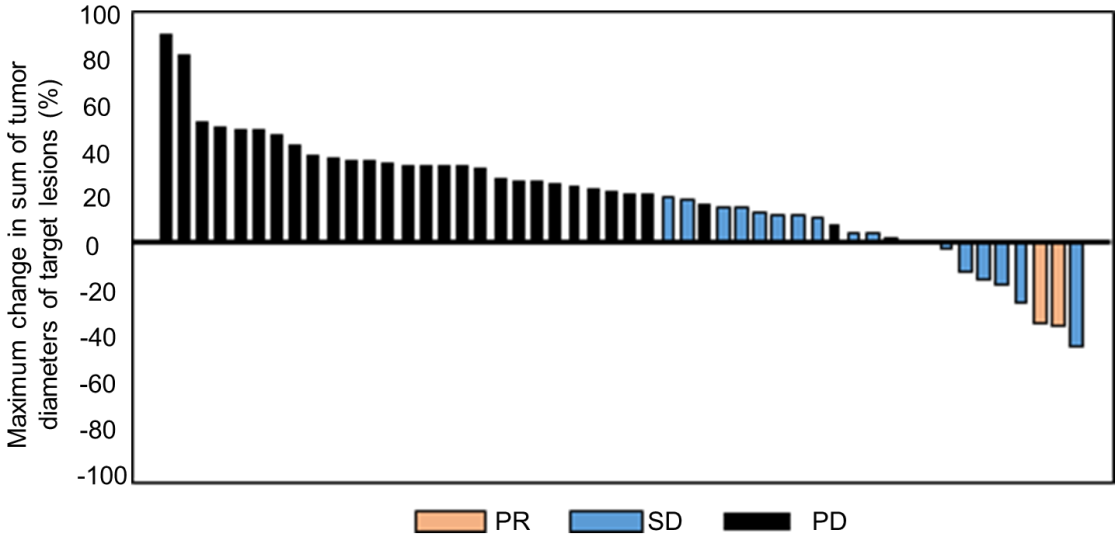
CR, complete response; DCR, disease control rate; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

# 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

# Results of studies in colorectal cancer

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

# Efficacy Results

## Subgroup Analysis by PD-L1 (CPS)

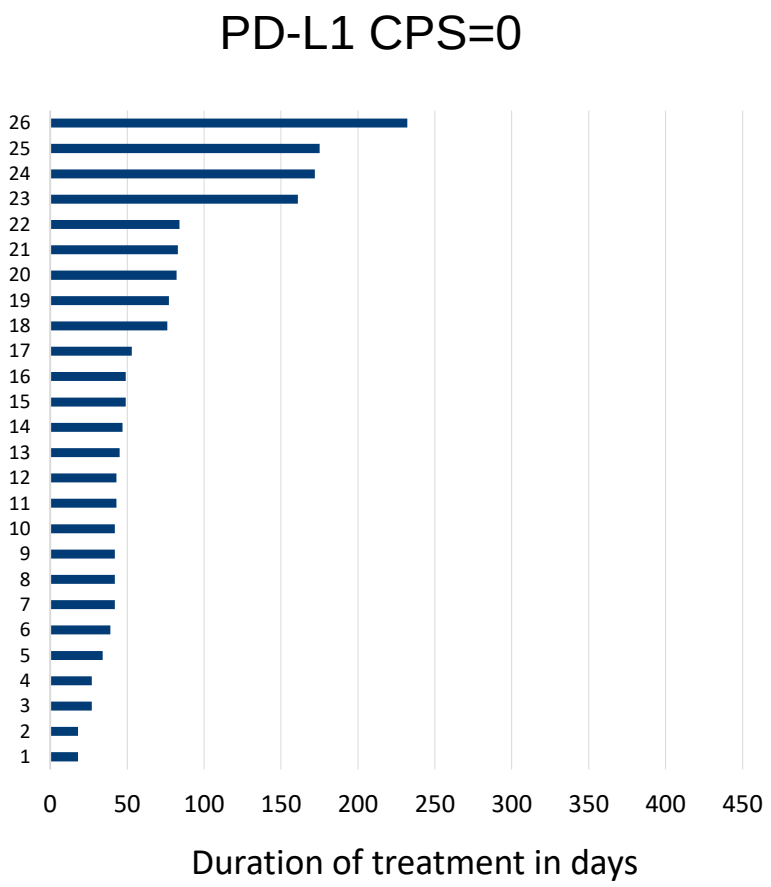
| | PD-L1 CPS=0 (n=22) | | PD-L1 CPS≥1 (n=25) | |
|---|---|---|---|---|
| | n (%) | [90% CI] | n (%) | [90% CI] |
| ORR (CR+PR) | 1 (4.5) | [0.2–19.8] | 1 (4.0) | [0.2–17.6] |
| DCR (CR+PR+SD) | 8 (36.4) | [19.6–56.1] | 12 (48.0) | [30.5–65.9] |

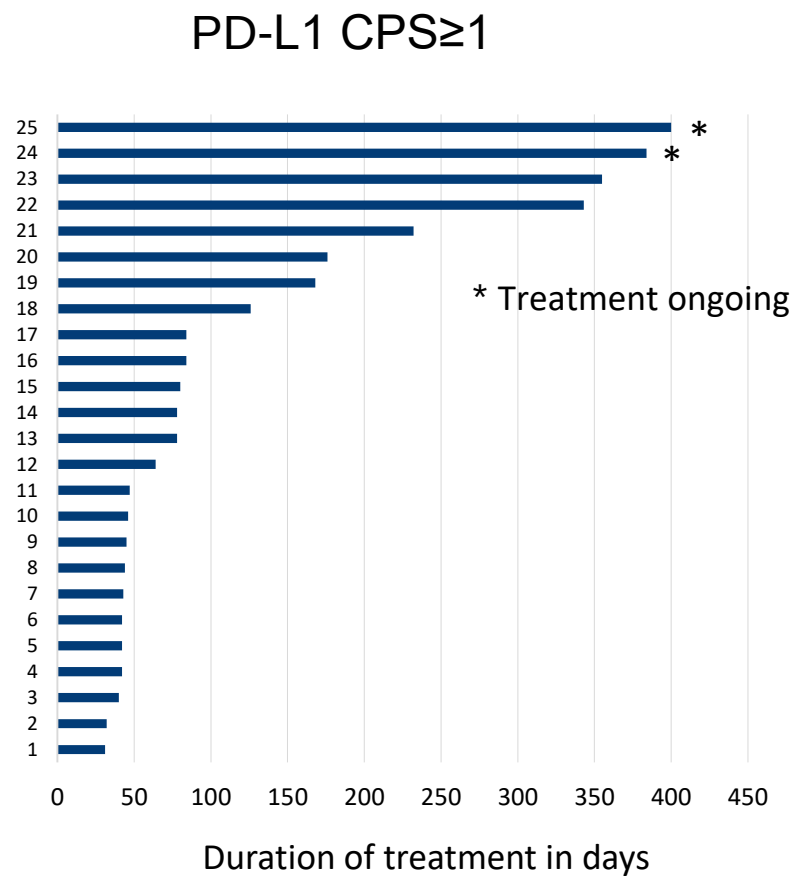
CPS, combined positive score; CR, Complete Response; DCR, Disease Control Rate; ORR, Objective Response Rate; PD, Progressive Disease; PD-L1, programmed death ligand-1; PR, Partial Response; SD, Stable Disease

# 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**



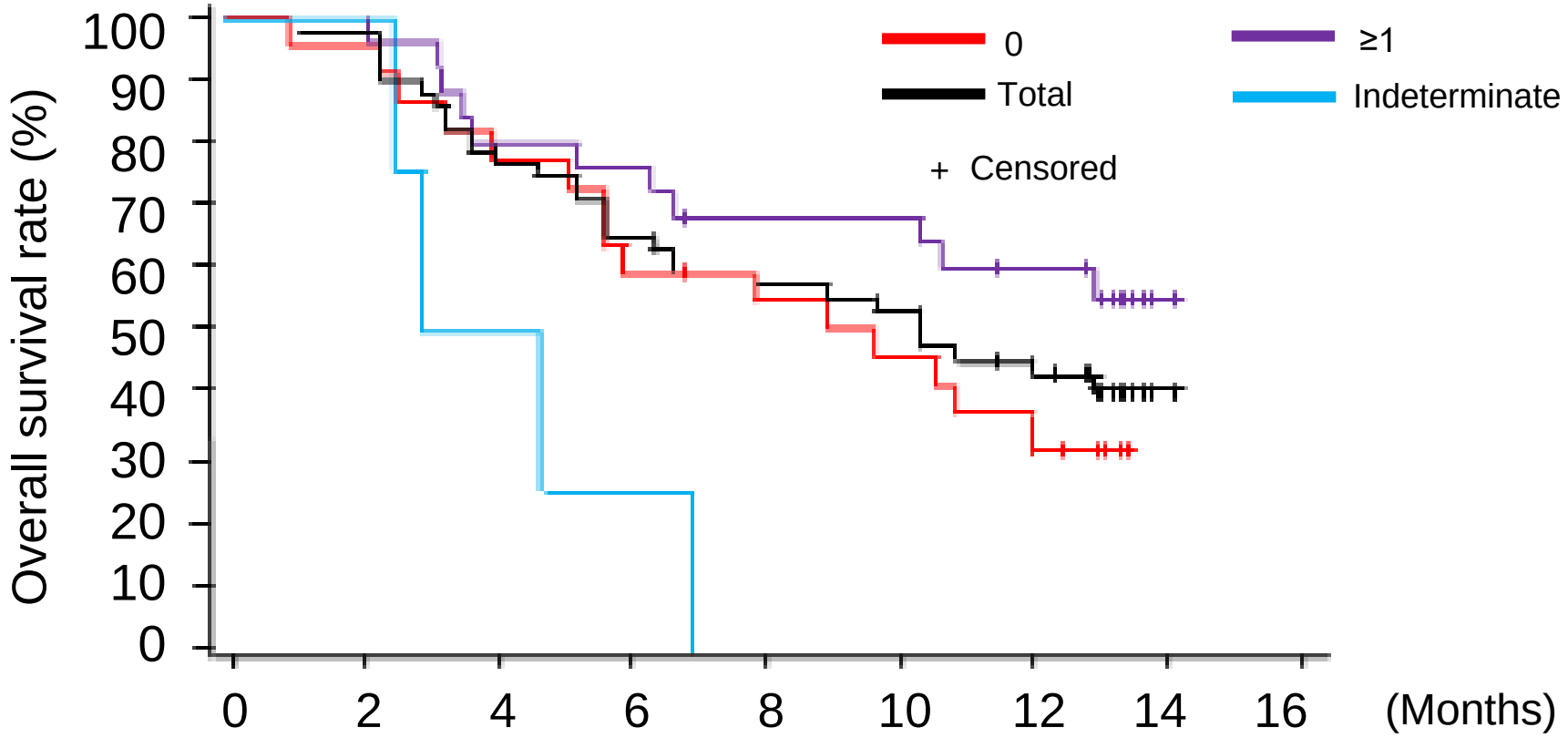




PD-L1, programmed death ligand-1; CPS, combined positive score

# 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



# 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

# 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.**

# Updates of Open Innovation and ONO-8250 Introduction

# INDEX

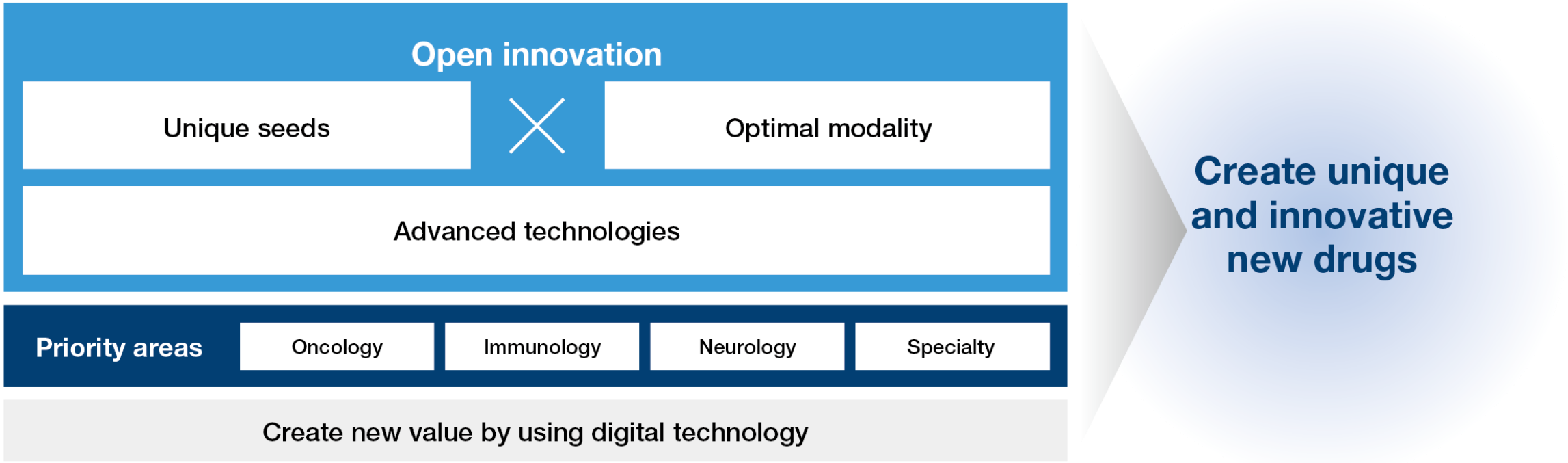
# 01

## Drug Discovery Strategy & Priority Areas

# Drug Discovery Strategy

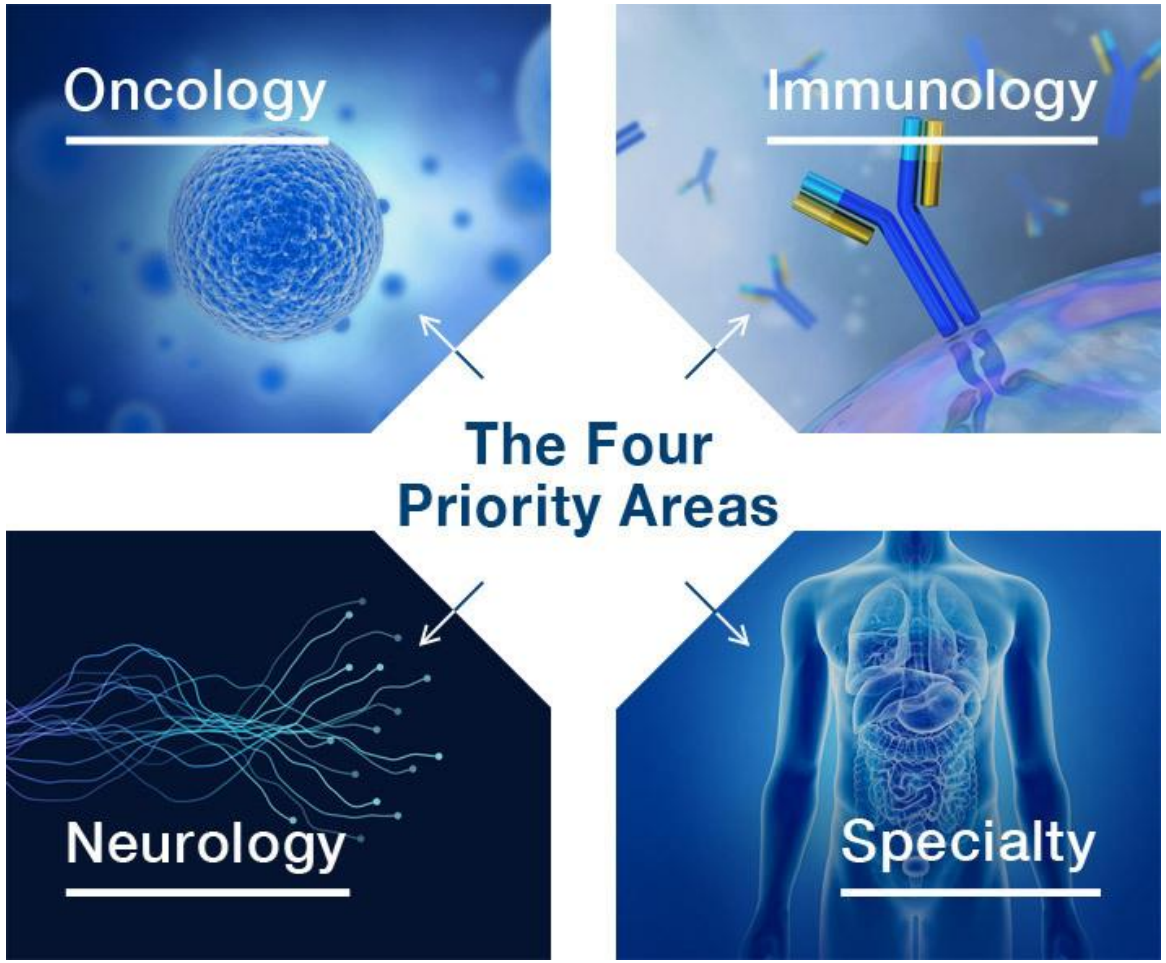
## Promoting open innovation in multiple fields and aiming to create innovative new drugs that meet medical needs

**ONO focuses on the areas of oncology, immunology, neurology and specialties; all of which include diseases with high medical needs. In each of these areas, we are working to strengthen our drug discovery capabilities by delving into the biology of human disease with the aim of discovering new drugs that can satisfy medical needs. In particular, by actively promoting open innovation, which is one of our strengths, we aim to create breakthrough new drugs with medical impact by not only utilizing a variety of cutting-edge technologies, such as informatics, robotics, and genome editing, but also selecting the optimal modality (therapeutic approach), including small molecule compounds, antibodies, and cells for the unique drug discovery seed. In addition, we are working to improve the quality and speed of drug discovery research through the use of digital technology.**



# Priority Areas of Drug Discovery Research

**"developing original and innovative new drugs."**



# 02

## Updates of Open Innovation

# Updates of Open Innovation (2021～)

## 2021

| Month | Partner |
|---|---|
| Feb | Lab Central / MBC biolabs (Enabling awesome) |
| Mar | PeptiDream |
| Mar | UCDDC (University of California Drug Discovery Consortium) |
| Aug | healx |
| Aug | MiraBiologics |
| Dec | Vanderbilt Univ. |

## 2022

| Month | Partner |
|---|---|
| Jan | neurimmune (Promind antibody therapeutics) |
| Mar | IKTOS (Artificial Intelligence for new drug design) |
| Apr | Domain Therapeutics / Université de Montréal |
| Jun | Fate Therapeutics |
| Aug | knowledge palette |
| Nov | MEMO Therapeutics AG |
| Nov | Captor Therapeutics |
| Dec | precisionlife (improving health \| for everyone) |

## 2023

| Month | Partner | Keywords | Tx Area |
|---|---|---|---|
| Jan | MONASH University | Anti-GPCR Antibodies (Abs) | Immunology |
| Jan | KSQ | DNA Damage Response (DDR) | Oncology |
| Feb | CUE Biopharma | Modified Cytokine | Immunology |
| Mar | MOLCURE | AI-Antibody | undisclosed |
| Mar | PeptiDream | PDPS (cyclic peptide) | undisclosed |
| Mar | macomics | Macrophage modulating Ab | Oncology |
| Aug | TWIST Bioscience | Functional Abs | Immunology |
| Sep | 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 | BioMed X (Two worlds - one institute) | Cancer Immunotherapy by targeting Neutrophil | Oncology |

NEW

## 2024

| Month | Partner | Keywords | Tx Area |
|---|---|---|---|
| Feb | NUMAB | Multispecific Macrophage Engager | Oncology |
| Feb | SHATTUCK LABS | Bifunctional Fusion Proteins | Immunology |
| Feb | InveniAI (Innovate with Intelligence) | AI-Target ID | undisclosed |
| Feb | EMB Epsilon Molecular Engineering® | VHH Abs | undisclosed |
| | | | |

NEW

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

# Updates of Open Innovation (2021～)

## 2021

| Month | Partner |
|---|---|
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| Mar | UCDDC (University of California Drug Discovery Consortium) |
| Aug | healx |
| Aug | MiraBiologics |
| Dec | Vanderbilt Univ. |

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

## 2022

| Month | Partner |
|---|---|
| Jan | neurimmune (Promind antibody therapeutics) |
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| Nov | Captor Therapeutics |
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## 2023

| Month | Partner | Keywords | Tx Area |
|---|---|---|---|
| Jan | MONASH University | Anti-GPCR Antibodies (Abs) | Biologics ogy |
| Jan | KSQ | DNA Damage Response (DDR) | Seeds gy |
| Feb | CUE Biopharma | Modified Cytokin | Biologics ogy |
| Mar | MOLCURE | AI-Antibody | Biologics s AI |
| Mar | PeptiDream | PDPS (cyclic peptide) | undisclosed |
| Mar | φmacomics | Macrophage modulating Ab | Biologics gy |
| Aug | TWIST Bioscience | Functional Abs | Biologics logy |
| NEW | ADIMAB | Bispecific Abs | Biologics gy |
| Oct | turbine. | Target ID & Validation | Seeds AI |
| Dec | EVQLV | Generative AI for Antibody | Biologics s AI |
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| Dec | BioMed X (Two worlds - one institute) | Cancer Immunotherapy by targeting Neutrophil | Seeds gy |

## 2024

| Month | Partner | Keywords | Tx Area |
|---|---|---|---|
| Feb | NUMAB | Multispecific Macrophage Engager | Biologics logy |
| Feb | SHATTUCK LABS | Bifunctional Fusion Protei | Biologics nology |
| Feb | Inveni AI (Innovate with Intelligence) | AI-Target ID | Seeds AI |
| Feb | EM3 (Epsilon Molecular Engineering ®) | VHH Abs | Biologics losed |

NEW

## 2023～ Open Innovation Updates

| Biologics | Discovery Seeds | AI |
|---|---|---|
| 10 | 5 | 4 |

# Discovery Technology and Therapeutic Modalities

**Biologics collaborations**

| | Tech & Seeds | Small Molecule | Peptide | Protein & Antibody | Cell Therapy |
|---|---|---|---|---|---|
| **Oncology** | turbine AI<br>BioMedX | ribon therapeutics<br>KSQ<br>Chordia Therapeutics<br>CANCER RESEARCH UK<br>ONO-7018 | ONO-4685 | macomics<br>NUMAB<br>ADIMAB<br>MEMO THERAPEUTICS AG<br>Merus<br>NUMAB<br>LifeArc | Fate THERAPEUTICS<br>ONO-8250 |
| **Immunology** | | | | MONASH University<br>TWIST BIOSCIENCE<br>NUMAB<br>CUE BIOPHARMA<br>SHATTUCK LABS | |
| **Neurology** | UK Dementia Research Institute<br>precisionlife improving health \| for everyone | Captor Therapeutics<br>Vanderbilt Univ.<br>ARIA PHARMACEUTICALS AI | | neurimmune Promind antibody therapeutics | |
| **Specialty** | | DOMAIN THERAPEUTICS<br>Université de Montréal | | | |
| **Undisclosed** | Inveni AI AI<br>knowledge palette<br>MBC biolabs Enabling awesome<br>Lab Central<br>UCDDC | heal AI<br>IKTOS AI<br>Artificial Intelligence for new drug design<br>SCHRÖDINGER<br>Cyclenium pharma | PeptiDream | EVQLV AI<br>MOLCURE AI<br>EM3 Epsilon Molecular Engineering<br>Ligand<br>MiraBiologics | |

□ 2023~

# 02

## Updates of Open Innovation

### ◆ Biologics Collaboration

# 5 Key Features of Biologics Collaborations

**1 Antibody Libraries**

ADIMAB, EMB Epsilon Molecular Engineering, MOLCURE, TWIST BIOSCIENCE, neurimmune Promind antibody therapeutics

**2 AI・Digital**

MOLCURE, EVOLV

**3 Multispecific Abs**

ADIMAB, MiraBiologics, NUMAB, Merus

**4 Advanced PJ Introduction**

SHATTUCK LABS — Bifunctional Fusion Proteins

NUMAB — Multi-specific Macrophage Engager

macomics — Macrophage modulating antibodies

MEMO THERAPEUTICS AG — Cancer Immunotherapy

MONASH University — Anti-GPCR Abs

**5 Diversified Modalities**

Fate THERAPEUTICS — CAR-T Cell Therapy

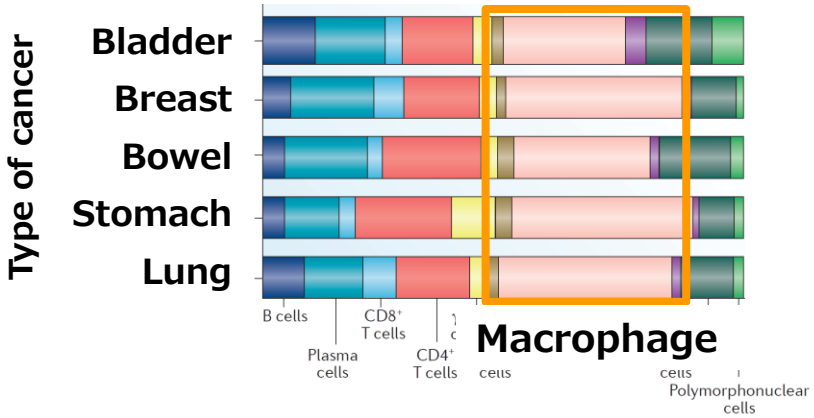
CUE BIOPHARMA — Modified Cytokine

SHATTUCK LABS — Bifunctional Fusion Proteins

# Drug Discovery Collaboration with Macomics to Develop Macrophage-targeting Antibody for the Treatment of Cancer（2023.03.23）



## 【Tumor-associated macrophage (TAM)】



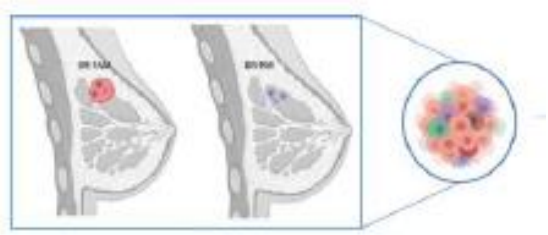

**TAM：**

Macrophages represent the major population infiltrating most human cancers.

Luca Cassetta & Jeffrey W. Pollard
Nat Rev Drug Discov 17, 887-904 (2018)

## 【ENIGMAC™ Discovery Platform】

**RNA seq of purified TAM vs Resident macrophages**



**Bioinformatic filtering and target identification**

**Target validation**
**with iPSC-derived macrophages**

**Creating antibody drug candidates against**
**novel macrophage targets**

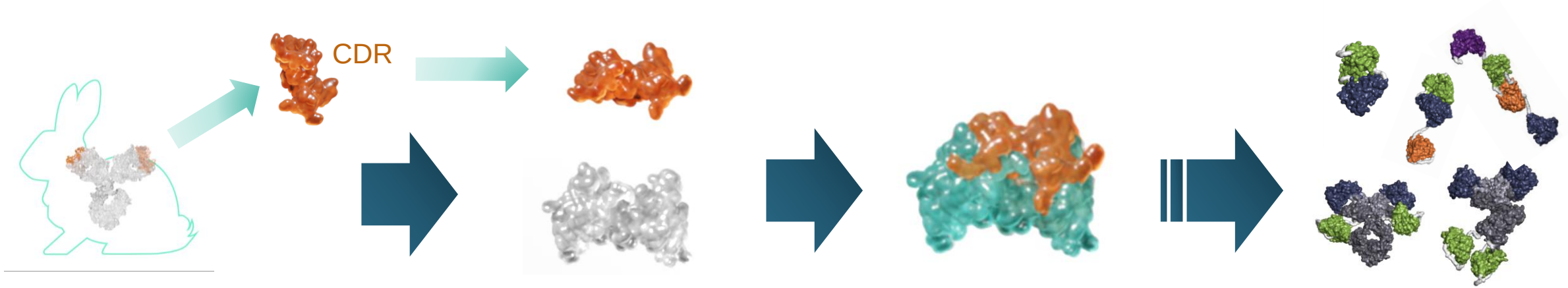
**Antibody drug candidate**

# Option and Collaboration Agreement with Numab to Develop Multi-specific Antibody NM49 (2024.02.14)



## Next-generation Plug & Play Novel Multispecific Therapeutic Platform

Various Multivalent Antibody Format Generation Technologies Based on Optimized Humanized scFv (Hu-Fv)




Ultra-high throughput antibody discovery for high yield and affinity rabbit antibody

Fusion of rabbit CDR with human Fv

Humanized antibody Fv fragments that recognize specific targets

Various Multivalent Antibody Format

From Numab website

Acquisition of an exclusive option to license **Macrophage Engager NM49**

# 【Library of Libraries】

**an expansive collection of synthetic antibody libraries based on naturally occurring sequences**

**Hyperimmune Libraries**
1. Original Fab
2. Common LC Fab

**VHH Libraries**
1. VHH Ratio
2. VHH Shuffle
3. VHH hShuffle
4. VHH hShuffle HI
5. VHH GPCR

**Structural scFv Library**

**Ancestral scFv Library**

**Minotaur scFv Library**

**AI Hypermutated scFv Library**

**GPCR Libraries**
1. GPCR 2.0 scFv
2. GPCR 3.0 scFv

**Ion Channel scFv Library**

**Carbohydrate scFv Library**

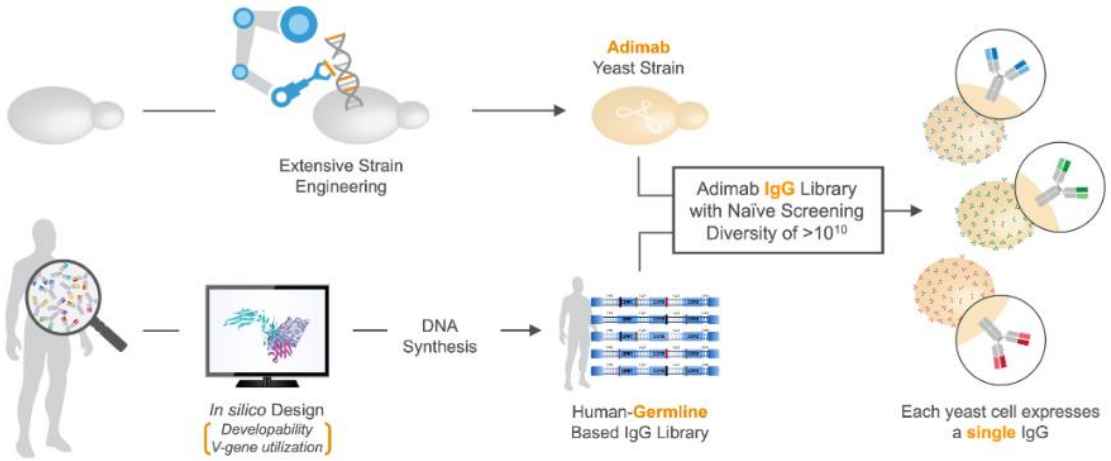
**High probability of obtaining functional antibodies to targets**

**Twist will utilize the Twist Biopharma Solutions Library of Libraries to conduct research activities to discover novel antibodies against therapeutic target(s) identified by Ono**

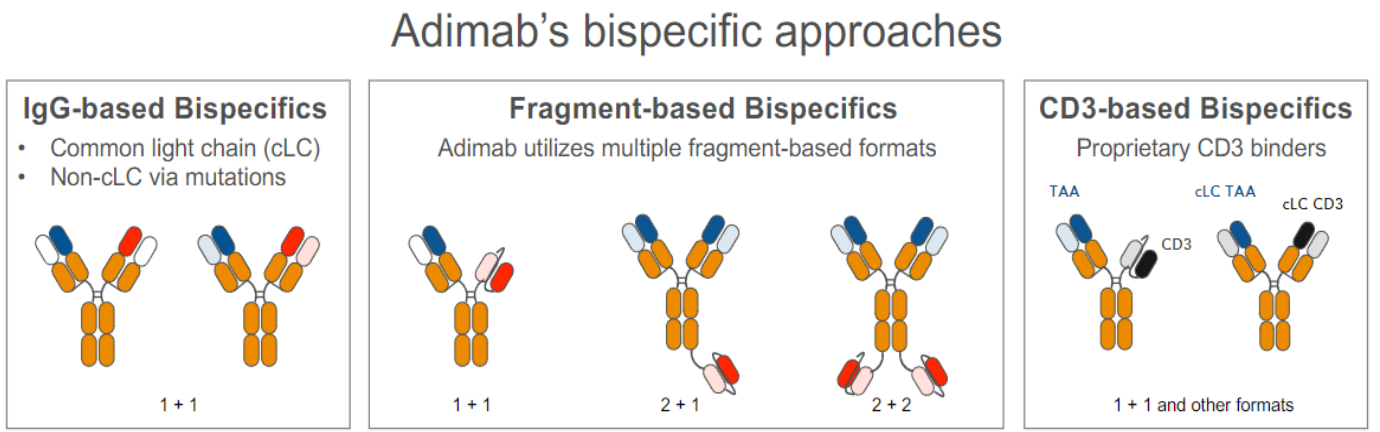
1 Antibody Libraries 3 Multi-specific Abs

# 【Adimab's platform technology】

## Yeast Library




## Rich experiences of multi-specific antibodies



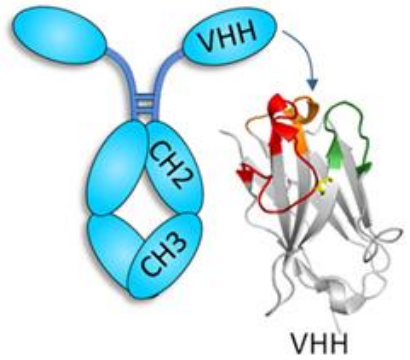

**Adimab will discover novel therapeutic antibodies against multiple targets selected by Ono and generate bispecific antibody product candidates**

# Ono Enters into Collaboration Agreement with EME to Generate Novel VHH Antibodies against Multiple Therapeutic Targets（2024.02.21）

1 Antibody Libraries

## 【What is VHH】

Camelid HcAb



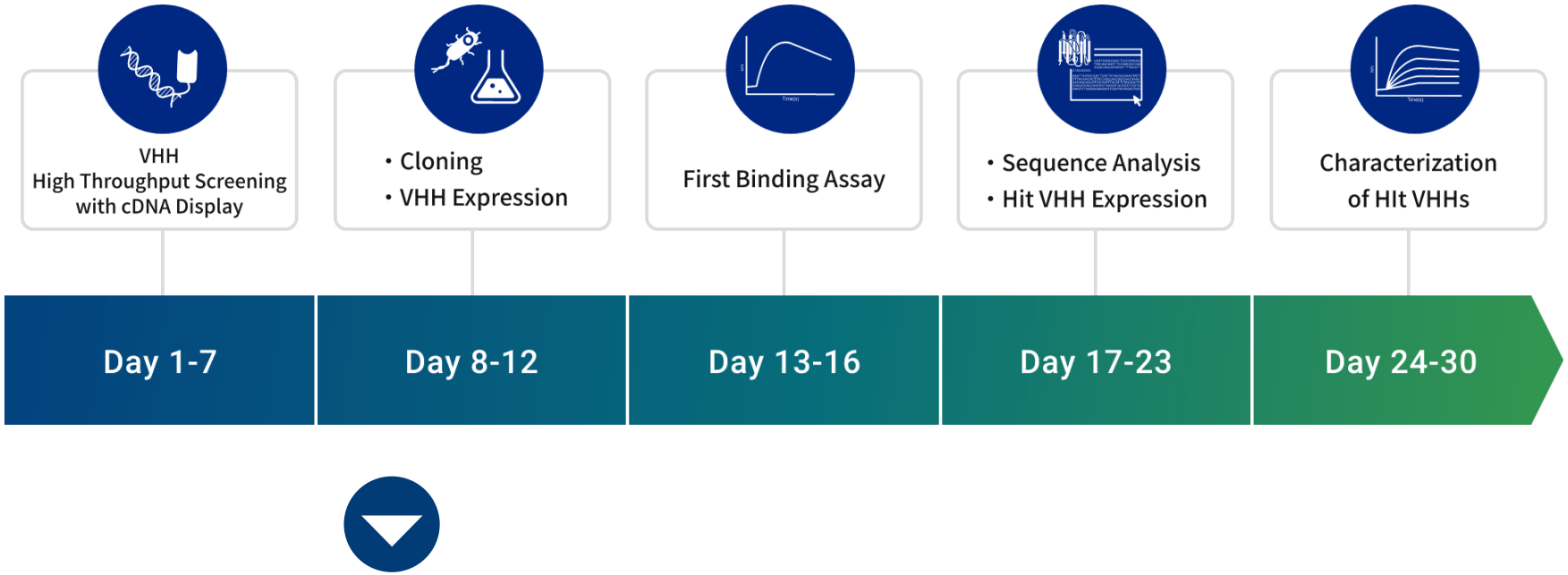

Front. Immunol., 21 August 2017 Sec.
Vaccines and Molecular Therapeutics Volume 8 - 2017

**Feature of VHH**

- **small molecular weight (ca. 15kDa)**
- **binding to different types of epitopes from conventional antibodies**

## 【HTS Platform “The Month”】

**it only takes approximately a month for obtaining hit VHH to a drug target**

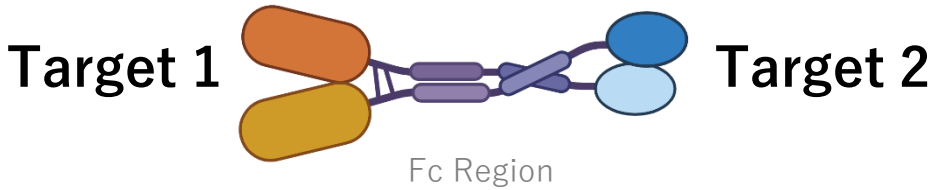



**EME generate novel VHH antibody drugs against multiple therapeutic targets selected by Ono, using EME’s proprietary humanized VHH screening platform “The Month”**

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



## 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)

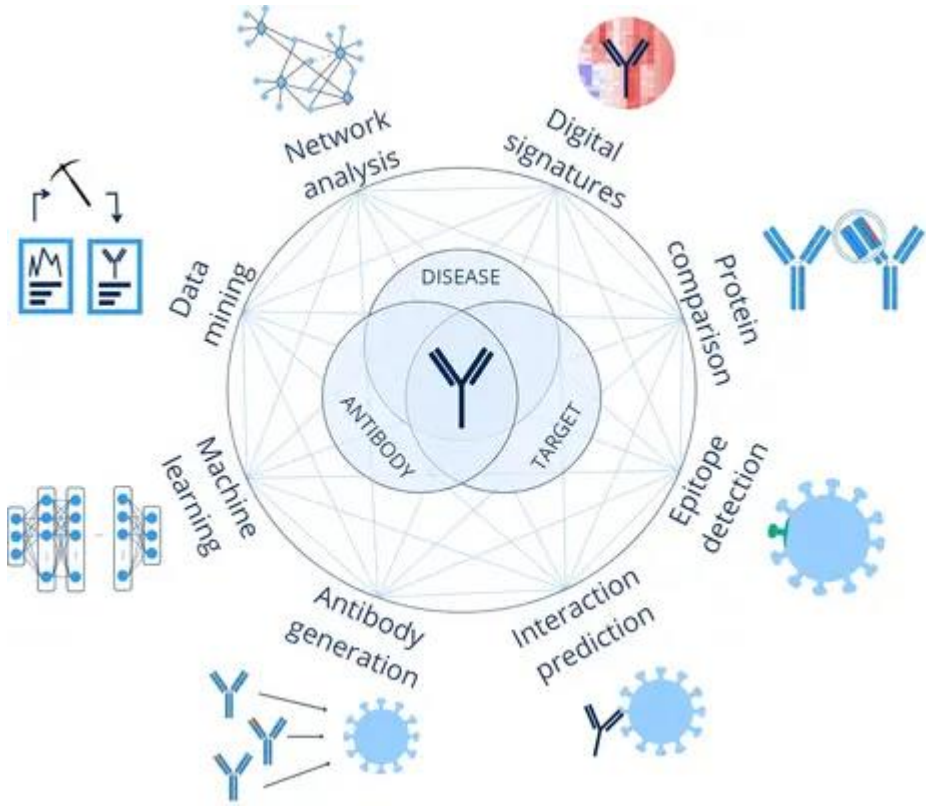
# 02

## Updates of Open Innovation

### ◆ AI・Digital Collaboration

# 【EVQLV Platform】

## AI-powered Antibody Design Engine




## The platform

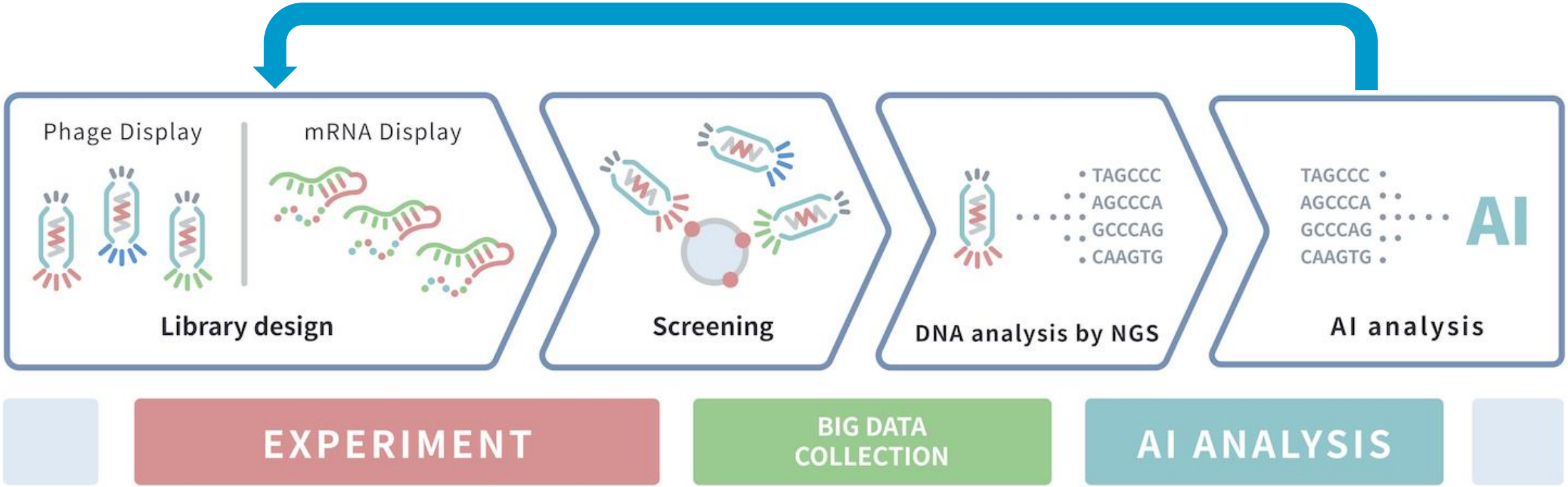
**designs** and **modifies antibodies while retaining conformational** and **functional integrity** using **AI**

**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**

# Ono Enters into a Drug Discovery Collaboration Agreement with MOLCURE to Discover and Develop Innovative Antibody Drugs for Multiple Targets Utilizing MOLCURE's AI-driven Platform Technology（2023.03.23）

1 Antibody Libraries　2 AI・Digital




For more details, please refer to Molcure website (https://molcure.com/).

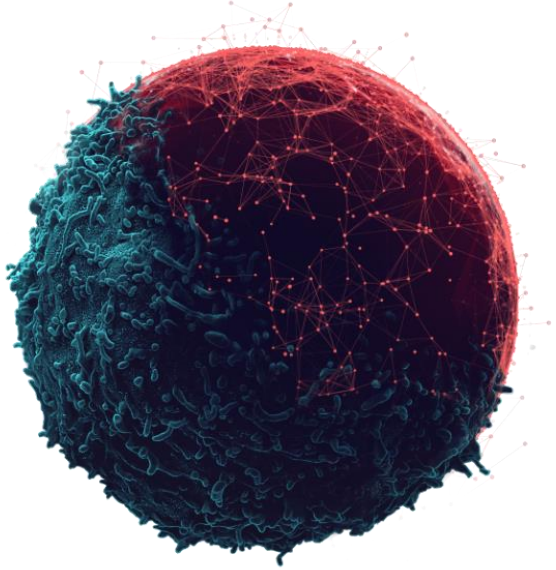
**Utilize MOLCURE's proprietary AI-driven platform technology to discover and identify antibodies or molecules for multiple targets of interest selected by Ono**

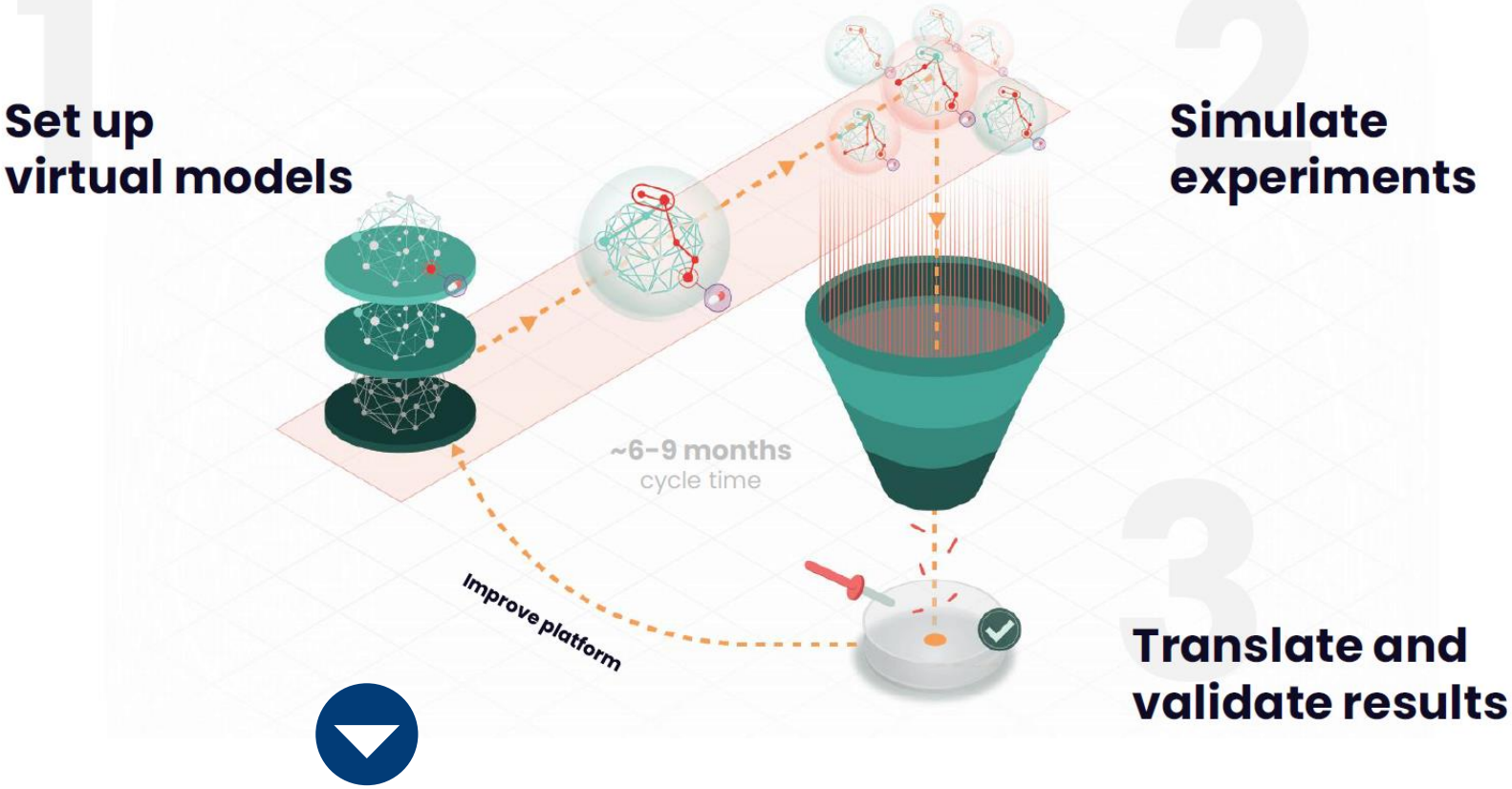
# Research Collaboration with Turbine to Identify and Validate Novel Therapeutic Targets in Oncology (2023.10.24)



## 【Simulated Cell™ Platform】

The virtual cells capture cancer biology and are used for in silico cell simulation.





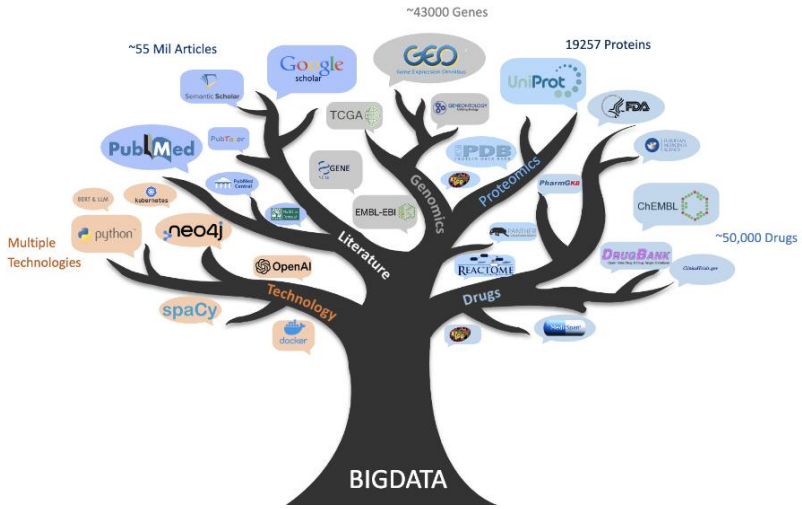

**Leveraging Turbine's AI-driven cell simulation, we are committed to identifying novel therapeutic targets in oncology.**

# Ono Enters into a Research Collaboration Agreement with InveniAI to Identify Novel Therapeutic Targets（2024.02.19）



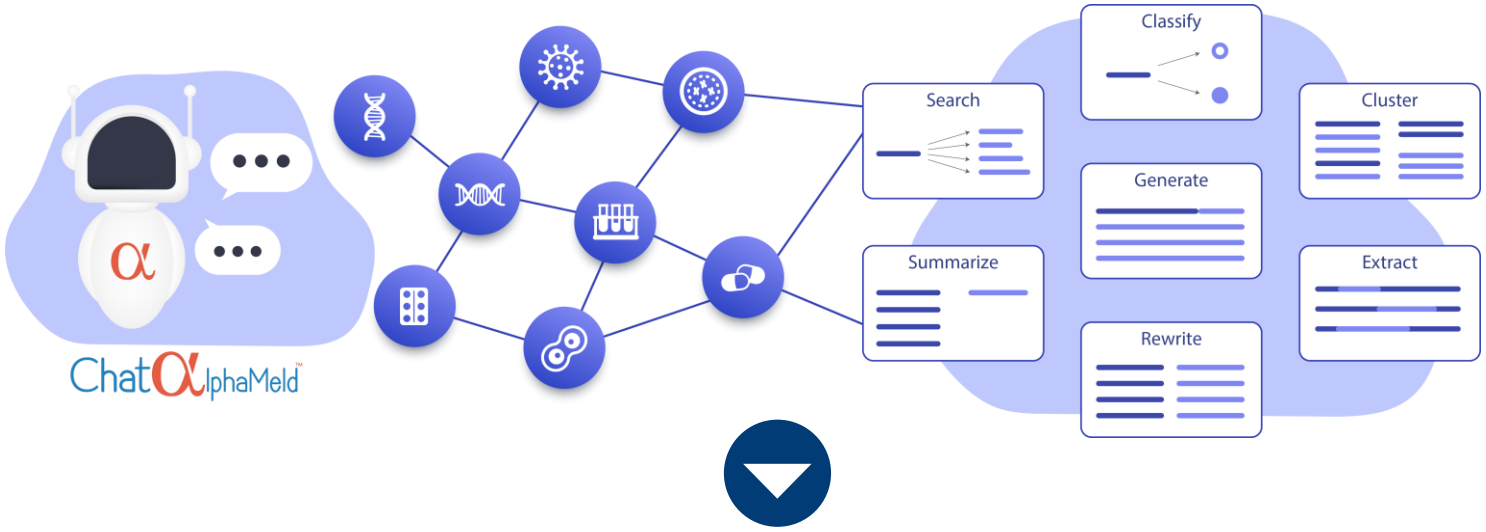
## 【AlphaMeld】 InveniAI's proprietary AI platform technology based on machine learning, advanced natural language processing and large language models

### Data Source（Big Data）




- Ideal mode of pharmacotherapy
- Disease severity
- Gene ontology
- Disease pathways
- Proteinopathies
- Standard of care
- Emerging innovation

### AI technology



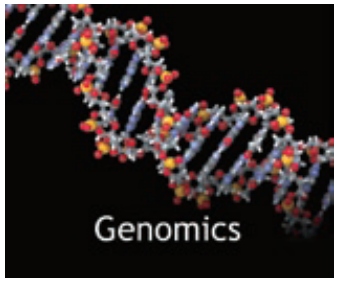

## Generate Testable Hypotheses

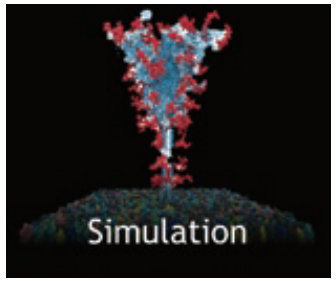
factoring in medical, scientific, strategic, and commercial considerations.

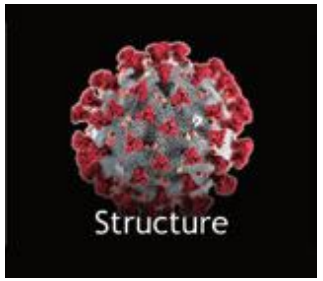
**We will interactively use a data-driven approach to identify new therapeutic targets and drug discovery hypotheses across multiple indications.**

# Accelerating AI Drug Discovery with the Supercomputer 'Tokyo-1' (2024.02.01)






The photo above shows a supercomputer dedicated to drug discovery. It processes and analyzes massive amounts of chemical data and biochemical information at high speeds to identify promising drug candidates.

**Vast amounts of genetic information data**

↓

**Assessment of the value of proprietary seeds**

**Image analysis, video analysis, natural language processing**

↓

**Significantly reduce time and effort**

**Analysis of molecular structures and prediction of interactions**

↓

**Creation of high-quality new drug candidates**

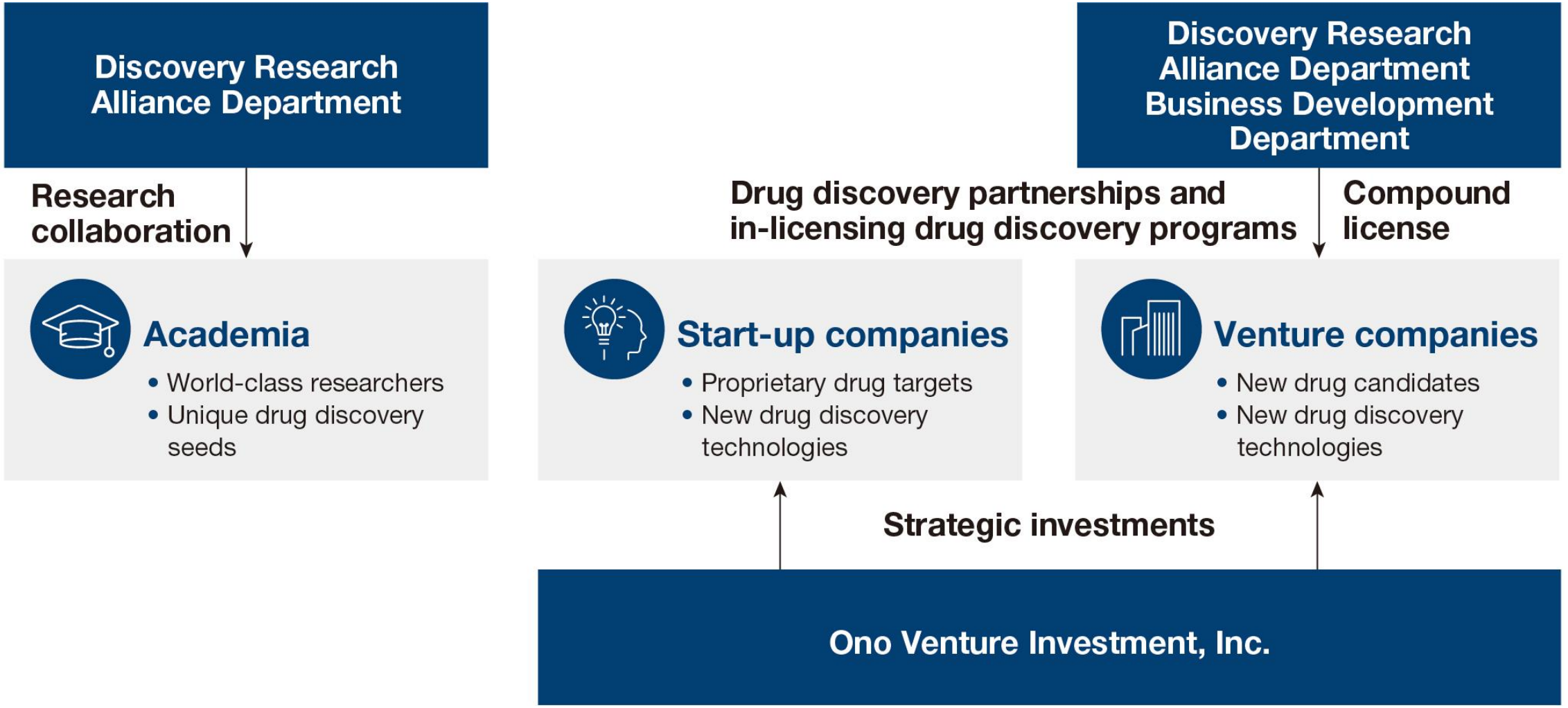
**Challenging the transformation of the drug discovery process**

# 02

## Updates of Open Innovation

- Strategic Investment by Ono Venture Investment
- Research Grants by Foundations

# Open Innovation That Supports Drug Discovery




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

# 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 |

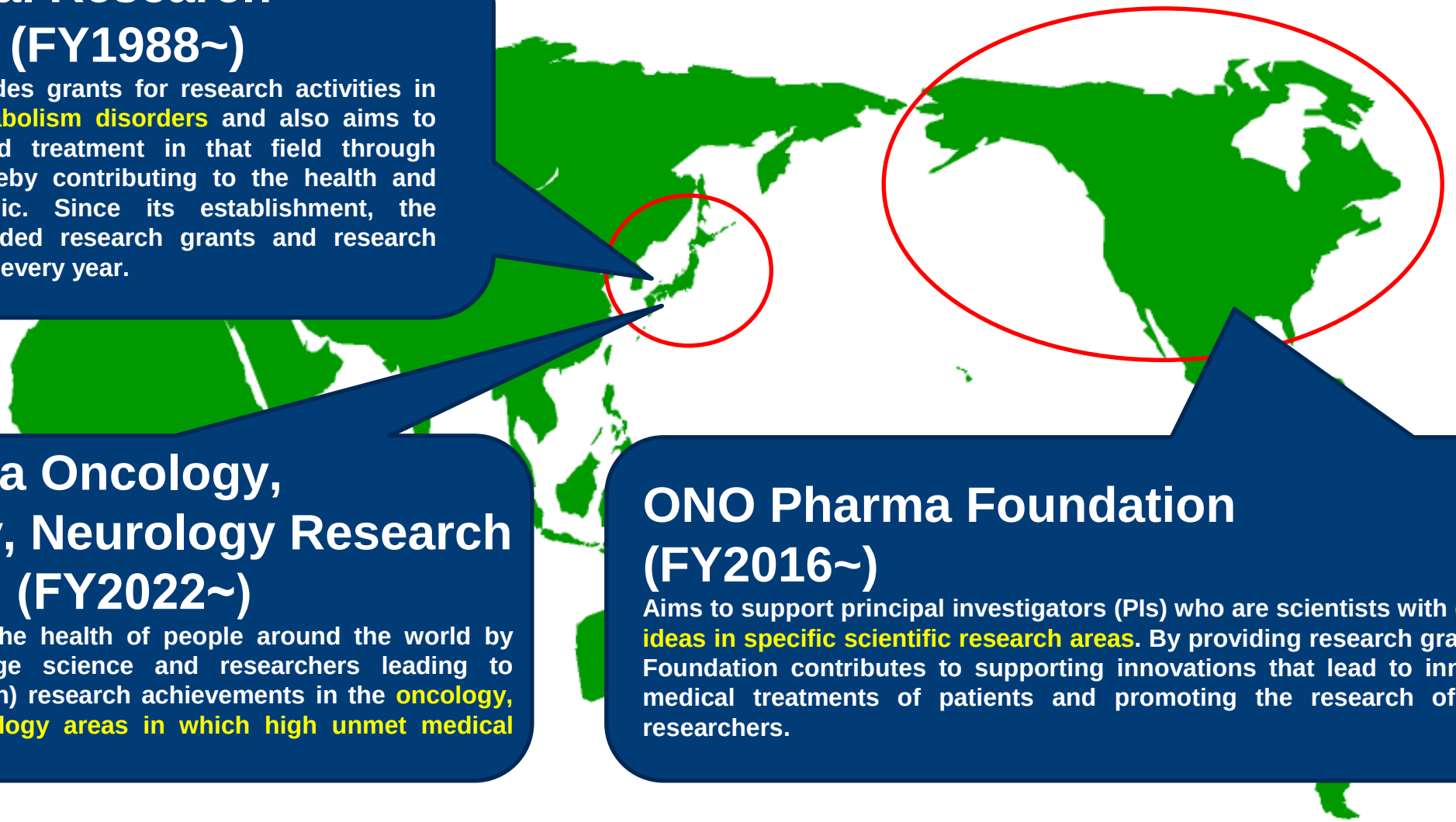
ONO VENTURE INVESTMENT, INC.

https://www.onoventure.com/news

# Research Grants Through Foundations and Donated Courses

## ONO Medical Research Foundation (FY1988~)

The Foundation provides grants for research activities in the field of lipid metabolism disorders and also aims to promote research and treatment in that field through various projects, thereby contributing to the health and welfare of the public. Since its establishment, the Foundation has provided research grants and research encouragement grants every year.



## "Ono Pharma Oncology, Immunology, Neurology Research Foundation“ (FY2022~)

Aims to contribute to the health of people around the world by supporting cutting edge science and researchers leading to innovative (breakthrough) research achievements in the oncology, immunology and neurology areas in which high unmet medical needs still remain.

## ONO Pharma Foundation (FY2016~)

Aims to support principal investigators (PIs) who are scientists with creative ideas in specific scientific research areas. By providing research grants, the Foundation contributes to supporting innovations that lead to innovative medical treatments of patients and promoting the research of young researchers.

https://sustainability.ono-pharma.com/ja/themes/126

# 03

## ONO-8250 Introduction

# Strategic Collaboration with Fate Therapeutics to Develop iPSC-derived CAR-T （2018.09.18）
# Exercise Option to HER2-targeted CAR-T Cell Product Candidate for Solid Tumor（2022.11.07）

1. Preference of killing activity on HER2-expressing tumor cells and optimal killing signaling to avoid T cell exhaustion

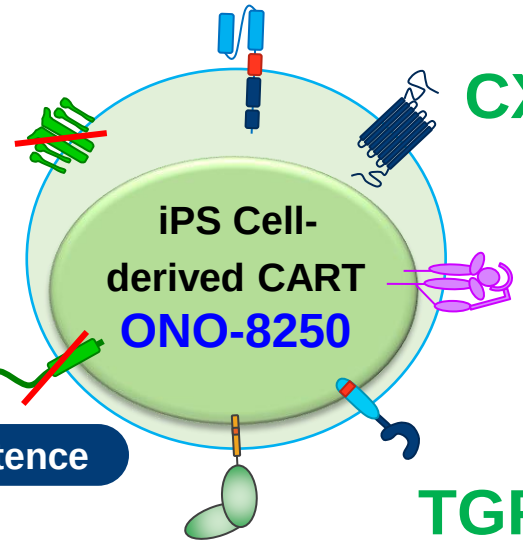
$H_2$CasMab-2 CAR＋1xx

T-cell receptor（TCR）deletion

7. Avoidance of GVH reaction

CXCR2

2. Improvement of migration into tumor tissues




IL7RF

3. Improvement of persistency

CD38 deletion

6. Enhanced effector cell metabolic fitness and persistence

TGFβR2-IL18R

hnCD16a

4. Overcome of immune suppressive environment

5. Combination effect with other therapeutic antibody

## “Off the Shelf” iPSC-derived HER-2 CAR-T incorporate 7 Functional Edits

Please refer to Clinicaltrials.gov for information on the clinical trial of ONO-8250.
https://clinicaltrials.gov/study/NCT06241456?term=FT825&checkSpell=false&rank=1

# Novel binder incorporated into ONO-8250

Fate THERAPEUTICS

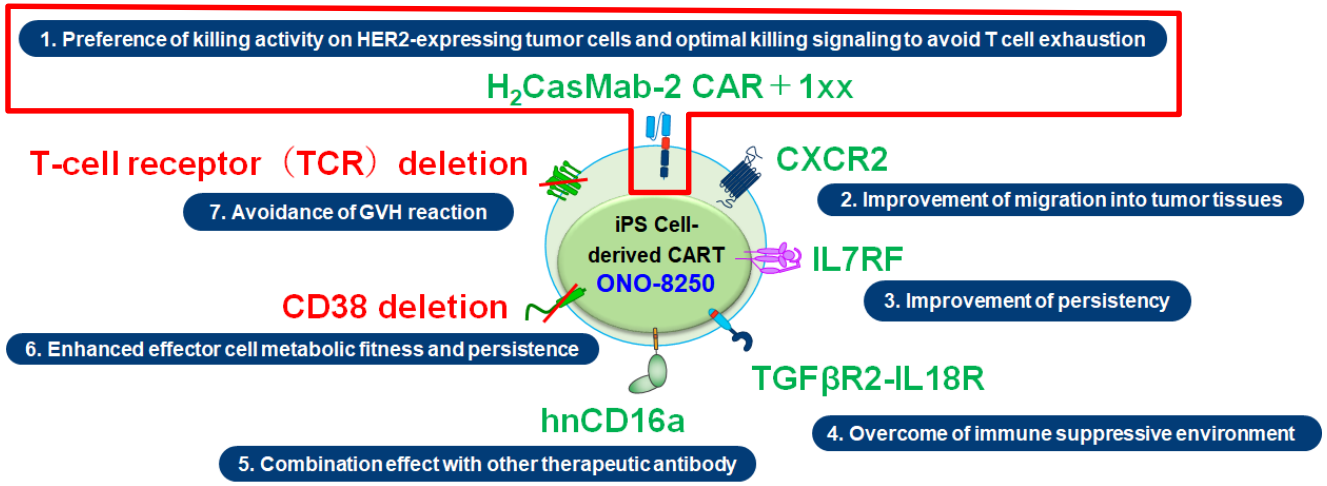
Jan 08 2024

## 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。

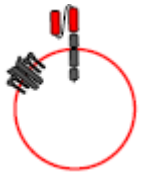
令和6年1月8日、小野薬品工業株式会社の提携企業であるFate Therapeutics社（米国カリフォルニア州サンディエゴ）は、H2CasMab-2の遺伝子を導入した多重遺伝子編集キメラ抗原受容体（CAR）T細胞製品候補であるFT825/ONO-8250の第I相臨床試験において、患者登録を開始したことを発表しました（https://ir.fatetherapeutics.com/news-releases/news-release-details/fate-therapeutics-announces-initiation-phase-1-clinical-trial）。

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。

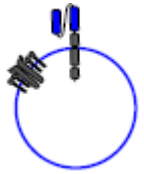
なお、H2Mab-250/H2CasMab-2の作製については、プレプリント（https://www.preprints.org/manuscript/202309.0906/v5）で公表されています。

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

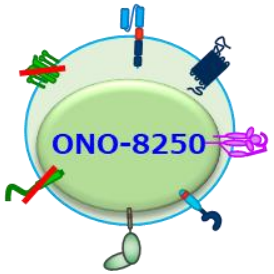
# Preferential targeting of HER2 expressed on tumor rather than normal cells is uniquely enabled by the novel $H_2$CasMab-2 binder



Trastuzumab CAR-T



$H_2$CasMab-2 CAR-T

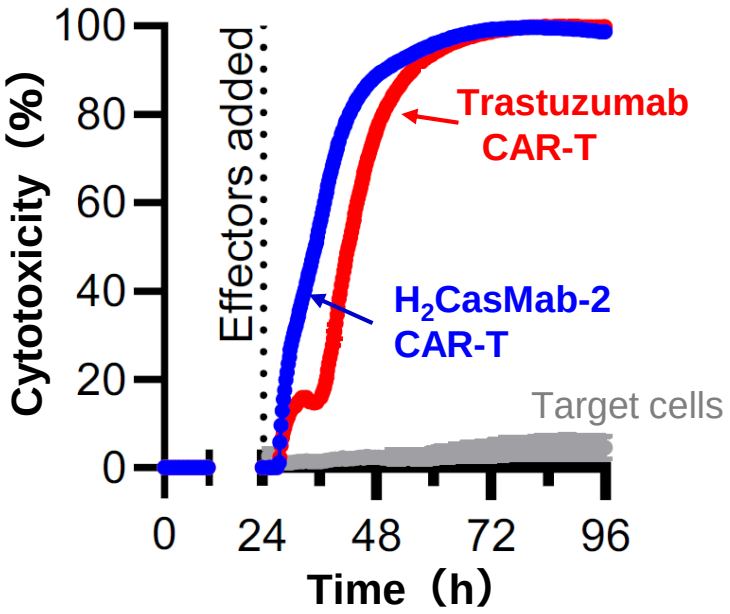



VS

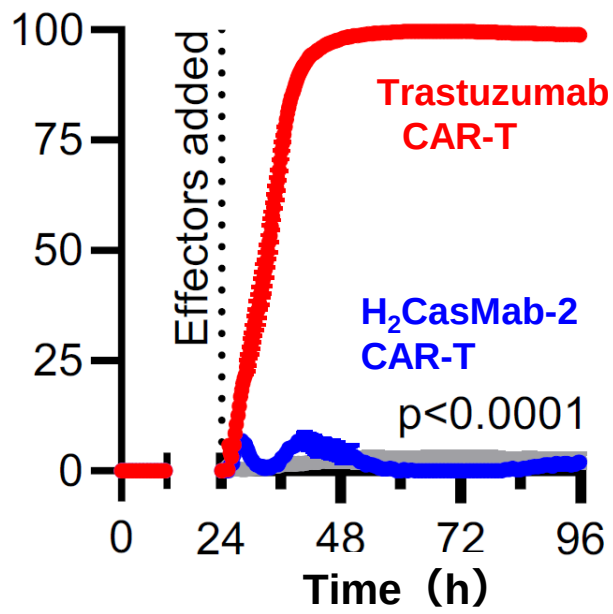
HER2$^{high}$ tumor cells (SKOV3)

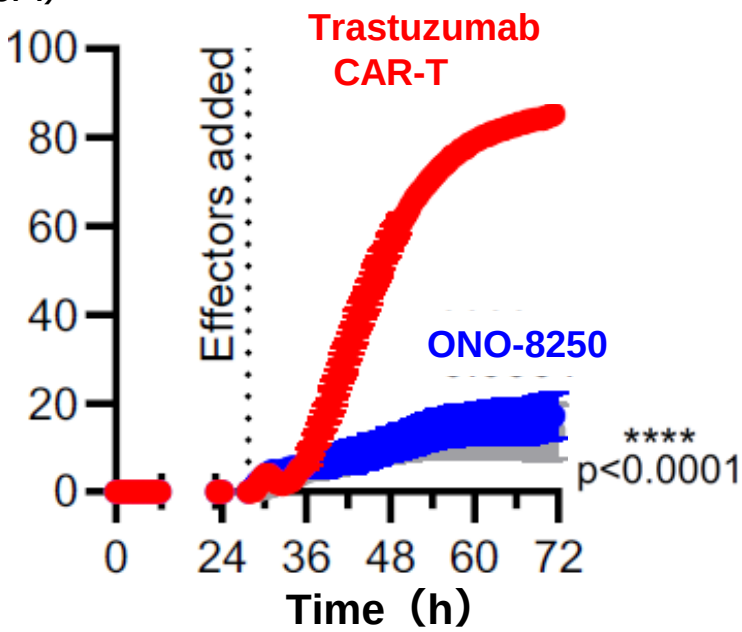
HER2$^{+}$ normal cells (MCF10A)

HER 2 $^{high}$ tumor cells (SKOV3)




HER2$^{+}$ normal cells (MCF10A)



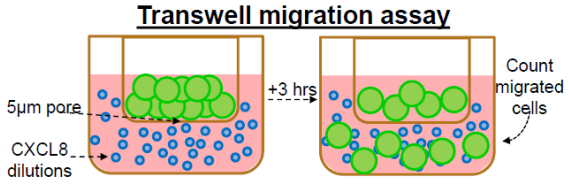




Hosking M, et al. SITC 2023 #268

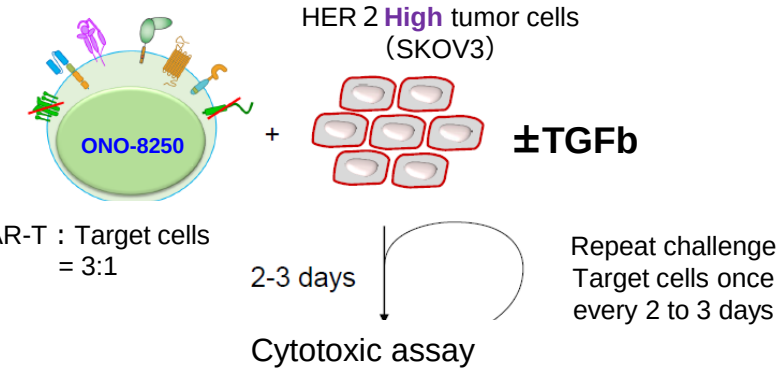
**ONO-8250 which expressed H2CasMab-2 based CAR showed preferential targeting of HER2 on tumor cells and not on normal cells**

# ONO-8250：Multiplex-engineered CAR T designed to address and overcome challenges currently faced by cell therapies in solid tumors

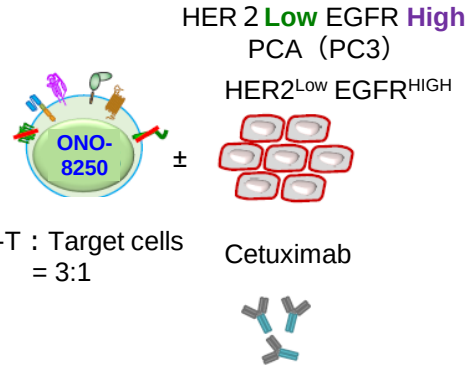
## Promote tumor trafficking (CXCR2)



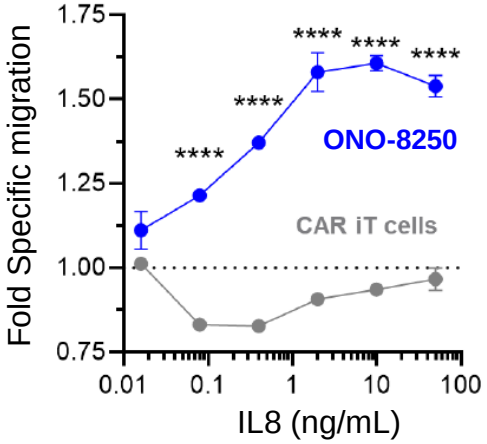

## Resistance to TME Suppression (TGFbR-IL18)



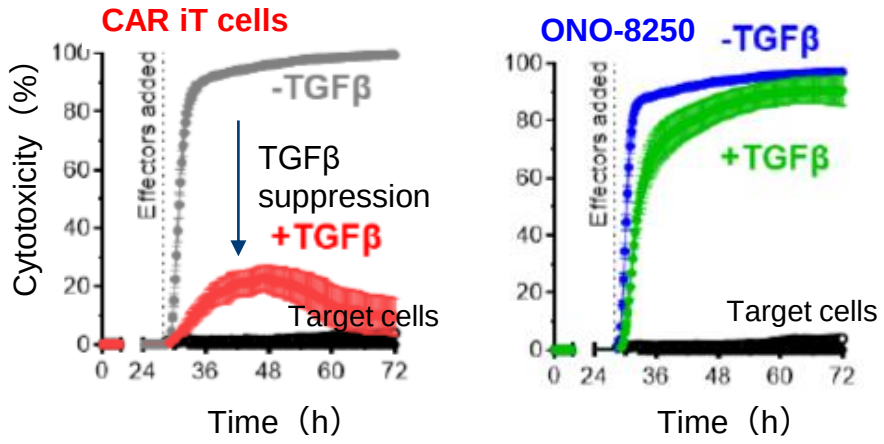

## Multi-antigen Targeting (hnCD16a)



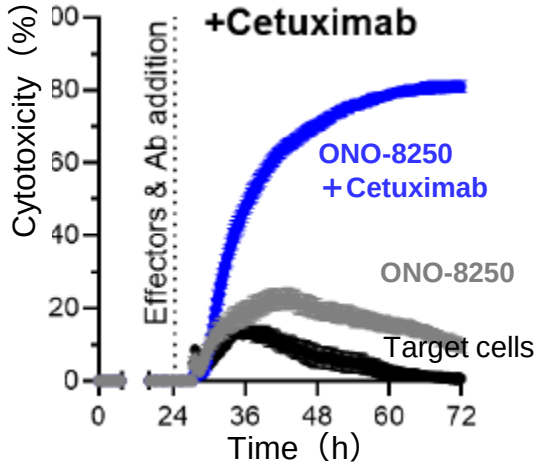

## CXCR2 Expression Enables IL8 (CXCL8) -specific migration




## Resistance to TGFβ Suppression



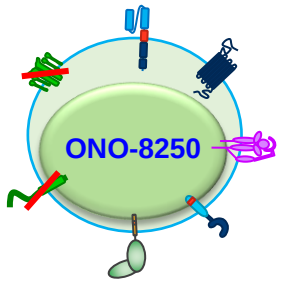

## Combo with Cetuximab




Hosking M, et al. SITC 2023 #268

**The transgenic elements incorporated into ONO-8250 have successfully demonstrated their intended functionality**

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

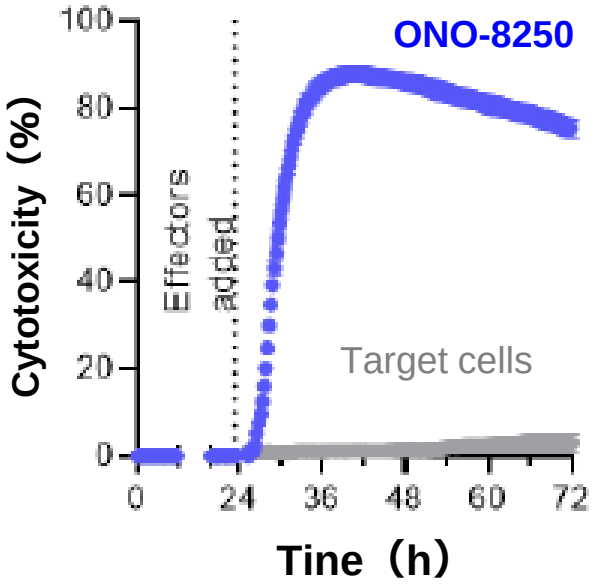



VS

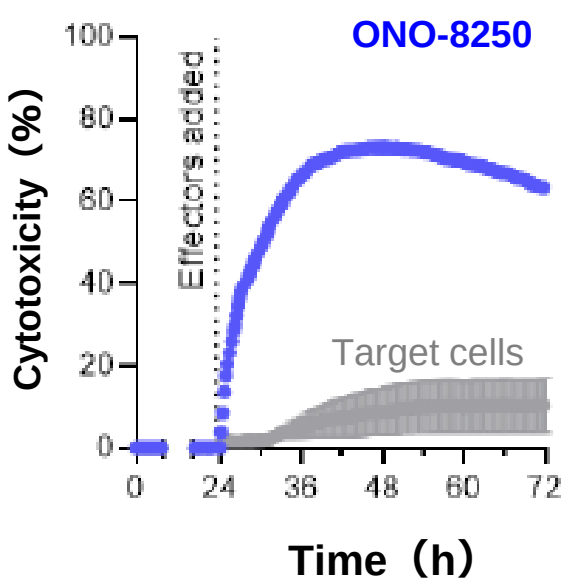
Target cells

CAR-T : Target cells
= 10:1

HER 2 high OVCA
（SKOV3）



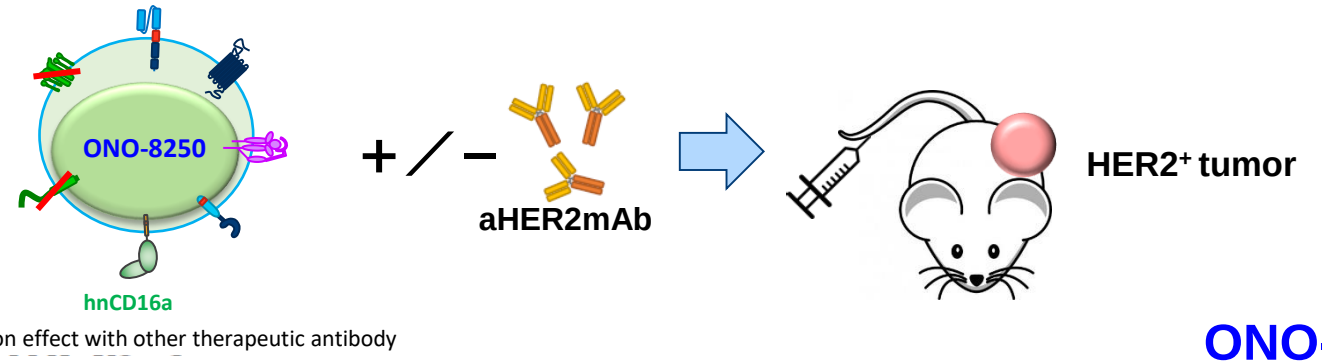

HER 2 Low PCA
（PC3）



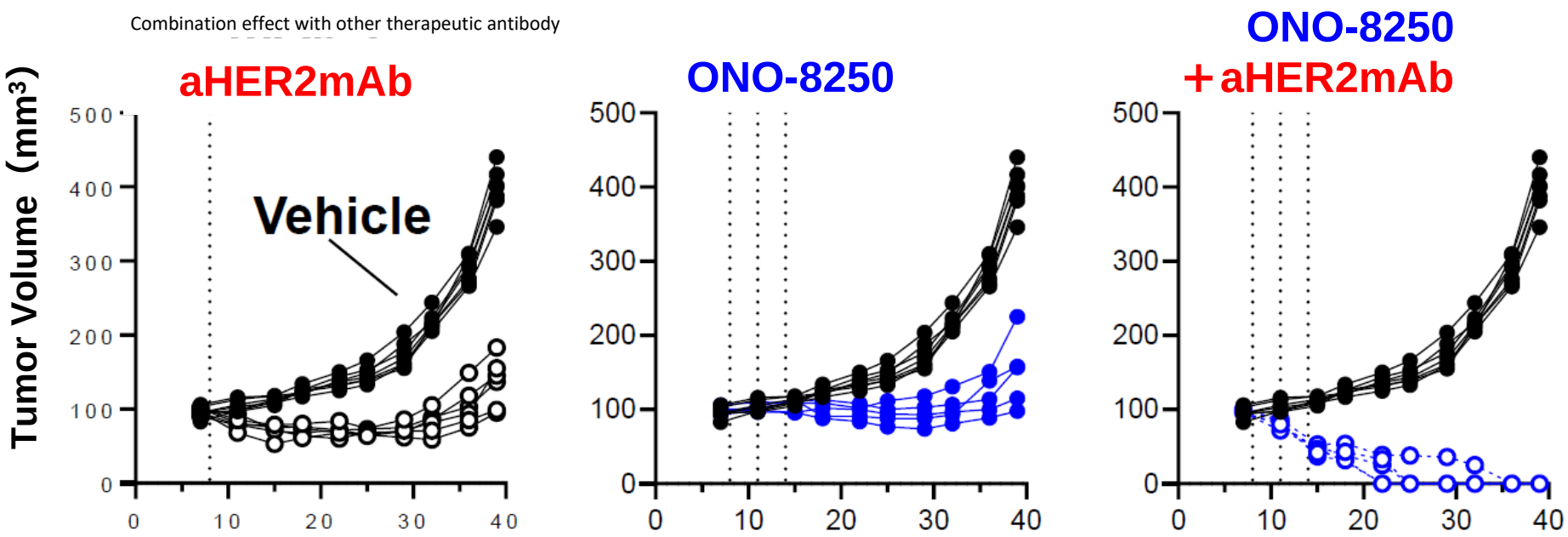

Hosking M, et al. SITC 2023 #268

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

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




Combination effect with other therapeutic antibody




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**

# Discovery Technology and Therapeutic Modalities

**Biologics collaborations**

| | Tech & Seeds | Small Molecule | Peptide | Protein & Antibody | Cell Therapy |
|---|---|---|---|---|---|
| **Cancer** | turbine AI<br>BioMed X | ribon therapeutics<br>KSQ<br>Chordia Therapeutics<br>CANCER RESEARCH UK<br>ONO-7018 | ONO-4685 | macomics<br>NUMAB<br>ADIMAB<br>MEMO THERAPEUTICS AG<br>Merus<br>NUMAB<br>LifeArc | Fate THERAPEUTICS<br>ONO-8250 |
| **Immunology** | | | | NUMAB<br>MONASH University<br>TWIST BIOSCIENCE<br>CUE BIOPHARMA<br>SHATTUCK LABS | |
| **Neurology** | UK Dementia Research Institute<br>precisionlife improving health \| for everyone | Captor Therapeutics<br>Vanderbilt Univ.<br>ARIA PHARMACEUTICALS AI | | neurimmune Promind antibody therapeutics | |
| **Specialty** | | DOMAIN THERAPEUTICS<br>Université de Montréal | | | |
| **Undisclosed** | InveniAI AI<br>knowledge palette<br>MBC biolabs Enabling awesome<br>Lab Central<br>UCDDC | heal AI<br>IKTOS AI<br>Artificial Intelligence for new drug design<br>SCHRÖDINGER<br>Cyclenium pharma | PeptiDream | EVQLV AI<br>MOLCURE AI<br>EMB Epsilon Molecular Engineering<br>Ligand<br>MiraBiologics | |

□ 2023~

# 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<br>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<br>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 |


ONO PHARMACEUTICAL CO.,LTD.
Dedicated to the Fight against Disease and Pain