ONO PHARMACEUTICAL CO., LTD.

R&D Day

June 8, 2026

[Number of Speakers]	4	
	Toichi Takino	Representative Director, President and Chief Operating Officer
	Tatsuya Okamoto	Corporate Officer/Executive Vice President, Clinical Development
	Seishi Katsumata	Corporate Officer/Executive Vice President, Discovery & Research
	Ryuta Imura	Vice President, Corporate Communications

Presentation

Imura: Thank you very much for your participation in today's R&D meeting of ONO PHARMACEUTICAL CO., LTD.

Now, let me introduce today's attendees. Takino, Representative Director, President and COO, Okamoto, Corporate Officer/Executive Vice President, Clinical Development, and Katsumata, Corporate Officer/Executive Vice President, Discovery & Research.

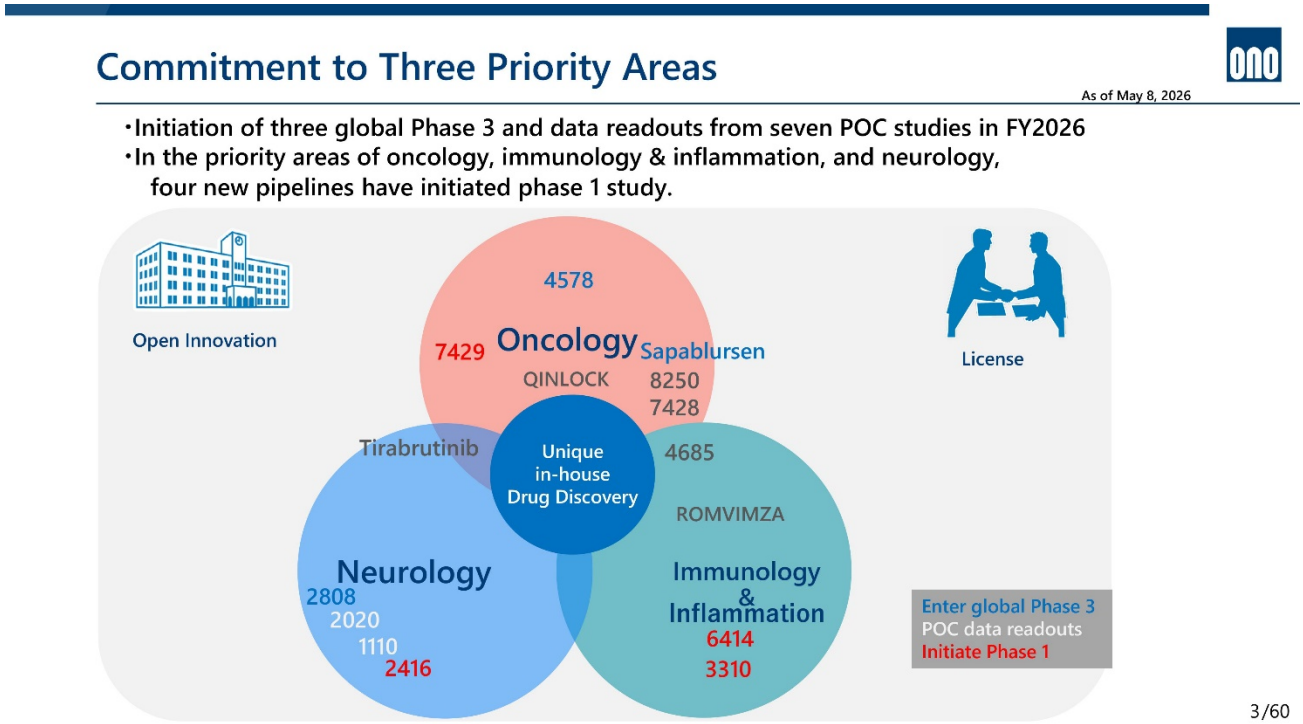
Our president, Takino, will give an opening speech with slides.

Okamoto, Executive Vice President of Clinical Development, will continue by presenting the details of the data from ONO-4578 and ONO-2808, which were recently presented at an academic conference.

After that, Katsumata, Executive Vice President of Discovery & Research, will introduce our drug discovery activities, especially in the field of the central nervous system.

The relevant materials are already posted on our website for your reference.

We would like to begin with an opening speech by Takino, our president.

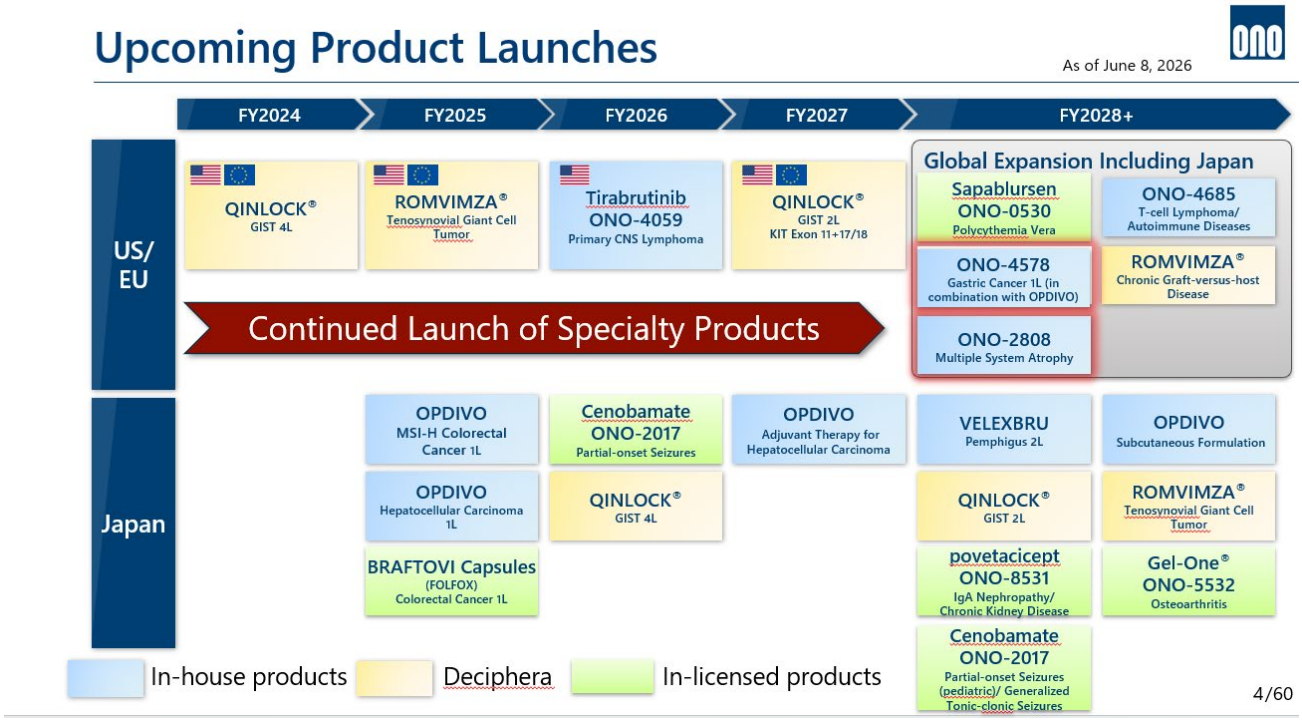


Takino: I'm Takino, and I would like to explain the opening part with a few slides.

Since we do not often have the opportunity to discuss the details of R&D with you, I hope that today's session will provide an opportunity for in-depth discussions and further your understanding of Ono's pioneering new drug development efforts and pipeline.

As you know, our R&D activities are focused on three highly unmet medical needs: oncology, neurology, and immunology and inflammation. We are working to expand the development pipeline, which will be the next growth driver of OPDIVO, through open innovation with academia and bio-ventures, in which we are relatively strong, as well as through licensing and other measures.

In this context, we are particularly looking forward to this year as a year of significant progress in our pipeline. Shown here is a simple diagram, but the project is newly entering Phase 3 of the global project—or proof-of-concept, a new project with a clinical signal. And then we are going into clinical trials again, and this is another new project to start Phase I trials. As these things are progressing in each of these phases, I feel that the pipeline is becoming much thicker.



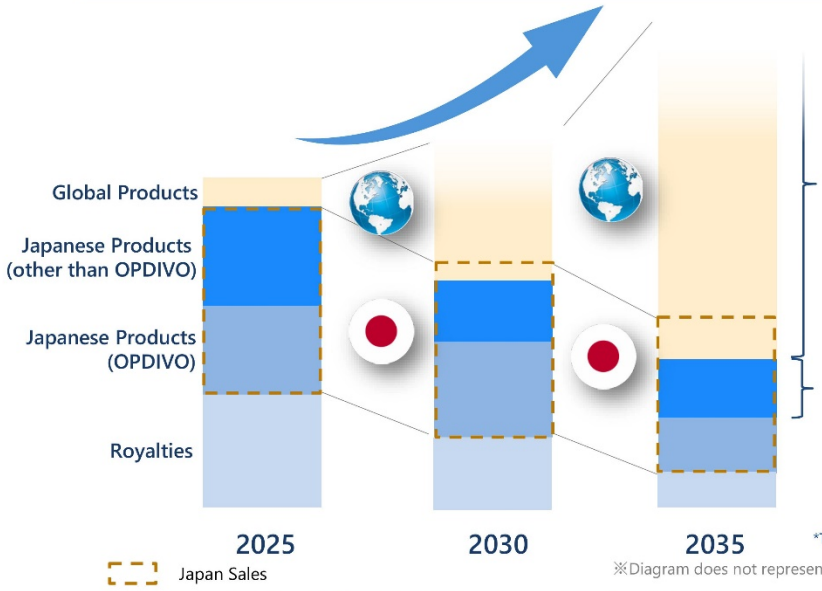
This chart shows the most recent schedule for the launch of each new product.

Although we've categorized them by color, it's not just the yellow Deciphera products or the green in-licensed products; there are also several in-house products in the blue category that we're really looking forward to.

Since the acquisition of Deciphera, we have been working to launch new products in the US and Europe that will steadily satisfy unmet needs, one product at a time, using Deciphera's infrastructure.

As mentioned at the beginning of this presentation, we would like to introduce the recent data on ONO-4578 and ONO-2808 presented by Okamoto from Clinical Development.

Prospect for the Future



※Diagram does not represent actual sales of each product

Growth Drivers

Pipeline	Peak Sales (JPY bn)
Global	
QINLOCK (GIST)	50 – 70
ROMVIMZA (TGCT)	50 – 70
Tirabrutinib (PCNSL)	20 – 30
Sapablursen (PV)	50 – 100
ONO-4578 (GC)	100 -
ONO-2808 (MSA)	100 -
Japan*	
Povetacicept	50 -
Cenobamate	
Gel-One®	

*Total estimated peak sales, including products other than the three listed.

As of May 8, 2026

GIST: Gastrointestinal Stromal Tumor, TGCT: Tenosynovial Giant Cell Tumor, PCNSL: Primary Central Nervous System Lymphoma, PV: Polycythemia Vera, GC: Gastric Cancer, MSA: Multiple System Atrophy

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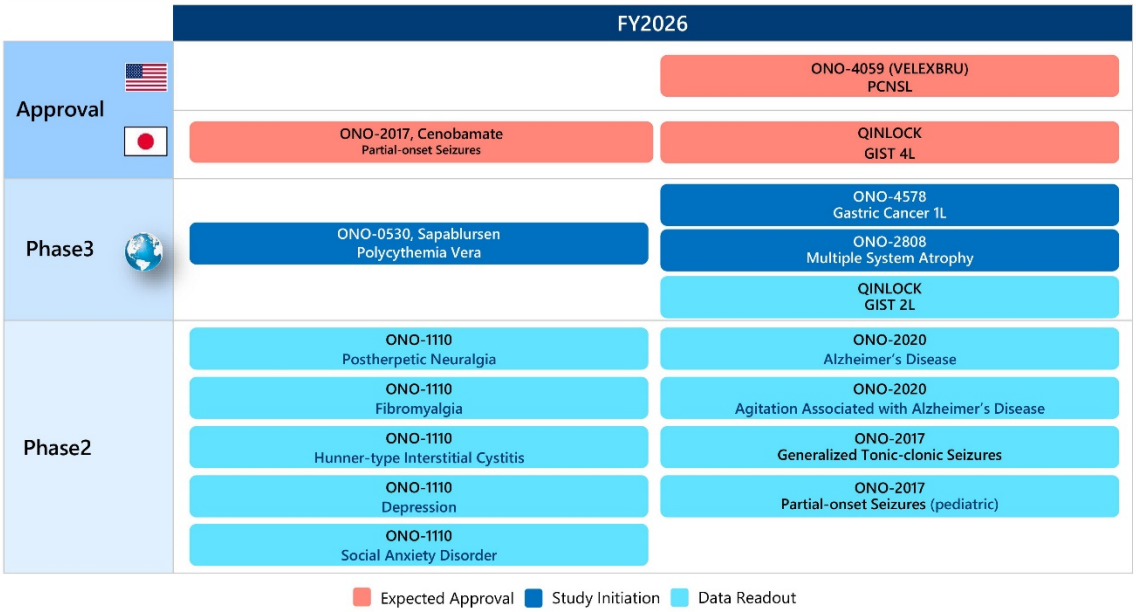
As we have already had several opportunities to explain, this chart shows our future sales and earnings.

While we anticipate a decline in revenue following the expiration of OPDIVO's patent, we are committed to ensuring the steady growth of our global products to minimize this decline and drive future growth beyond OPDIVO. In particular, ONO-4578 and ONO-2808, which we are introducing today, are product candidates with the potential to grow to 100 JPY bn or even more in annual sales respectively if they are successfully launched.

Key Event Schedule for FY2026



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This slide summarizes the key events we expect this fiscal year. In terms of approvals, we anticipate cenobamate for epilepsy in Japan, and ONO-4059, or VELEXBRU, for PCNSL in the US.

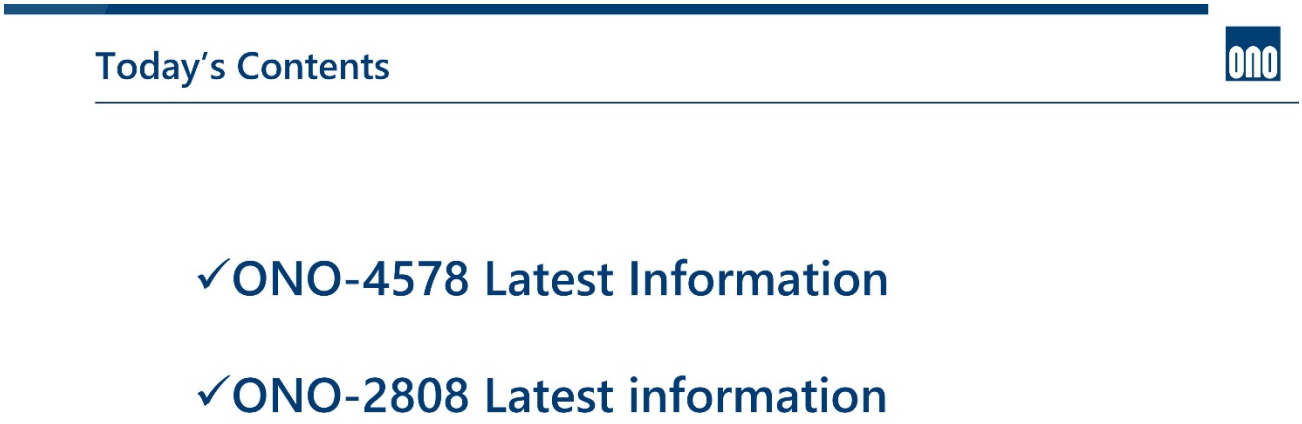
The programs newly entering Phase 3 are Sapablursen, ONO-4578, and ONO-2808. As for Phase 2, results are expected for ONO-1110 and ONO-2020. As these studies cover multiple indications, data from a total of seven POC studies will be released gradually toward the end of the year.

After this, Okamoto from Clinical Development will explain the data of ONO-4578 and ONO-2808, which were presented at a recent conference. Then, Katsumata from Discovery & Research will introduce the recent progress of drug discoveries in neurology, where the pipeline seems to be gaining momentum relatively smoothly these days, including the efforts to date, and I hope that this will provide an opportunity for you to learn more about it.

That concludes my remarks. We hope today's session will provide an opportunity or active discussion on our drug discovery and development and help deepen your understanding of our company.

Imura: Next, Okamoto, Executive Vice President of Clinical Development, will present detailed data on ONO-4578 and ONO-2808.

Okamoto: I am Okamoto from Clinical Development.



Today, I would like to introduce the latest status of ONO-4578 and ONO-2808. Since you may already be familiar with the slides from the conference, I would like to give you a brief overview of the contents and then talk about what we think you will be most interested in.

2026 ASCO ANNUAL MEETING

ONO-4578 combined with nivolumab (NIVO) and chemotherapy (chemo) as First-line (1L) treatment for patients with HER2-negative unresectable advanced or recurrent (adv/rec) gastric/gastroesophageal junction cancer (G/GEJ): A randomized, double-blind, phase 2 trial (ONO-4578-08)

Sung Hee Lim[1*], Izuma Nakayama[2], Min-Hee Ryu[3], Jong Gwang Kim[4], Takeshi Omori[5], Sang Cheul Oh[6], Jin Young Kim[7], Sun Young Rha[8], Keun-Wook Lee[9], Nozomu Machida[10], Sun Jin Sym[11], Yukiya Narita[12], Young-Iee Park[13], Hiroki Hara[14], Hisashi Hosaka[15], Beodeul Kang[16], In-Ho Kim[17], Li-Yuan Bai[18], Kohei Shitara[2], ONO-4578-08 Study Group

[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]National Cancer Center Hospital East, Kashiwa, Japan; [3]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; [4]Kyungpook National University, Daegu, Republic of Korea; [5]Osaka International Cancer Institute, Osaka, Japan; [6]Korea University Guro Hospital, Korea University College of Medicine, Seoul, Republic of Korea; [7]Keimyung University Dongsan Hospital, Daegu, Republic of Korea; [8]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [9]Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Republic of Korea; [10]Kanagawa Cancer Center, Yokohama, Japan; [11]Gachon University Gil Medical Center, Incheon, Republic of Korea; [12]Aichi Cancer Center Hospital, Nagoya, Japan; [13]Research Institute and Hospital, National Cancer Center, Goyang, Republic of Korea; [14]Saitama Cancer Center, Saitama, Japan; [15]Gunma Prefectural Cancer Center, Gunma, Japan; [16]CHA Bundang Medical Center, CHA University, Seongnam, Republic of Korea; [17]Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Republic of Korea; [18]China Medical University Hospital, Taichung, Taiwan

*Presenting

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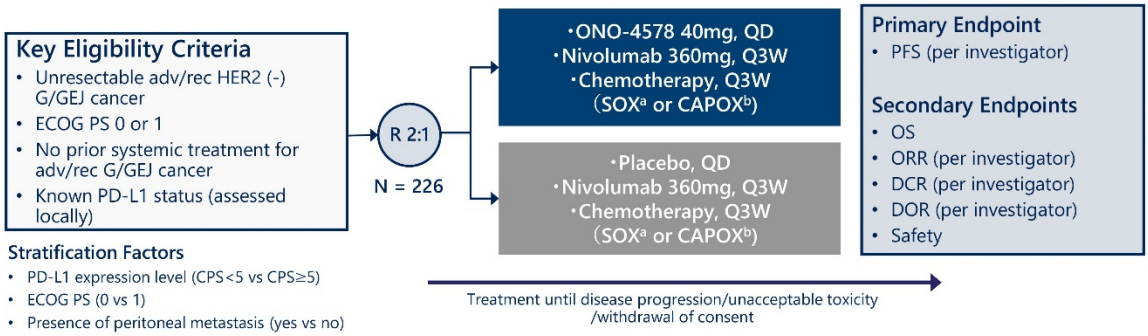
I'd like to walk you through the results of the Phase 2 study of ONO-4578 in first-line treatment for gastric cancer, which were presented orally at ASCO on June 1.

ONO-4578-08 Trial Design

ONO-4578-08: Asian (Japan/Korea/Taiwan), randomized, double-blinded, Phase 2 trial (NCT06256328)



- **Planned sample size: 210 patients, providing ≥70% power (two-sided α=0.10) to detect a HR of 0.65 (median PFS; 12.3 vs 8.0 months) with 117 events**
- **Patients were randomized from December 2023 to September 2024**
- **All analyses are based on a clinical data cutoff of 14th April 2025, with the median PFS follow-up of 8.5 months**

[a]**SOX therapy:** Oxaliplatin 130 mg/m^2 IV once daily (day1), and S-1 40 mg/m^2/dose orally twice daily (day1-14) , Q6W; [b]**CapeOX therapy:** Oxaliplatin 130 mg/m^2 IV once daily (day1), and Capecitabine 1000 mg/m^2/dose orally twice daily (day1-14), Q3W.

Abbreviations: G/GEJ, gastric/gastroesophageal junction; PFS, progression free survival; OS, overall survival; ORR, objective response rate; DCR, disease control rate; DOR, duration of response; Q3W, every 3 weeks; Q6W, every 6 weeks; SOX, S-1 (tegafur/gimeracil/oteracil)/oxaliplatin; CapeOX, capecitabine/oxaliplatin;

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This slide summarizes the trial design.

This was a Phase 2, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of adding ONO-4578 on top of one of the standard first-line regimens for gastric cancer: OPDIVO in combination with chemotherapy. The primary endpoint was PFS assessed by investigators. Key secondary endpoints included OS, objective response rate, and safety.

Demographics and Baseline Characteristics

	ONO-4578 group (n = 150)	Placebo group (n = 76)
Age, median (range), years	66.0 (27–84)	67.5 (36–86)
Male sex	113 (75.3)	64 (84.2)
Country		
Japan	54 (36.0)	37 (48.7)
Korea	87 (58.0)	35 (46.1)
Taiwan	9 (6.0)	4 (5.3)
ECOG PS		
0	78 (52.0)	41 (53.9)
1	72 (48.0)	35 (46.1)
Disease status		
Advanced	103 (68.7)	55 (72.4)
Recurrent	47 (31.3)	21 (27.6)
Primary Tumor location[*1]		
GEJ	17 (16.5)	7 (12.7)
Gastric	82 (79.6)	46 (83.6)
Unknown	4 (3.9)	2 (3.6)
Histologic type (Lauren's criteria)		
Intestinal type	72 (48.0)	31 (40.8)
Diffuse type	67 (44.7)	37 (48.7)
Others	11 (7.3)	8 (10.5)
Peritoneal metastasis		
Yes	82 (54.7)	42 (55.3)
No	68 (45.3)	34 (44.7)

	ONO-4578 group (n = 150)	Placebo group (n = 76)
Number of organs with metastases		
≤1	63 (42.0)	29 (38.2)
>1	87 (58.0)	47 (61.8)
PD-L1 expression level (CPS)		
<1	32 (21.3)	17 (22.4)
≥1 and <5	44 (29.3)	21 (27.6)
≥5	73 (48.7)	36 (47.4)
Indeterminate	1 (0.7)	2 (2.6)
Planned chemotherapy regimen		
SOX	89 (59.3)	45 (59.2)
CapeOX	61 (40.7)	31 (40.8)
Claudin 18.2		
Positive	50 (33.3)	28 (36.8)
Negative	96 (64.0)	47 (61.8)
Not Evaluated	4 (2.7)	1 (1.3)
MSI status[*2]		
MSS	32 (21.3)	19 (25.0)
MSI-low	2 (1.3)	0
MSI-high	4 (2.7)	0
Not determined	2 (1.3)	3 (3.9)

*2 The results of patients who locally underwent MSI test

*1 Primary tumor location was categorized into three groups: gastroesophageal junction (GEJ; ICD-10 C16.0), gastric (C16.1–C16.4), and unknown ; percentages are based on the number of participants with advanced gastric cancer.

- Baseline characteristics were well balanced across the two groups

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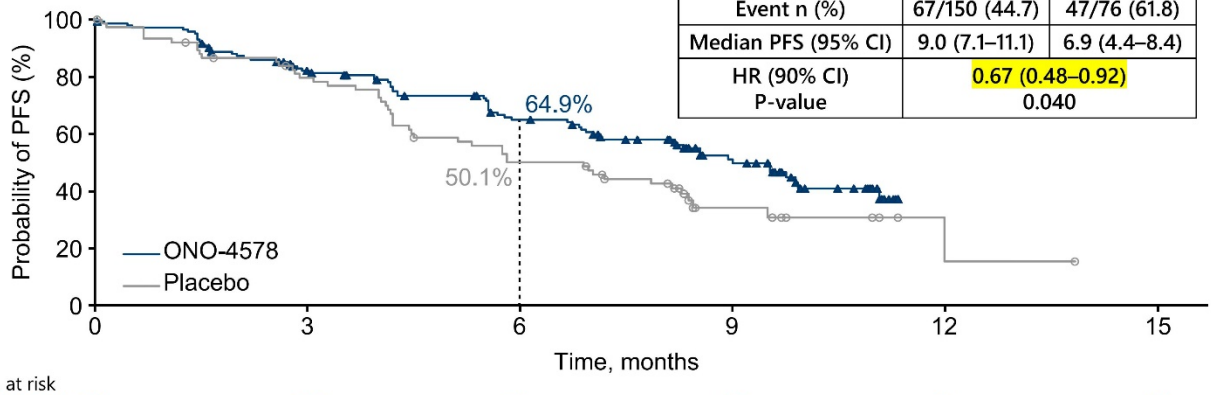
These are the demographics and baseline characteristics of the enrolled patients.

In terms of enrollment, 150 patients were assigned to the ONO-4578 group and 76 to the placebo group, for a total of 226 patients. We believe baseline characteristics were generally well balanced between the two arms.

PFS per investigator : Primary Endpoint

median PFS follow-up of 8.5 months

	ONO-4578 group	Placebo group
Event n (%)	67/150 (44.7)	47/76 (61.8)
Median PFS (95% CI)	9.0 (7.1–11.1)	6.9 (4.4–8.4)
HR (90% CI)	0.67 (0.48–0.92)	
P-value	0.040	



No. at risk

ONO-4578	150	106	77	37	0	0
Placebo	76	57	35	10	1	0

- **ONO-4578 group demonstrated a statistically significant improvement in PFS compared with placebo group**

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Let me now move to the efficacy results.

First, the primary endpoint, PFS per investigator. The median PFS was 9.0 months in the ONO-4578 group versus 6.9 months in the placebo group. The hazard ratio versus placebo, as highlighted in yellow, was 0.67, showing a statistically significant difference. In other words, the study met its primary endpoint.

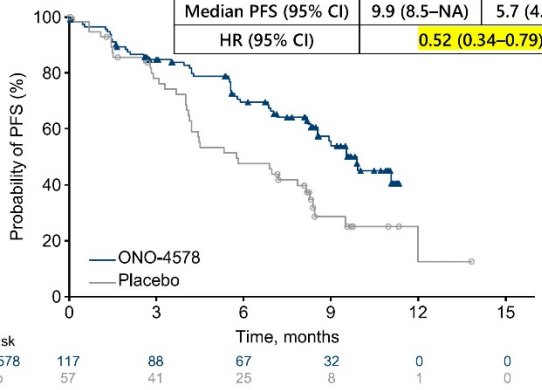
I will come back later to the question of whether these median PFS values appear “long” or “short,” although there will probably be some debate.

PFS by PD-L1 CPS (≥1 vs <1)

median PFS follow-up of 8.5 months

CPS≥1

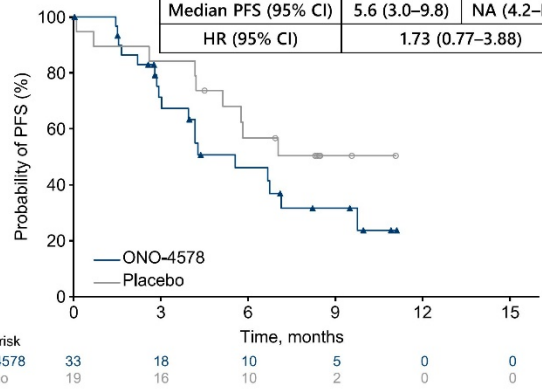
	ONO-4578 group	Placebo group
Event n (%)	49/117 (41.9)	38/57 (66.7)
Median PFS (95% CI)	9.9 (8.5–NA)	5.7 (4.1–8.3)
HR (95% CI)	0.52 (0.34–0.79)	



No. at risk						
ONO-4578	117	88	67	32	0	0
Placebo	57	41	25	8	1	0

CPS<1 or Indeterminate

	ONO-4578 group	Placebo group
Event n (%)	18/33 (54.5)	9/19 (47.4)
Median PFS (95% CI)	5.6 (3.0–9.8)	NA (4.2–NA)
HR (95% CI)	1.73 (0.77–3.88)	



No. at risk						
ONO-4578	33	18	10	5	0	0
Placebo	19	16	10	2	0	0

- PFS benefit of the ONO-4578 group appeared to be more pronounced in patients with CPS ≥1

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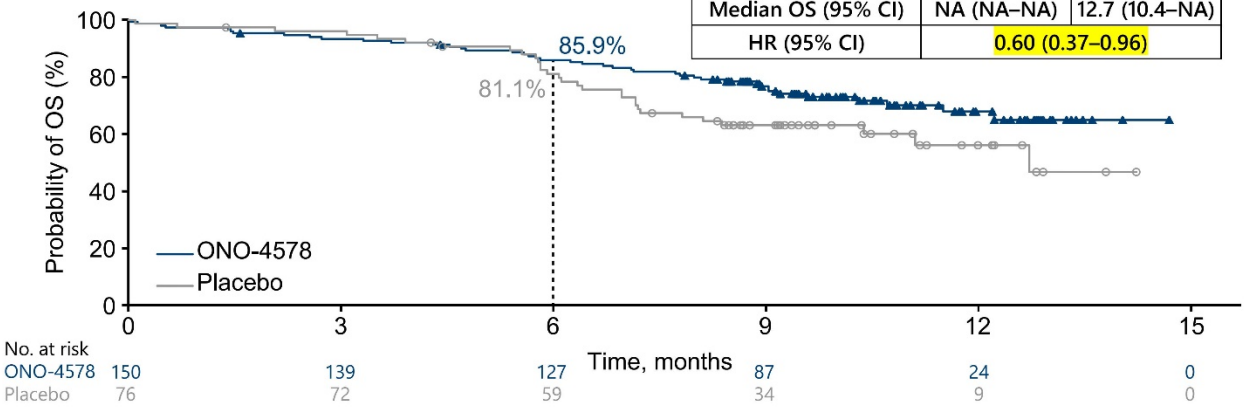
This slide shows the subgroup analysis for PFS.

Results are shown for CPS-positive and CPS-negative populations. In the CPS-positive population, the hazard ratio for PFS was 0.52, which is highlighted, indicating a marked improvement.

In the CPS-negative population, the placebo group appeared numerically better.

OS : Secondary Endpoint

	ONO-4578 group	Placebo group
Event n (%)	42/150 (28.0)	30/76 (39.5)
Median OS (95% CI)	NA (NA–NA)	12.7 (10.4–NA)
HR (95% CI)	0.60 (0.37–0.96)	



- Although OS data are immature (minimum FU: 7.4 months) and should be interpreted with caution, OS favored the ONO-4578 group compared with the placebo group

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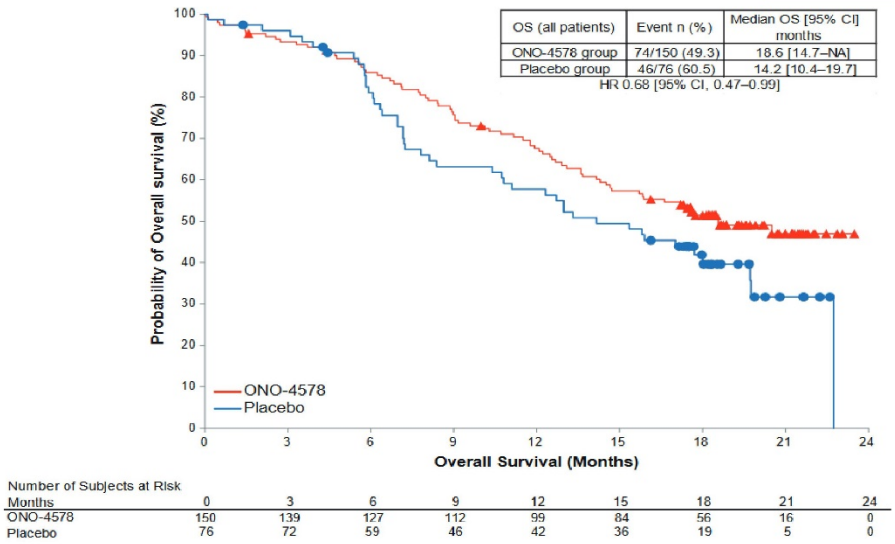
This shows OS in the overall population.

As you can see on the right side, at the time of this analysis, the minimum follow-up was short, with a minimum of 7.4 months, there was substantial censoring. So, the OS data was immature. Median OS was 12.7 months in the placebo group, while it was not reached in the ONO-4578 group, with a hazard ratio of 0.60.

Post-hoc extended OS

minimum OS follow-up of 16.1 months



Nakayama I, Ryu M-H, Lim S H, et al. Journal of Clinical Oncology10.1200/JCO-26-01072R1 Epub 2026 June 1.

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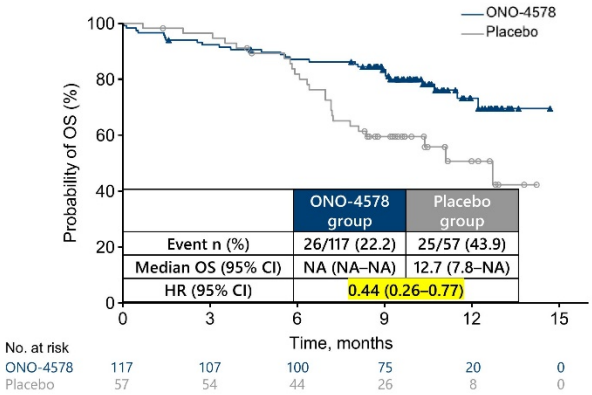
I just mentioned that OS was immature. The data were published at the same time as the ASCO presentation in the JCO, the Journal of Clinical Oncology, including updated OS follow-up.

Minimum follow-up period, compared to a presentation at ASCO, is highlighted at upper right. Compared with the ASCO cut, the minimum follow-up period was more than doubled. In that dataset, median OS in the ONO-4578 group was also reached, at 18.6 months. The hazard ratio was 0.68, and we believe the OS benefit remains favorable.

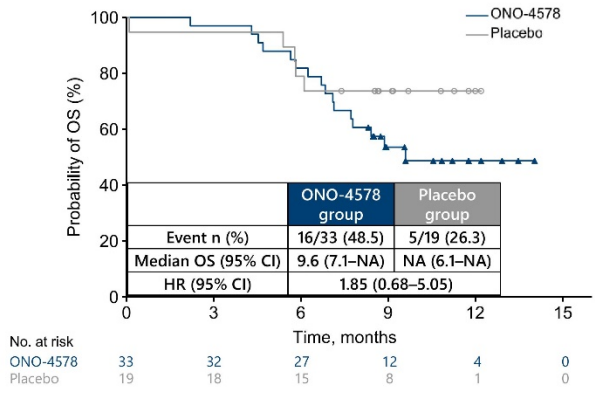
Overall Survival by PD-L1 CPS (≥1 vs <1)

CPS≥1



	ONO-4578 group	Placebo group
Event n (%)	26/117 (22.2)	25/57 (43.9)
Median OS (95% CI)	NA (NA–NA)	12.7 (7.8–NA)
HR (95% CI)	0.44 (0.26–0.77)	

CPS<1 or Indeterminate



	ONO-4578 group	Placebo group
Event n (%)	16/33 (48.5)	5/19 (26.3)
Median OS (95% CI)	9.6 (7.1–NA)	NA (6.1–NA)
HR (95% CI)	1.85 (0.68–5.05)	

- As with the PFS, the efficacy of the ONO-4578 group was more marked in patients with CPS ≥1

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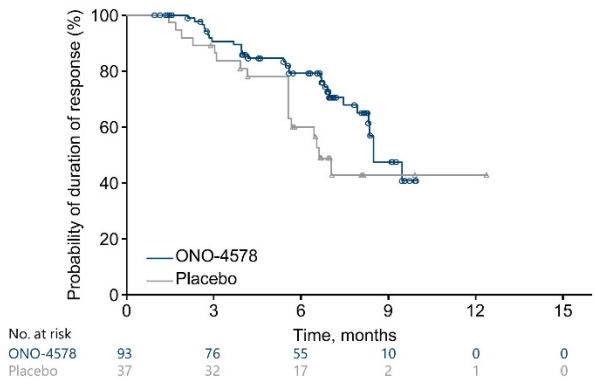
Going back to the ASCO presentation, this slide shows the subgroup analysis for OS.

As with PFS, the CPS-positive population showed a pronounced OS benefit, with a hazard ratio of 0.44, meaning a more than 50% reduction in the risk of death. I have to say this is an exceptional number.

Summary of Anti-tumor Response

	ONO-4578 group (n = 150)	Placebo group (n = 76)
ORR (95% CI), %	62.0 (53.7–69.8)	48.7 (37.0–60.4)
Odds ratio (95% CI)	1.72 (0.98–3.00)	
BOR, n (%)		
CR	4 (2.7)	0
PR	89 (59.3)	37 (48.7)
SD	31 (20.7)	26 (34.2)
PD	12 (8.0)	9 (11.8)
NE	14 (9.3)	4 (5.3)
DOR, median (95% CI), months	8.5 (8.3–N.A.)	6.6 (5.6–N.A.)



	CPS≥1		CPS<1	
	ONO-4578 group (n = 117)	Placebo group (n = 57)	ONO-4578 group (n = 33)	Placebo group (n = 19)
ORR (95% CI), %	70.9 (61.8–79.0)	50.9 (37.3–64.4)	30.3 (15.6–48.7)	42.1 (20.3–66.5)
Odds ratio (95% CI)	2.36 (1.22–4.54)		0.60 (0.18–1.94)	

- The ONO-4578 group showed higher ORR and longer DOR compared with the placebo group

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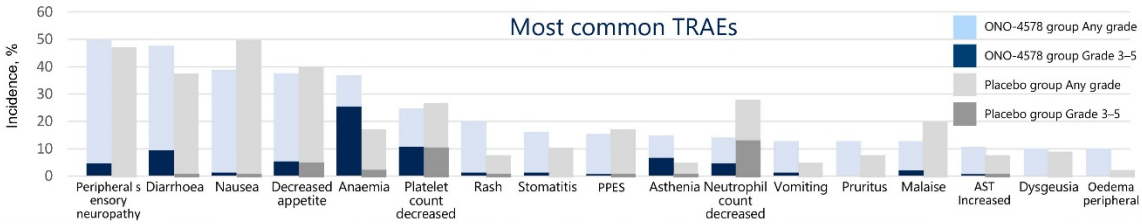
This is the final efficacy slide. It shows the objective response rate and duration of the response.

I'd like to highlight the response rate by CPS. In the CPS-positive population, while the placebo group had a response rate of 50.9%, the treatment group showed a response rate of 70.9%, indicating a 20% increase in efficacy.

Overall Safety Summary

All treated	ONO-4578 group (n = 149)		Placebo group (n = 75)	
	Any grade	Grade3–5	Any grade	Grade3–5
Any AEs	149 (100.0)	118 (79.2)	75 (100.0)	52 (69.3)
Serious AEs	80 (53.7)	72 (48.3)	32 (42.7)	26 (34.7)
AEs leading to death	12 (8.1)		3 (4.0)	
Any TRAEs	146 (98.0)	89 (59.7)	74 (98.7)	37 (49.3)
Serious TRAEs	51 (34.2)	46 (30.9)	19 (25.3)	16 (21.3)
TRAEs leading to discontinuation of ONO-4578/Placebo	12 (8.1)	7 (4.7)	1 (1.3)	1 (1.3)
TRAEs leading to discontinuation of nivolumab/chemotherapy	58 (38.9)	24 (16.1)	20 (26.7)	6 (8.0)
TRAEs leading to death	4 (2.7)		2 (2.7)	



- TRAEs leading to death were pneumonia klebsiella, febrile neutropenia and hepatitis in the ONO-4578 group, pneumonia interstitial and pneumonia in the placebo group
- The safety profile of ONO-4578 regimen appeared manageable with appropriate supportive care

Abbreviations: PPES, Palmar-plantar erythrodysaesthesia syndrome; AST, Aspartate aminotransferase 19/60

This is the last part of the ASCO presentation: safety.

Since this is an add-on study, in which ONO-4578 was added to the standard treatment regimen of OPDIVO combined with chemotherapy, it is expected that the ONO-4578 group would have a higher incidence of adverse events than the placebo group. Overall, however, the conclusion was that the safety profile was manageable and there was no problem.

That concludes my overview of the ASCO presentation.

[Prognostic Factors] Comparison with Checkmate-649 study (CM649)

- ✓ The proportion of patients aged ≥65, with diffuse type and peritoneal metastasis was approximately 10–30% higher than in CM649.
- ✓ The proportion of patients with PS 1 and ≥2 metastatic organs was approximately 10–20% lower than in CM649.

	ONO-4578-08 (Investigator-assessed CPS)		Checkmate-649 (Centrally-assessed CPS)	
	ONO-4578 group N=150	Placebo group N=76	Nivo + chemo N=789	chemo N=792
Age ≥65	80 (53.3%)	49 (64.5%)	316 (40%)	304 (38%)
ECOG PS 1				
0	78 (52.0%)	41 (53.9%)	326 (41%)	336 (42%)
1	72 (48.0%)	35 (46.1%)	462 (59%)	452 (57%)
Histologic type (Lauren's criteria)				
Intestinal type	72 (48.0%)	31 (40.8%)	272 (34%)	267 (34%)
Diffuse type	67 (44.7%)	37 (48.7%)	254 (32%)	273 (34%)
Others	11 (7.3%)	8 (10.5%)	263 (33%)	252 (32%)
Presence of peritoneal metastasis	82 (54.7%)	42 (55.3%)	188 (24%)	188 (24%)
Number of organs with metastases				
≤1	63 (42.0%)	29 (38.2%)	164 (21%)	183 (23%)
≥2	87 (58.0%)	47 (61.8%)	602 (76%)	583 (74%)

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From here, I would like to go a little further into areas that may be of particular interest to you and share additional perspectives.

Earlier, I discussed the point of whether the median PFS is long or short, which has been a topic of debate. This compares our results with those from other trials evaluating first-line treatment for gastric cancer, specifically, the CheckMate-649 study conducted by Ono and BMS. As you all know, for time-to-event endpoints such as PFS and OS, direct cross-trial comparisons are inherently difficult, and the interpretation requires caution.

What is shown here is a comparison of patient demographics from the CheckMate-649 study and the present ONO-4578 POC study. The factors shown here have all been reported in some literature that this affects the prognosis of gastric cancer.

As you can see, there are differences between the two studies. For example, peritoneal metastasis—an allocation factor in our study because we consider it particularly prognostic in ONO-4578 POC trial—differs by roughly 30 percentage points between the two studies.

Our impression is that the patients enrolled in this study, tended to have a somewhat poor-prognosis than those in previous Phase 3 trials of PD-1 antibody drugs, including CheckMate-649. In other words, we consider that we were able to show good results for time-to-event endpoints such as PFS and OS, even though the baseline situation was somewhat unfavorable.

Although, as I just mentioned, cross-trial comparisons about median OS and PFS should be interpreted with caution, for reference, we have summarized the results of prior Phase 3 trials of PD-1 antibodies together with the results of the present ONO-4578 study.

What I would like to highlight here is the hazard ratios in the PD-L1–positive population across these trials. In Phase 3 trials of anti–PD-1 antibodies, chemotherapy, which was the standard of care at the time, was used as the control, and the added benefit of PD-1 antibodies was evaluated.

The results generally show risk reductions versus control in the range of low-to-mid 20% for both OS and PFS.

In contrast, for ONO-4578, while this is a Phase 2 study and therefore smaller in scale, the hazard ratio for OS was 0.44, corresponding to a 56% reduction in the risk of death. The hazard ratio for PFS was 0.52, a 48% reduction in the risk of progression or death. Importantly, whereas chemotherapy alone was used as the control in earlier trials, the hazard ratios in this ONO-4578 POC study were obtained against a control of combination therapy with an anti–PD-1 antibody and chemotherapy.

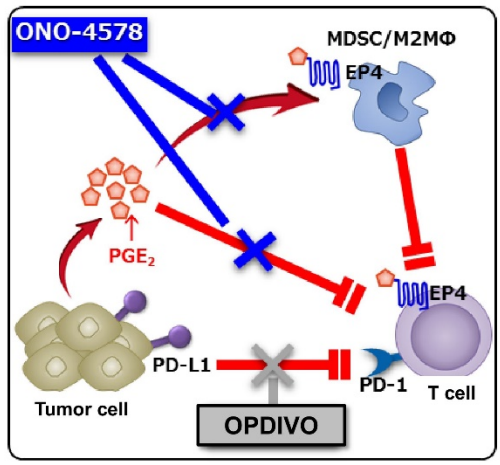
In addition, the response rate, which is a time-independent efficacy measure, improved by approximately 20%. Overall, we believe these ONO-4578 POC results in the PD-L1–positive population were truly excellent, and as we have said stated previously, we believe we can move into Phase 3 with confidence.

Mechanism of ONO-4578

- Prostaglandin E_2 (PGE_2) is derived from arachidonic acid via cyclooxygenase-2 (COX-2).
- COX-2 is overexpressed in solid tumor.[1] PGE_2PGE2 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 PGE2 constructs via EP4.

Concept: Addressing limitations of PD-1 antibody therapy alone

- **Increasing patients responding to PD-1 antibody therapy to improve response rates**
- **Reducing patients losing response to PD-1 antibody therapy to prolong progression-free survival (PFS)**



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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This slide shows the mechanism of action of ONO-4578.

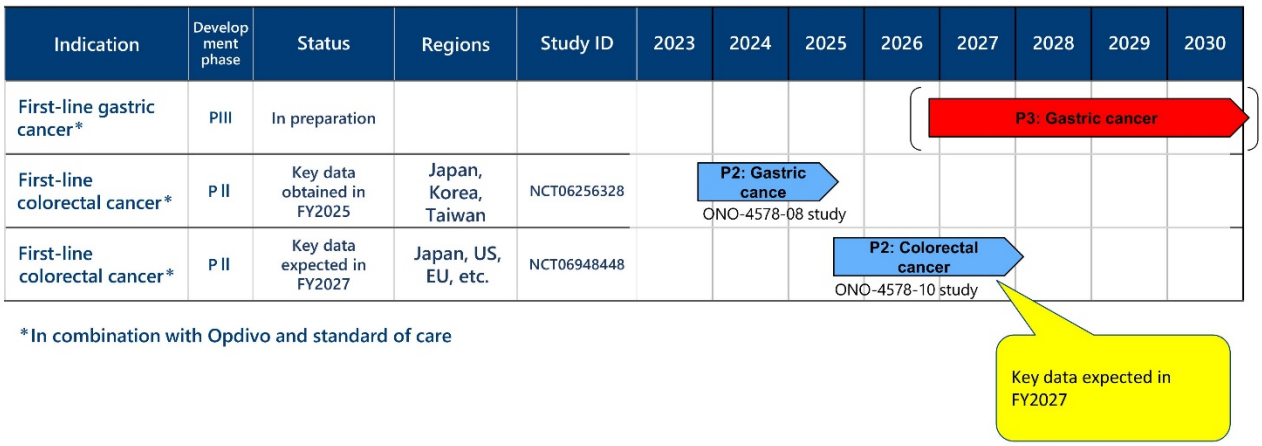
Simply put, ONO-4578 activates anti-tumor immunity through a pathway different from anti–PD-1 antibodies such as OPDIVO. In other words, we believe it has the potential to address challenges that PD-1 antibodies alone cannot overcome.

Anti-PD-1 antibodies have become a standard treatment option across many tumor types. However, from the beginning, it has been recognized that some patient populations have limited responsiveness. In addition, this is not unique to PD-1 antibodies but is a general issue with anticancer therapies, where resistance can develop and treatment becomes less effective over time.

We believe that one contributing factor is tumor immune suppression driven by PGE2. This has been the rationale behind the development of ONO-4578. As shown earlier, the Phase 2 results demonstrated substantial improvements in OS and PFS, along with an improvement in response rate. At least in gastric cancer, we believe this provides support for our concept.

ONO-4578 Development Status

Indication	Development phase	Status	Regions	Study ID
First-line gastric cancer*	PIII	In preparation		
First-line colorectal cancer*	P II	Key data obtained in FY2025	Japan, Korea, Taiwan	NCT06256328
First-line colorectal cancer*	P II	Key data expected in FY2027	Japan, US, EU, etc.	NCT06948448



*In combination with Opdivo and standard of care

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I would like to touch briefly on future plans.

First of all, as President Takino mentioned at the beginning of this presentation, for first-line gastric cancer, we are currently preparing to initiate a Phase 3 study within this fiscal year. We have already discussed the study design with the US regulatory authorities. The target population is patients who receive anti-PD-1 antibody therapy in combination with chemotherapy as a first-line treatment, that is, the CPS-positive population.

Next, for colorectal cancer, we are currently conducting a proof-of-concept study in patients with PD-L1 positive disease receiving first-line treatment. We expect to obtain the POC results within the next fiscal year.

ESMO GASTROINTESTINAL CANCERS
Annual Congress
MUNICH GERMANY
26-29 JUNE 2024

Safety, Efficacy, And Biomarkers Of ONO-4578, An EP4 Antagonist, In Combination With Nivolumab And Chemotherapy In Treatment-naive And Proficient Mismatch Repair (pMMR)/Microsatellite Stable (MSS) Metastatic Colorectal Cancer (mCRC)

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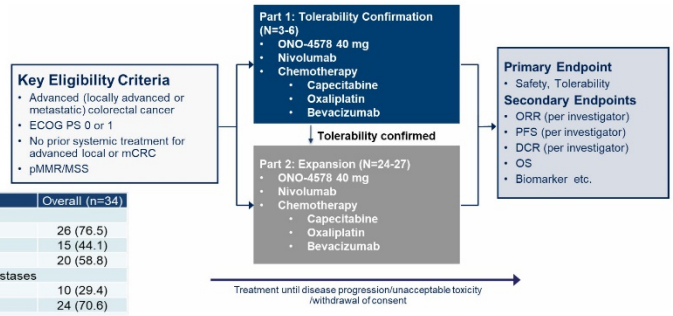
On colorectal cancer, I'd like to take this opportunity to revisit data we previously announced.

At ESMO GI, held in Munich in June 2024, we presented results from a Phase I study conducted in Japan.

Study Design & Patient Characteristics

- The ONO-4578-02 study (NCT06547385) was an open-labelled, phase 1 study, conducted at 9 sites in Japan
- The minimum follow-up was 15.0 months at data cutoff (July 21, 2023)
- Patients with high frequency microsatellite instability (MSI-H) or mismatch repair mechanism deficiency (dMMR) were excluded per protocol



Characteristics	Overall (n=34)
Age (years)	
Median	66.0
Min-Max	40-80
Sex	
Female	17 (50.0)
Male	17 (50.0)
ECOG PS at baseline	
0	30 (88.2)
1	4 (11.8)
Initial or recurrent	
Initial	31 (91.2)
Recurrent	3 (8.8)
Organ location of initial disease	
Left	26 (76.5)
Rectum	16 (47.1)
Sigmoid colon	9 (26.5)
Rectosigmoid Junction	1 (2.9)
Right	8 (23.5)
Cecum	3 (8.8)
Ascending colon	2 (5.9)
Transverse colon	3 (8.8)
Disease stage	
IV	31 (91.2)
Missing	3 (8.8)

Characteristics	Overall (n=34)
Organ location of metastasis	
Liver	26 (76.5)
Lung	15 (44.1)
Lymph node	20 (58.8)
Number of organs showing metastases	
≤1	10 (29.4)
≥2	24 (70.6)
Prior treatment	
Colorectal cancer specific surgeries	8 (23.5)
Radiotherapies	0
Colorectal cancer specific medications	2 (5.9)
BRAF mutation status	
V600E	3 (8.8)
Wild type/No mutation	31 (91.2)
RAS mutation status[a]	
Mutated	21 (61.8)
Wild type	13 (38.2)
PD-L1 CPS	
<1	14 (41.2)
≥1	17 (50.0)
Indeterminate/Unknown	1 (2.9)
Missing	2 (5.9)
TMB (Muts/Mb)	
<10	29 (85.3)
≥10	0
Missing	5 (14.7)

Data presented as n (%) unless specified otherwise; [a]*RAS* mutation present means *KRAS* or *NRAS* mutation present; CPS, combined positive score; ECOG PS, eastern cooperative oncology group performance status; Min, minimum; Max, maximum; Muts/Mb, mutations per megabase; PD-L1, programmed cell death-ligand 1; TMB, tumour mutation burden

This study, called ONO-4578-02, evaluated the safety and exploratory efficacy of OPDIVO and ONO-4578 in combination with standard chemotherapy in first-line colorectal cancer, specifically fluoropyrimidine and oxaliplatin. A total of 34 patients were enrolled.

Results: Efficacy (Overall Population)

	n (%)	[95% CI]
Objective response rate[a]	25 (73.5)	[55.6, 87.1]
Disease control rate[a]	31 (91.2)	[76.3, 98.1]
Best overall response[a]		
Complete Response	0	[0.0, 10.3]
Partial Response	25 (73.5)	[55.6, 87.1]
Stable Disease	6 (17.6)	[6.8, 34.5]
Progressive Disease	2 (5.9)	-
Not Evaluable	1 (2.9)	-
Progression free survival in months[b]		
Median [95% CI]	12.3	[7.0, 17.1]
Progression free survival rate[b]		
At 6 months (%) [95% CI]	84.7	[67.1, 93.4]
At 12 months (%) [95% CI]	50.3	[31.2, 66.7]

[a]by Clopper-Pearson method ; [b]by Kaplan-Meier method; CI, confidence interval

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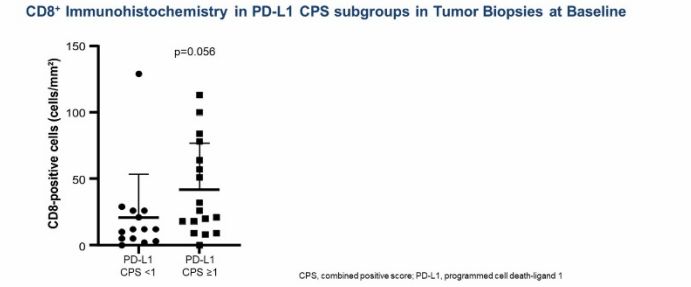
This slide shows efficacy in the overall population.

The objective response rate was 73.5% in the overall population. Prior reports for “chemotherapy alone” show a response rates—from the mid-40% range up to 70%. So, the interpretation of 73.5% is not straightforward. Still, our overall impression was that these results were encouraging.

Results: Efficacy & BM Analysis (CPS-Positive/Negative)

	PD-L1 CPS ≥1 (n=17)	PD-L1 CPS <1 (n=14)
Objective response rate, n (%) [95% CI][a]	15 (88.2) [63.6, 98.5]	9 (64.3) [35.1, 87.2]
Progression free survival in months[b]		
Median [95% CI]	12.3 [6.9, NA]	7.4 [6.9, NA]
Progression free survival rate		
At 6 months (%) [95% CI]	88.2 [60.6, 96.9]	85.7 [53.9, 96.2]
At 12 months (%) [95% CI]	57.4 [30.6, 77.0]	46.8 [19.6, 70.2]

[a]by Clopper-Pearson method; [b]by Kaplan-Meier method; CI, confidence interval, CPS, combined positive score; NA, not available; PD-L1, programmed cell death-ligand 1



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What I would particularly like you to focus on is CPS-positive versus CPS-negative .

You may notice some similarities, as this resembles the subgroup analysis seen earlier in gastric cancer.

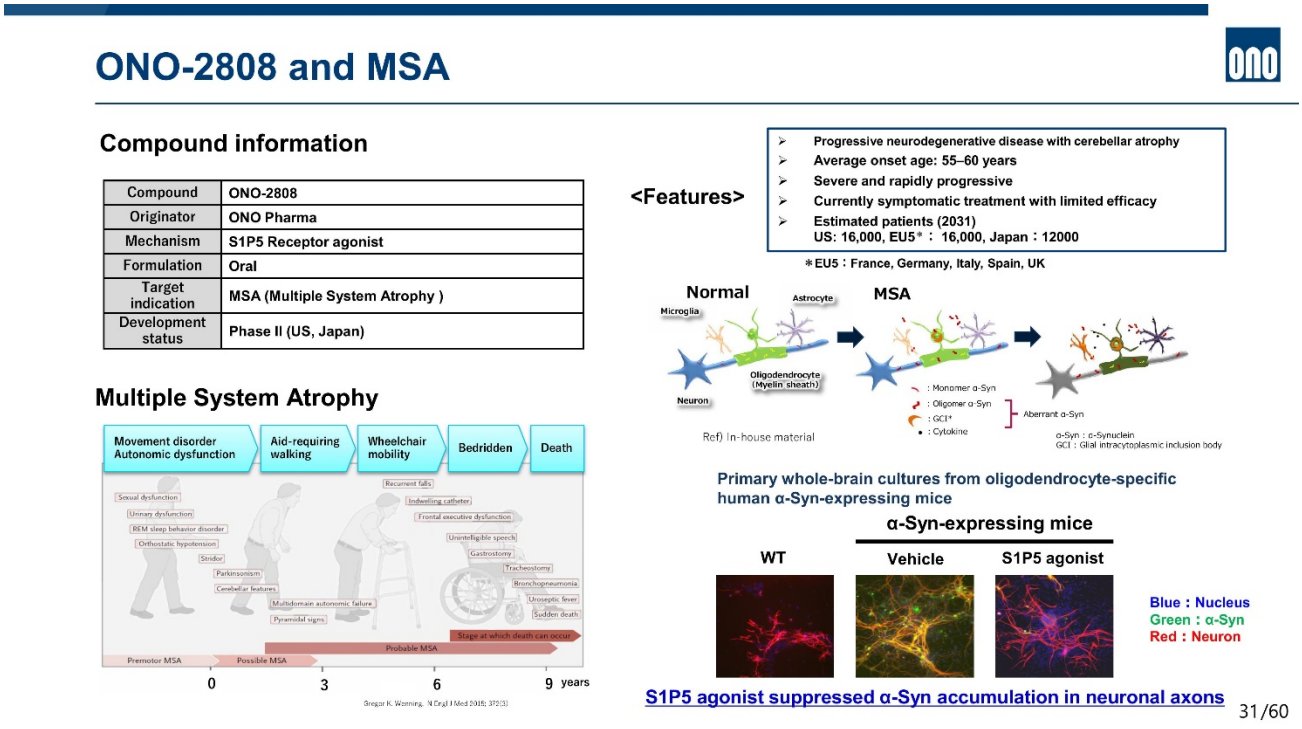
The response rate was 88.2% in the CPS-positive population, compared with 64.3% in the CPS-negative population. In addition, biomarker analyses using tumor biopsy samples showed greater T-cell infiltration in the CPS-positive population.

We previously mentioned that the concept of ONO-4578 was confirmed in gastric cancer. In MSS colorectal cancer, that is, non-MSI colorectal cancer, where T-cell infiltration is present, PD-1 antibodies have generally shown limited efficacy.

However, as you can see, a very high response rate was achieved in the CPS-positive population. We believe these results are consistent with those seen in the Phase 2 gastric cancer study.

In other words, the high response rate in the PD-L1-positive population, where the PD-1 antibodies are expected to be more effective, is very promising for future development. Confirmation of the ONO-4578 concept in gastric cancer is also encouraging, suggesting that it may be applicable to colorectal cancer. We are very much looking forward to the POC results in first-line colorectal cancer expected next fiscal year.

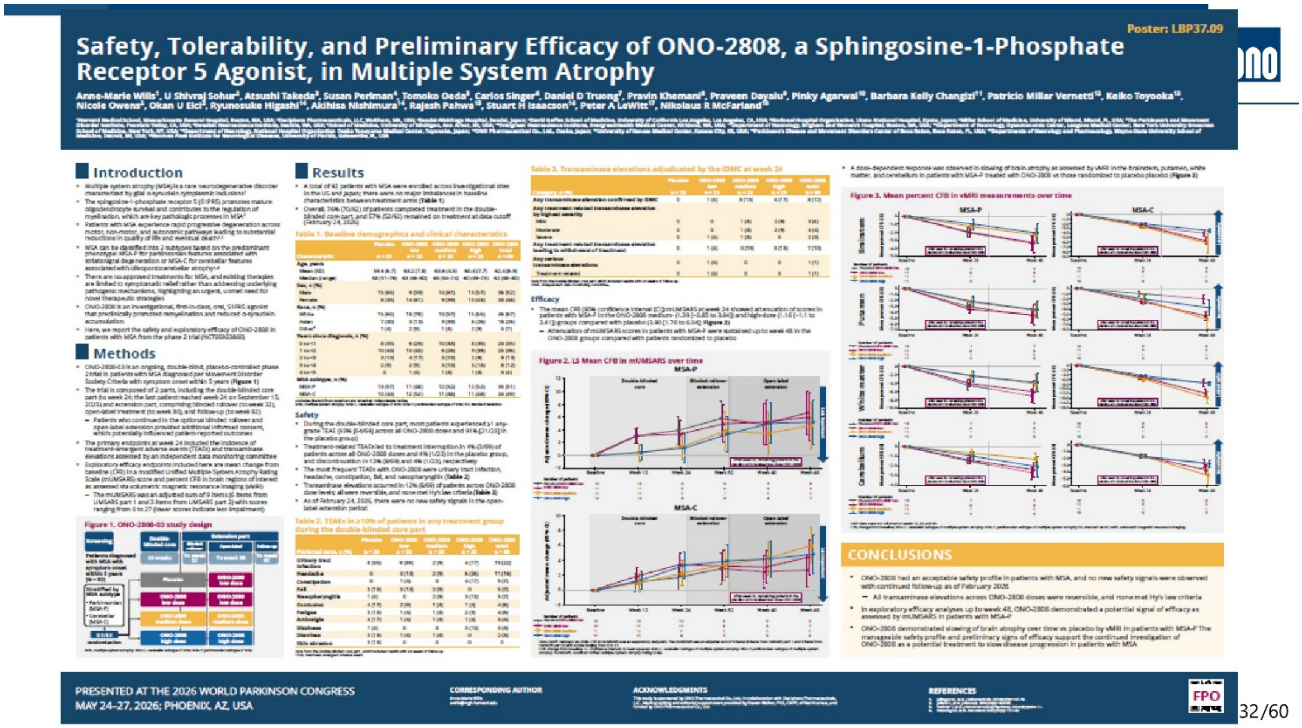
This concludes the presentation on ONO-4578.



Next, I would like to move on to ONO-2808.

ONO-2808 is an orally available selective S1P5 receptor agonist discovered in-house. We are currently developing it for multiple system atrophy, or MSA, a disease with very high unmet medical needs , for which no disease-modifying therapy currently exists.

In terms of the pathophysiology of MSA, abnormal aggregation and accumulation of a protein called alpha-synuclein is thought to occur in oligodendrocytes as well as neurons. Pre-clinical studies have shown that ONO-2808 regenerates the damaged myelin sheath covering the neuronal axons, while also suppressing the abnormal aggregation and accumulation of alpha-synuclein, and is currently being developed for multiple system atrophy.



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Safety, Tolerability, and Preliminary Efficacy of ONO-2808, a Sphingosine-1-Phosphate Receptor 5 Agonist, in Multiple System Atrophy

Introduction

Methods

Results

CONCLUSIONS

PRESENTED AT THE 2026 WORLD PARKINSON CONGRESS
MAY 24–27, 2026; PHOENIX, AZ, USA

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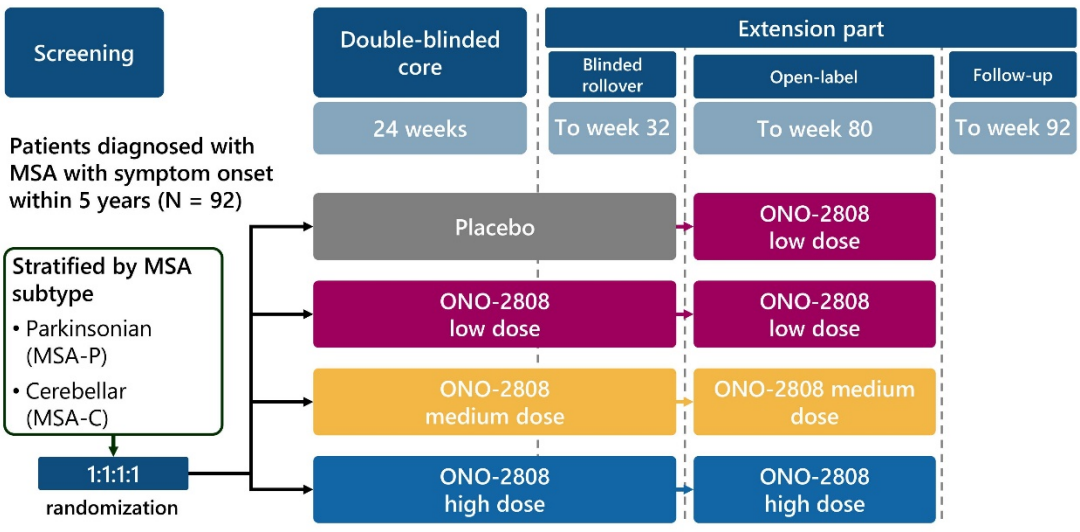
As many of you may already be aware, the results of our Phase 2 study of ONO-2808 conducted in Japan and the US were presented at the 7th World Parkinson Congress, WPC, held in Phoenix, Arizona from May 24 to 27. From here, I will walk you through what was shared at that meeting.

ONO-2808-03 study design (NCT05923866)



MSA, multiple system atrophy; MSA-C, cerebellar subtype of MSA; MSA-P, parkinsonian subtype of MSA.

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Let me start with the study design.

The ONO-2808-03 study is a multicenter, randomized Phase 2 study conducted in Japan and the US in patients with MSA, within five years from symptom onset. The study consisted of a double-blind core part and an

extension part for longer-term evaluation. In the core part, patients were randomized in a 1:1:1:1 ratio to four groups: placebo, and low-, medium-, and high-dose ONO-2808.

The primary endpoint of the study is safety, and although no statistical testing has been conducted for efficacy, the study includes evaluation using mUMSARS, as well as MRI-based assessments of brain volume atrophy, which are the commonly used as key endpoints in this disease worldwide.

Baseline demographics and clinical characteristics

Characteristic	Placebo n = 23	ONO-2808 low n = 23	ONO-2808 medium n = 23	ONO-2808 high n = 23	ONO-2808 total n = 69
Age, years					
Mean (SD)	59.6 (6.7)	63.2 (7.8)	63.6 (4.5)	60.4 (7.7)	62.4 (6.9)
Median (range)	58 (51–76)	63 (46–80)	65 (54–74)	60 (49–73)	62 (46–80)
Sex, n (%)					
Male	15 (65)	9 (39)	14 (61)	13 (57)	36 (52)
Female	8 (35)	14 (61)	9 (39)	10 (43)	33 (48)
Race, n (%)					
White	15 (65)	18 (78)	13 (57)	15 (65)	46 (67)
Asian	7 (30)	3 (13)	9 (39)	6 (26)	18 (26)
Other[a]	1 (4)	2 (9)	1 (4)	2 (9)	5 (7)
Years since diagnosis, n (%)					
0 to <1	8 (35)	6 (26)	10 (43)	8 (35)	24 (35)
1 to <2	10 (43)	10 (43)	6 (26)	9 (39)	25 (36)
2 to <3	3 (13)	4 (17)	3 (13)	2 (9)	9 (13)
3 to <4	2 (9)	2 (9)	3 (13)	3 (13)	8 (12)
4 to <5	0	1 (4)	1 (4)	1 (4)	3 (4)
MSA subtype, n (%)					
MSA-P	13 (57)	11 (48)	12 (52)	12 (52)	35 (51)
MSA-C	10 (43)	12 (52)	11 (48)	11 (48)	34 (49)

[a] Includes Black/African American and American Indian/Alaska Native.
MSA, multiple system atrophy; MSA-C, cerebellar subtype of MSA; MSA-P, parkinsonian subtype of MSA; SD, standard deviation.

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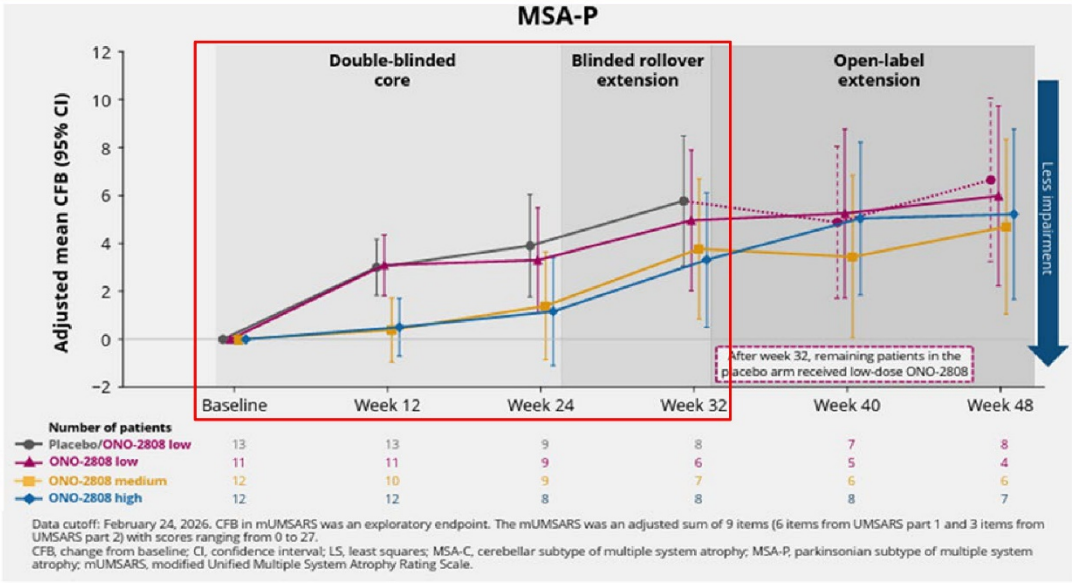
This slide shows baseline characteristics of the enrolled patients.

A total of 92 patients were enrolled across the four groups. There were no significant differences among the four groups in terms of age, years since diagnosis, and subtype. The subtypes included MSA-P, in which Parkinson's symptoms predominate, and MSA-C, in which cerebellar ataxia predominates.

As I mentioned earlier, the primary endpoint of this study was safety; however, I will first introduce the exploratory efficacy endpoint.

Efficacy-mUMSARS / MSA-P group



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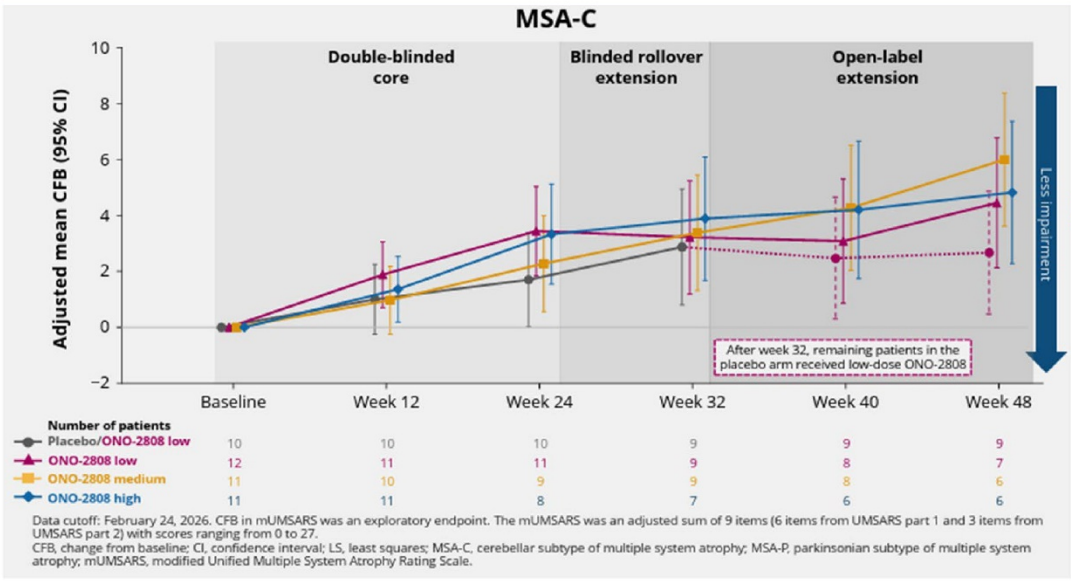
This figure shows the change over time in mUMSARS in the MSA-P population, with different colors indicating each dose group. Higher scores indicate worsening, while a decrease indicates suppression of disease progression. As you can see, through Week 32—when crossover from placebo to the active low dose was allowed—we observed dose-dependent suppression of disease progression.

Efficacy-mUMSARS / MSA-C group



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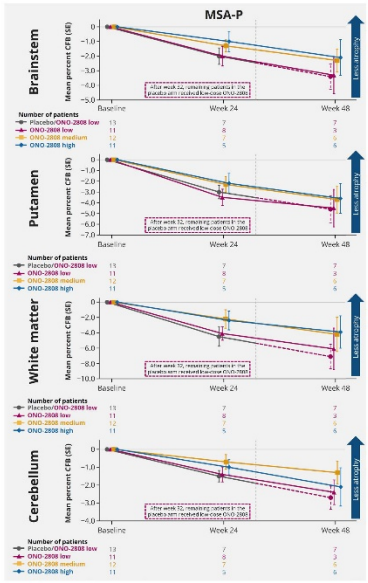
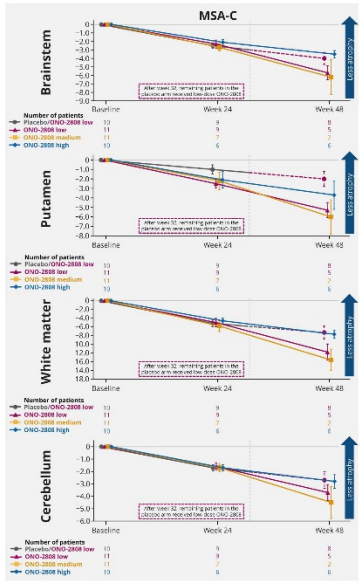
In contrast, this figure shows mUMSARS over time in the MSA-C population.

Unfortunately, unlike what we saw in MSA-P, we did not observe a dose-dependent response to ONO-2808 overall.

Efficacy-vMRI measurements





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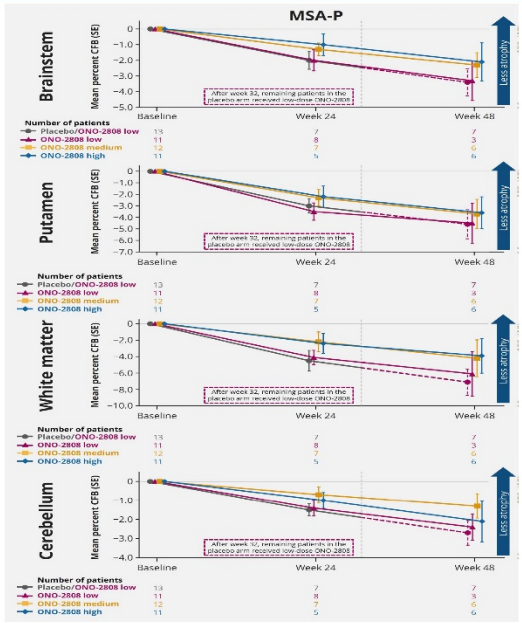
This slide summarizes the MRI-based brain volume results.

Efficacy-vMRI measurements / MSA-P group



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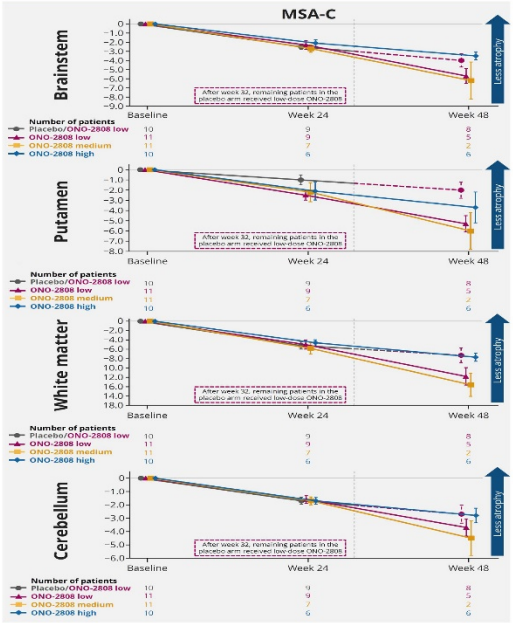
First, this shows the change in the brain volume assessed by MRI in the MSA-P population.

A downward trend indicates the progression of brain atrophy, and the flatter the slope, the more brain atrophy is suppressed. In the cerebellum only, a reversal between the medium- and high-dose groups was observed; however, compared with placebo and the low-dose group, the medium- and high-dose ONO-2808 groups consistently showed suppression of brain atrophy progression.

Efficacy-vMRI measurements / MSA-C group



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Next, this shows the change in the brain volume assessed by MRI in the MSA-C population.

Across multiple brain regions, the high-dose ONO-2808 group suggests suppression of brain atrophy progression. However, in white matter, the high-dose group appears to be below the placebo group, and no clear dose–response relationship is observed.

In MSA-P, by Week 24, the medium- and high-dose groups appeared to separate from placebo and low-dose group. In contrast, in MSA-C, in contrast, there is little difference between the groups.

TEAEs in ≥10% of patients in any treatment group during the double-blinded core part

Preferred term, n (%)	Placebo n = 23	ONO-2808 low n = 23	ONO-2808 medium n = 23	ONO-2808 high n = 23	ONO-2808 total n = 69
Urinary tract infection	8 (35)	9 (39)	2 (9)	4 (17)	15 (22)
Headache	0	3 (13)	2 (9)	6 (26)	11 (16)
Constipation	0	1 (4)	0	4 (17)	5 (7)
Fall	3 (13)	3 (13)	2 (9)	0	5 (7)
Nasopharyngitis	1 (4)	0	2 (9)	3 (13)	5 (7)
Contusion	4 (17)	2 (9)	1 (4)	1 (4)	4 (6)
Fatigue	3 (13)	1 (4)	1 (4)	2 (9)	4 (6)
Arthralgia	4 (17)	1 (4)	1 (4)	1 (4)	3 (4)
Dizziness	1 (4)	0	0	3 (13)	3 (4)
Diarrhea	3 (13)	1 (4)	1 (4)	0	2 (3)
Skin abrasion	3 (13)	0	0	0	0

Data from the double-blinded core part , which included results with 24 weeks of follow-up. Adjudicated transaminase elevation events are described in Table 3.
TEAE, treatment-emergent adverse event.

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Finally, let me turn to safety. This table shows adverse events, regardless of causality, that occurred in at least 10% of patients.

The main events were urinary tract infection, headache, falls, and nasopharyngitis. Although not shown in the table, the overall incidence of adverse events regardless of causality was 91% in the placebo group and 93% in the active groups—so there was no meaningful difference.

The incidence of adverse events that led to discontinuation, where a causal relationship to the study drug could not be ruled out, was 13% in the active groups and 4% in the placebo group.

Transaminase elevations adjudicated by the IDMC at week 24

Category, n (%)	Placebo n = 23	ONO-2808 low n = 23	ONO-2808 medium n = 23	ONO-2808 high n = 23	ONO-2808 total n = 69
Any transaminase elevation confirmed by IDMC	0	1 (4)	3 (13)	4 (17)	8 (12)
Any treatment-related transaminase elevation by highest severity					
Mild	0	0	1 (4)	2 (9)	3 (4)
Moderate	0	0	1 (4)	2 (9)	3 (4)
Severe	0	1 (4)	1 (4)	0	2 (3)
Any treatment-related transaminase elevation leading to withdrawal of treatment	0	1 (4)	3 (13)	3 (13)	7 (10)
Any serious transaminase elevations	0	1 (4)	0	0	1 (1)
Treatment-related	0	1 (4)	0	0	1 (1)

Data from the double-blinded core part, which included results with 24 weeks of follow-up.
IDMC, independent data monitoring committee.

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What I would like to highlight is that the main adverse events leading to discontinuation were elevations in ALT and AST—in other words, abnormal liver function test results.

Elevations in AST and ALT are known class effects of S1P agonists, and with this drug as well, hepatic events were observed in a certain proportion of patients. However, these events were resolved after discontinuation, and no serious cases were observed.

After completion of the core part, we have continued safety follow-up in the extension part. To date, we have not identified any new safety signals.

That conclude with the presentation at WPC.

Discussion on the Results of ONO-2808-03 Study

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As with ONO-4578, I would now like move on to our interpretation of the ONO-2808-03 study results.

Modified UMSARS for ONO-2808

Used in the ONO-2808 Phase 2 study (maximum score: 27)

-	**Part I: Historical Review** (Activities of Daily Living) Assesses average function over the past 2 weeks based on an interview with the patient and/or caregiver	**Part II: Motor Examination Scale** (Motor Function Assessment) Rated on the more affected side
1	Speech	Facial expression
2	Swallowing	Speech
3	Handwriting	Oculomotor dysfunction
4	Cutting food/handling utensils	Tremor at rest
5	Dressing	Action tremor
6	Hygiene	Increased tone
7	Walking	Rapid alternating movements
8	Falls	Finger taps
9	Orthostatic symptoms	Leg agility
10	Urinary function	Heel-knee-shin test
11	Sexual function	Arising from chair
12	Bowel function	Posture
13	---	Body sway
14	---	Gait
-	**Minimum 0, maximum 18**	**Minimum 0, maximum 9**

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This slide shows the efficacy endpoints.

As you may know, the mUMSARS is modified differently depending on the sponsor. In the ONO-2808 study, we used the nine items highlighted in yellow. Each item was scored on a 0 to 3 scale, for a total score ranging from 0 to 27.

Modified UMSARS for Amlenetug (Lu AF82422)

Used in Phase 2 study of Lundbeck's investigational drug (Amlenetug, Lu AF82422; maximum score, 48)

-	**Part I: Historical Review** (Activities of Daily Living) Assesses average function over the past 2 weeks based on an interview with the patient and/or caregiver	**Part II: Motor Examination Scale** (Motor Function Assessment) Rated on the more affected side
1	Speech	Facial expression
2	Swallowing	Speech
3	Handwriting	Oculomotor dysfunction
4	Cutting food/handling utensils	Tremor at rest
5	Dressing	Action tremor
6	Hygiene	Increased tone
7	Walking	Rapid alternating movements
8	Falls	Finger taps
9	Orthostatic symptoms	Leg agility
10	Urinary function	Heel-knee-shin test
11	Sexual function	Arising from chair
12	Bowel function	Posture
13	---	Body sway
14	---	Gait
-	**Minimum 12, maximum 48**	**0**

Adapted from Kjærsgaard L et al., Lancet Neurol. 2026 Jun;25(6):560–570.

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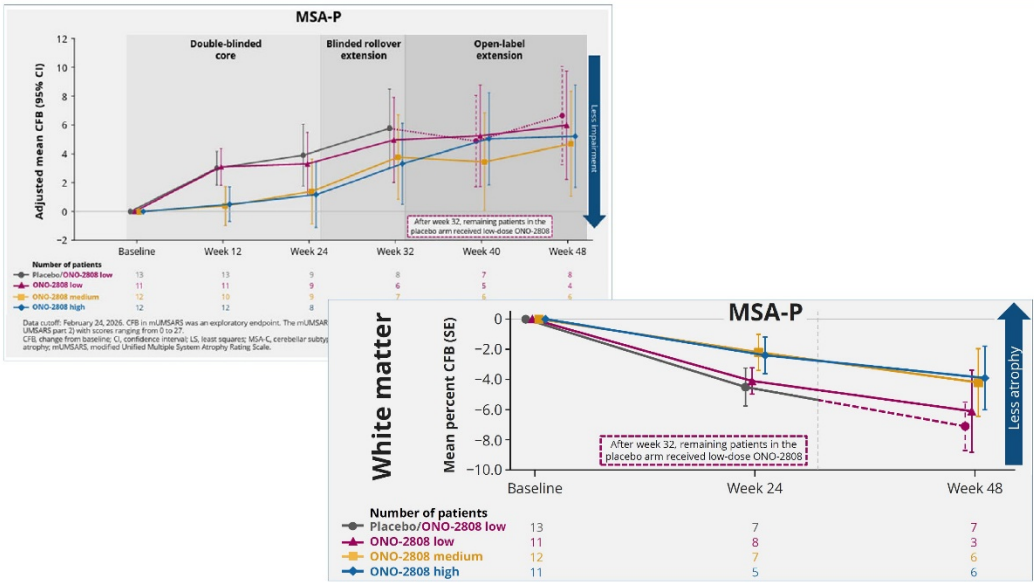
In contrast, this slide shows the mUMSARS used in amlenetug's Phase 2 study. They used the 12 items highlighted in green. Each item was scored on a 1 to 4 point scale, resulting in a total score ranging from 12 to 48.

While both studies used mUMSARS as an efficacy assessment, the selected items and scoring systems differ, which is one reason why a direct comparison is challenging.

As I've said repeatedly, a direct comparison between the two studies is difficult. So, what I'm showing here is for reference only—the results from the two trials side by side. Again, we cannot compare them directly, but at Week 24, ONO-2808 showed a 64% to 70% reduction in progression versus placebo. We believe that a relatively large reduction in disease progression was observed at 24 weeks, which is relatively early.

ONO-2808 Summary



45/60

This is the last slide of this discussion section.

In our Phase 2 study of ONO-2808, at least in the MSA-P population, we observed suppression of brain atrophy progression. We also interpret the mUMSARS results as showing a clinically meaningful slowing of progression compared with placebo, which we believe is substantial.

In addition, while the dose–response was not entirely clear between the medium- and high-dose groups, a dose-dependent trend was observed compared with placebo and low-dose group. Taking it together, we believe the drug discovery concept behind ONO-2808 has been confirmed at least in MSA-P.

ONO-2808 Development Status

Indication(s)	Development phase	Status	Regions	Study ID	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
MSA (MSA-P)	P3	In preparation	Planned in Japan, the US, and EU (TBD)	TBD						P3: MSA (planned)				
											ONO-2808-03-001 study			
MSA	P2	Key data obtained in FY2025	Japan and the US	NCT05923866			P2: MSA							
							ONO-2808-03 study							

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As I mentioned earlier, we recognize that MSA is a disease with a very high unmet medical need, for which no disease-modifying therapy currently exists. The absence of effective therapies also reflects the challenges in developing treatments for this disease.

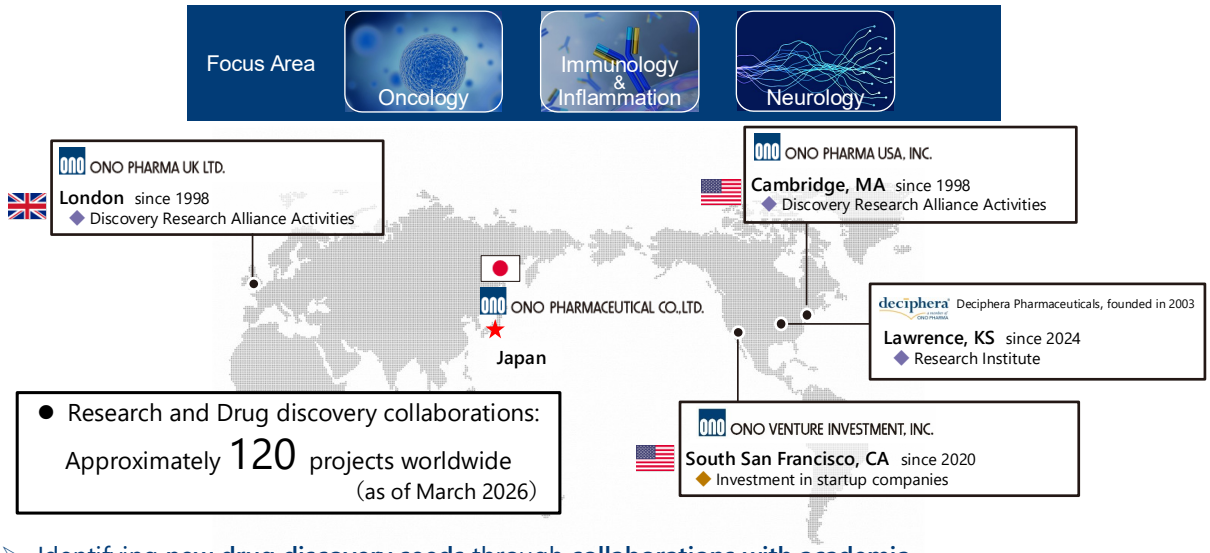
Based on the results of the Phase 2 study, we are now preparing to initiate a global Phase 3 study in MSA-P this year, in order to provide patients with a meaningful treatment option as soon as possible.

In addition, we have completed discussions with the US regulatory authorities regarding progression to the next phase of ONO-2808.

This is the end of my presentation. Thank you very much.

Imura: Finally, Katsumata, Executive Vice President, Discovery & Research, will now introduce our drug discovery research, especially in the central nervous system field.

ONO's Drug Discovery



- Identifying **new drug discovery seeds** through **collaborations with academia**
- Advancing drug discovery using **the optimal modality** through **collaborations with biotech companies**

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Katsumata: I'm Katsumata, Executive Vice President of Discovery & Research. I would like to introduce our drug discovery strategy and current initiatives in the field of neurology.

Let me outline our drug discovery strategy. We focus on three key therapeutic areas: oncology, immunology and inflammation, and neurology. Our goal is to create unique and innovative drugs that deliver meaningful clinical impact. To bring new therapies to patients, their families, and healthcare professionals as quickly as possible, we are advancing our drug discovery efforts not only at the Minase Research Institute and Tsukuba Research Institute, but also in collaboration with Deciphera's research site in Lawrence, Kansas.

Building on our in-house drug discovery expertise, we work with leading academic institutions and biotech companies worldwide and are actively leveraging cutting-edge technologies. In addition to Japan, we have dedicated partnership professionals in our local subsidiaries in the US and the UK, driving open innovation. We are currently engaged in approximately 120 research and drug discovery partnerships in Japan and internationally.

Furthermore, leveraging the ONO VENTURE INVESTMENT network, we are also working to identify and secure new partnership opportunities.

Drug Discovery Strategy in Neurology

✓ Elucidate disease biology to address unmet medical needs

✓ Develop disease-modifying therapies, not only symptomatic treatments

✓ Target glial cells, not only neurons

✓ Leverage clinical insights to improve translatability to humans

Deliver new drugs through cutting-edge technology and open innovation

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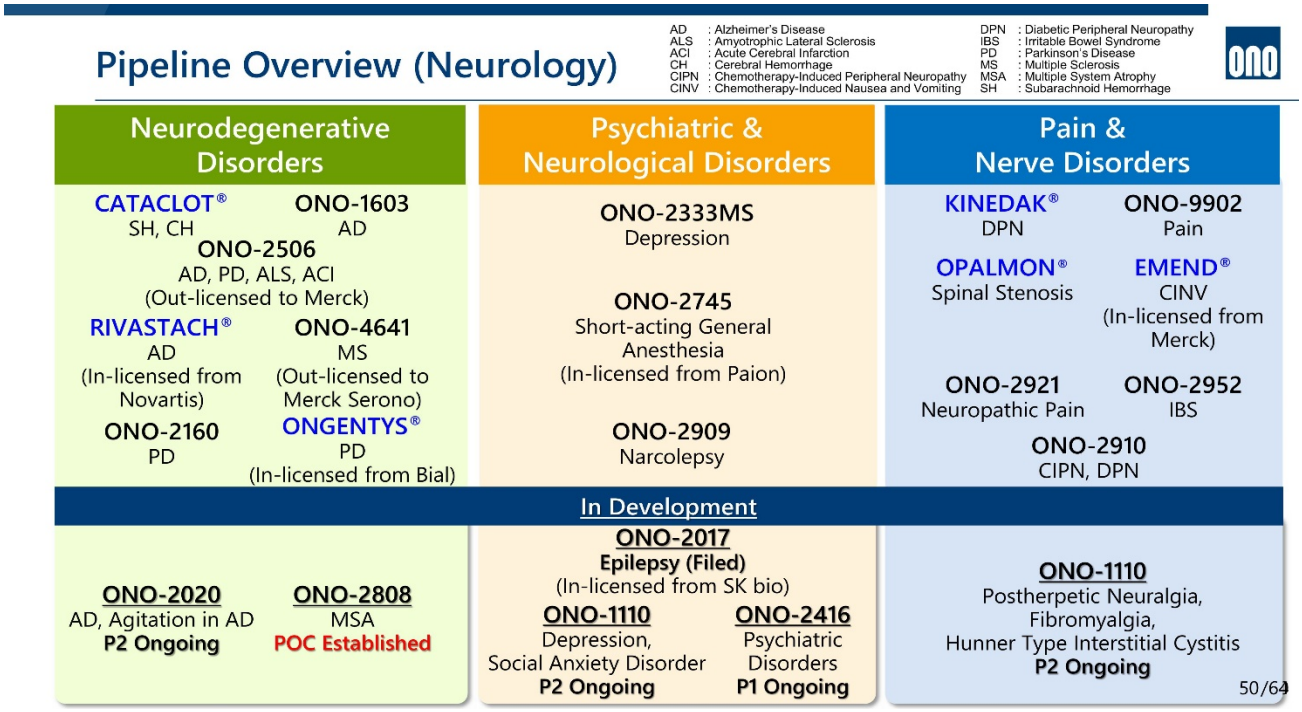
Now, let me turn to today's main topic: our drug discovery strategy in the neurology field.

Across our three focus areas, we place the highest priority on addressing unmet medical needs from the patient's perspective. A deep understanding of disease biology is the foundation of our approach.

In neurology, we go beyond symptomatic treatment. We aim to develop disease-modifying therapies that address the underlying cause of disease. To achieve this, we target not only neurons but also glial cells. This strategy has been built through accumulated experience and expertise at our Neurology Research Center.

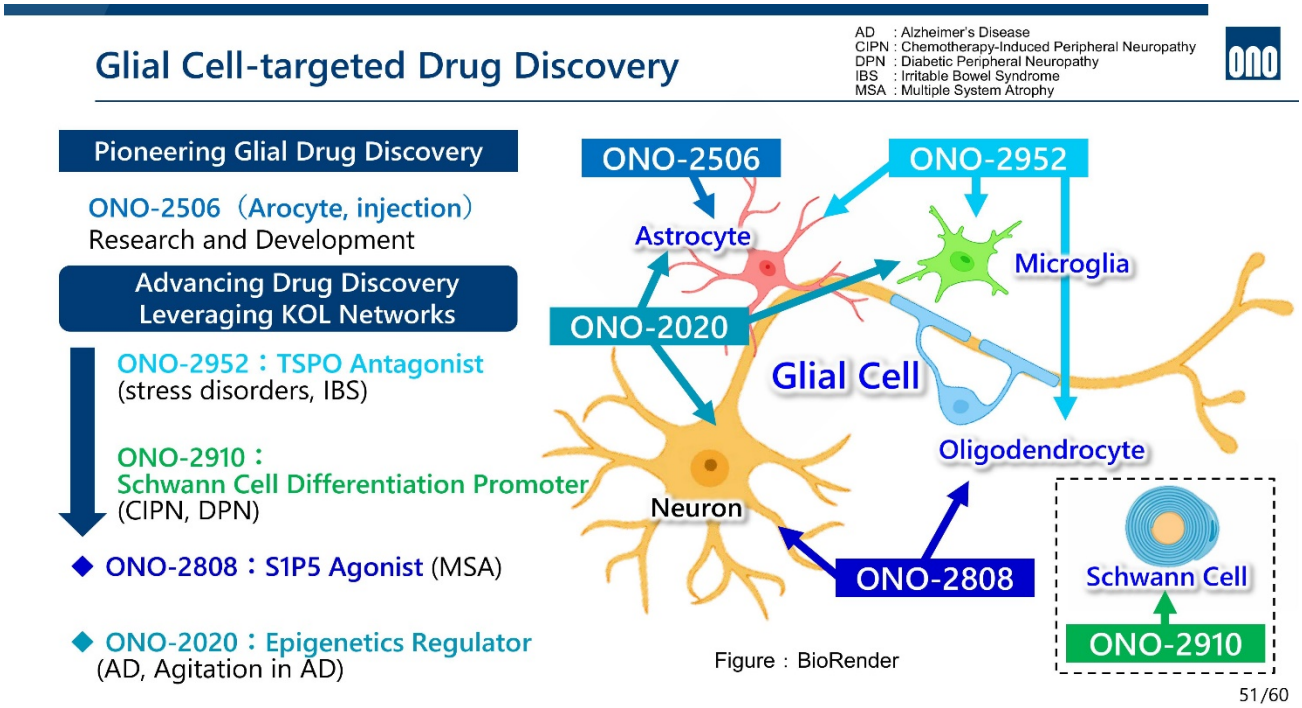
One of the key challenges in neurology is the limited translatability from nonclinical studies to humans. To address this, we integrate clinical insights and emerging biomarkers to improve human translatability.

In summary, our strategy is to advance drug discovery through cutting-edge technologies and open innovation. This is our strategy for drug discovery in the neurology field. This strategy was not built overnight. It is based on many years of experience in neurological drug discovery.



Here, we show how our neurology pipeline has evolved over time. As you can see, we have in fact been committed to drug discovery in this field for over 30 years, focusing on neurodegenerative disorders, psychiatric and neurological disorders, and pain and nerve disorders. We have launched the products shown in blue and have steadily accumulated research knowledge and know-how.

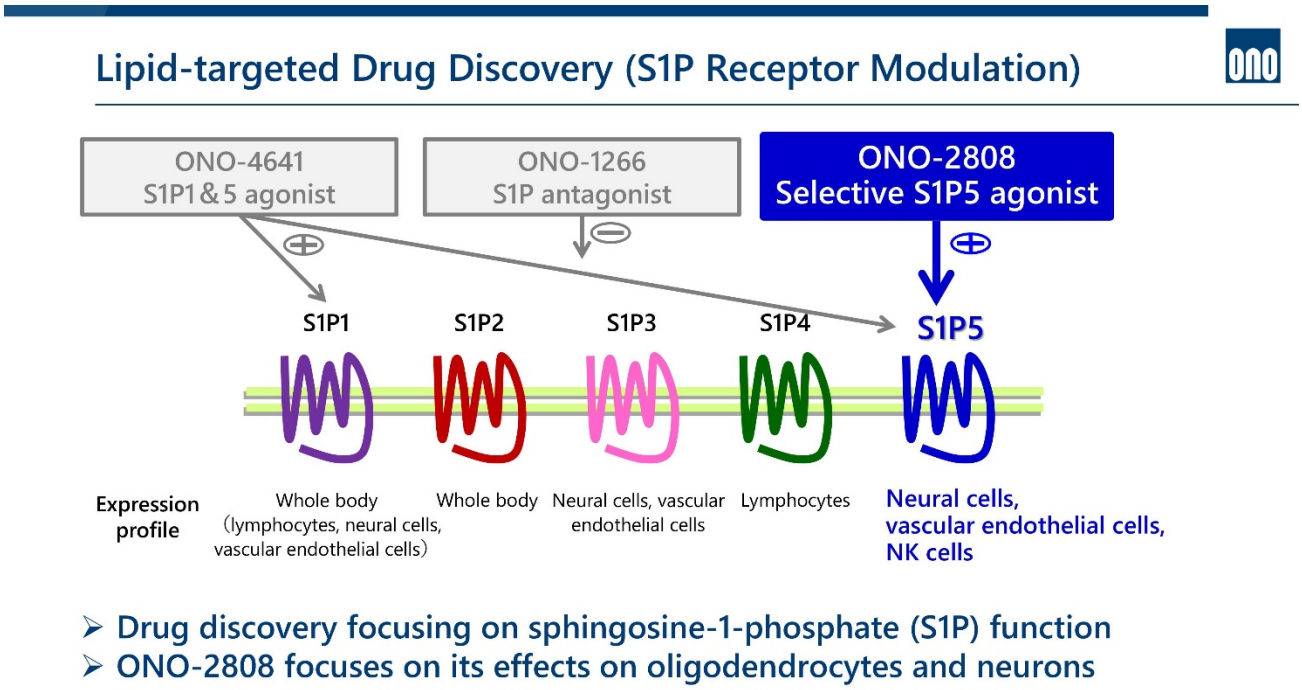
While leveraging our past research achievements, as mentioned earlier, in addition to ONO-2808, we have ongoing clinical programs such as ONO-1110 and ONO-2020, with Phase 2 results expected to become available soon. Next, I will explain the background behind these projects.



First, let me talk about drug discovery targeting glial cells as explained in the drug discovery strategy slide.

From the perspective of curing disease at its root, we have focused on the importance of glial cells. Through the research and development of astrocytes, the target of ONO-2506, we have built strong networks with experts in glial biology, as well as clinicians in neurodegenerative diseases.

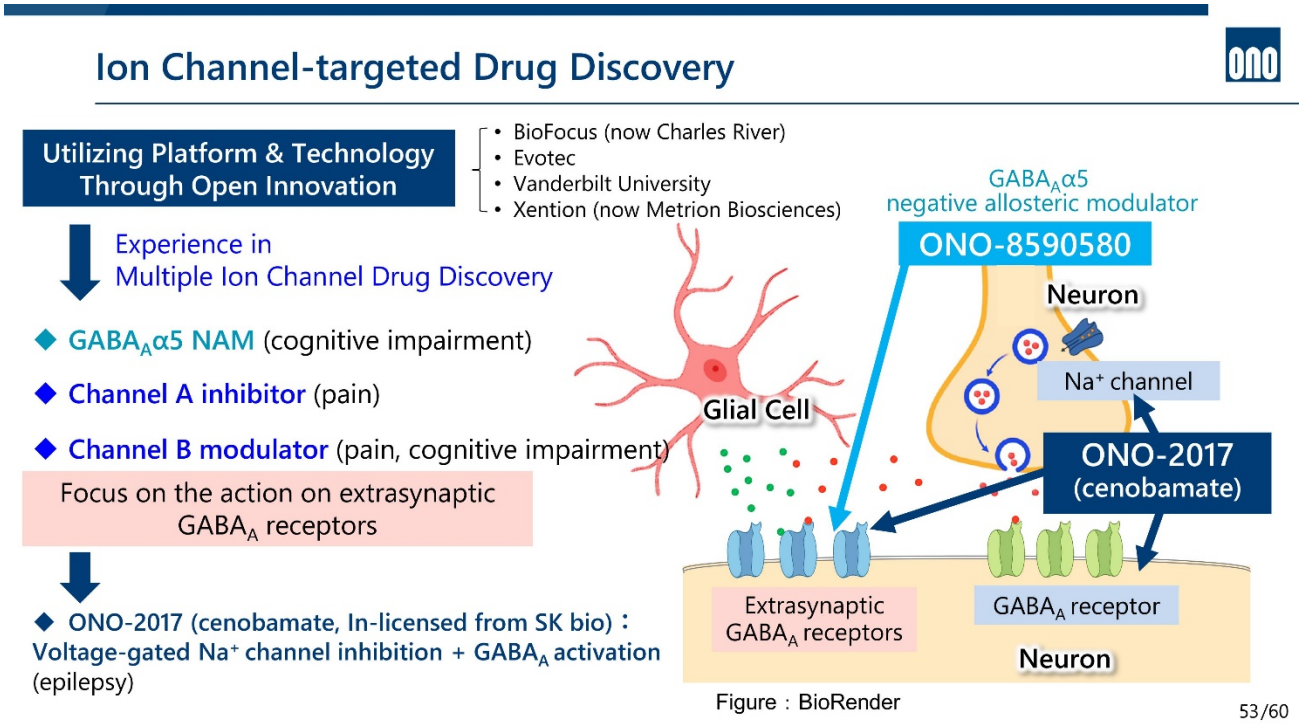
Although ONO-2506 did not reach commercialization, the knowledge gained has led to new drug discovery projects based on glial cell functions such as microglia, Schwann cells, and oligodendrocytes. This experience is now applied to current programs including ONO-2808 and ONO-2020.



We have also pursued drug discovery focused on specific target classes, and this has contributed to the sustained generation of our pipeline.

As you know, ONO PHARMACEUTICAL has strong expertise in lipid-targeted drug discovery, including prostaglandins.

Through our research on sphingosine-1-phosphate, or S1P, we analyzed its actions via the S1P1–5 receptors and identified the importance of its actions on glial cells and neurons. This finding eventually led to the discovery of ONO-2808.



We have also continued to deepen our understanding of ion channels.

Through collaborations with academia and biotech companies with strong expertise, we have worked on a variety of ion channel-targeted drug discoveries. Through this work, we identified the importance of extrasynaptic GABAA receptors as shown on the right. This insight led us recognize the unique mechanism behind the strong anti-epileptic effect of cenobamate, ultimately led to its in-licensing.

In this way, we have pursued a first-in-class drug discovery strategy, focusing on both neuronal and glial cell functions, and targeting target classes such as GPCRs and ion channels. However, this approach has not yet led to successful commercialization of in-house drug candidates.

So next, I will explain our current efforts to improve the probability of success.

Challenges and Strategies in Neurological Drug Discovery

Challenges	Strategies
Target Validation ● Understanding disease pathology ● Access to brain tissue and cerebrospinal fluid ● Appropriate disease models	✓ Research collaboration for target discovery ✓ Utilizing disease models and evaluation systems from academia that recapitulate disease pathology
Drug Discovery ● Identification of high-quality hits ● CNS penetration	✓ Leveraging drug discovery platforms through biotech collaboration ✓ Leveraging computational science capabilities from academia and biotech
Translational Research ● Prediction of clinical efficacy ● Appropriate clinical trial assessment	✓ Identifying and utilizing biomarkers from early stages of drug discovery ✓ Biomarker discovery through clinical research

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In addition to general challenges in drug discovery, there are specific challenges in neurology.

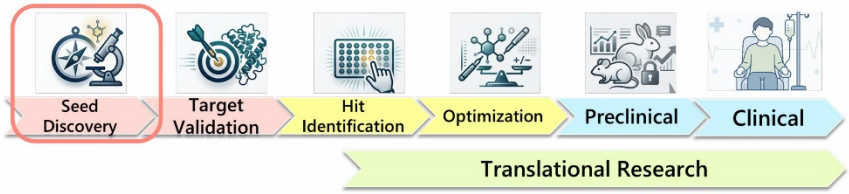
First, target validation. Many neurological diseases are complex and multifactorial and require a deep understanding of disease mechanisms. It is also very difficult to obtain clinical samples, which makes it challenging to reproduce human disease biology in preclinical models.

Second, drug discovery. To act on the central nervous system in a brain, compounds must cross the blood-brain barrier. This creates an additional layer of difficulty on top of already challenging targets.

Third, translation to humans. Clinical trials in neurodegenerative diseases take a long time, so it is important to identify biomarkers that can predict efficacy early on.

To address these challenges, we combine our internal expertise with open innovation and global cutting-edge technologies.

Challenges and Strategies in Neurological Drug Discovery

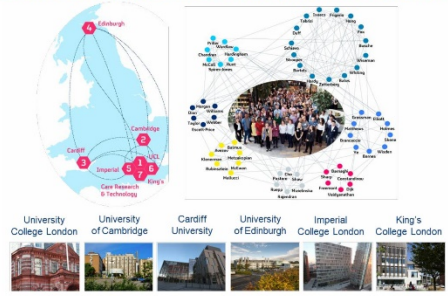


The Tohoku University Tohoku Medical Megabank Organization (ToMMo)

- Conducting community-based cohort study and three-generation cohort study launched in 2013
- Performing large-scale whole genome sequencing of the general population with follow-up capability
- Completing whole genome sequence of 100,000 Japanese individuals in June 2024 (one of the world's largest)
- Ono has participated in the Consortium for Integrated Analysis of Whole Genome Information and Medical/Health Information since March 2021.

Validating target relevance using global-scale genome analysis data

Collaboration with UK Dementia Research Institute



Identifying of new drug targets through research networks and strong research capabilities in the UK

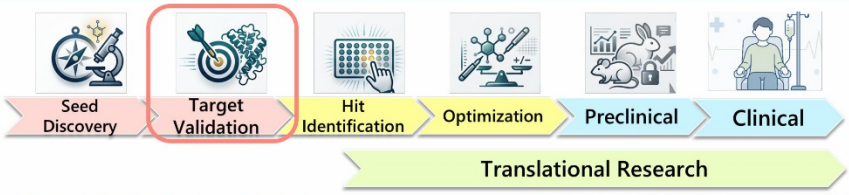
55/60

First, our approach to identifying drug targets.

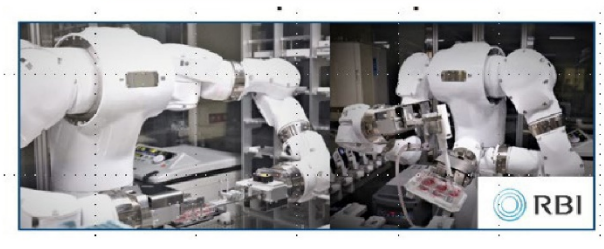
One approach is to compare healthy individuals with patients, to identify potential drug targets. As shown on the left, for example, through the Tohoku Medical Megabank project, we can access and analyze genomic data from 100,000 individuals across three generations. This enables a deeper understanding of target validity.

As shown on the right, in addition, through collaboration with the UK Dementia Research Institute, we use patient samples and a broad research network in the UK to identify new drug targets.

Challenges and Strategies in Neurological Drug Discovery

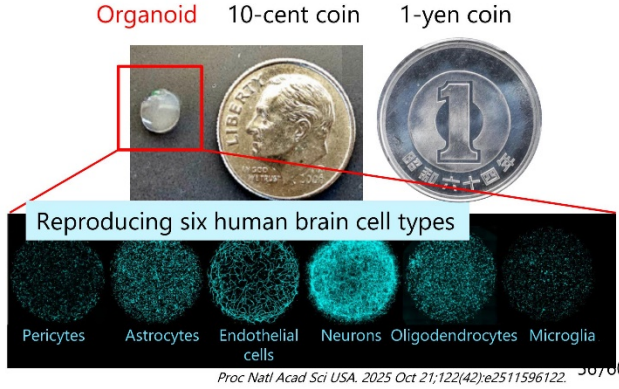


Introduction of Mahoro robots



Stably culturing iPS cells to support drug discovery projects

Brain organoid model using iPS cells



Proc Natl Acad Sci USA. 2025 Oct 21;122(42):e2511596122.

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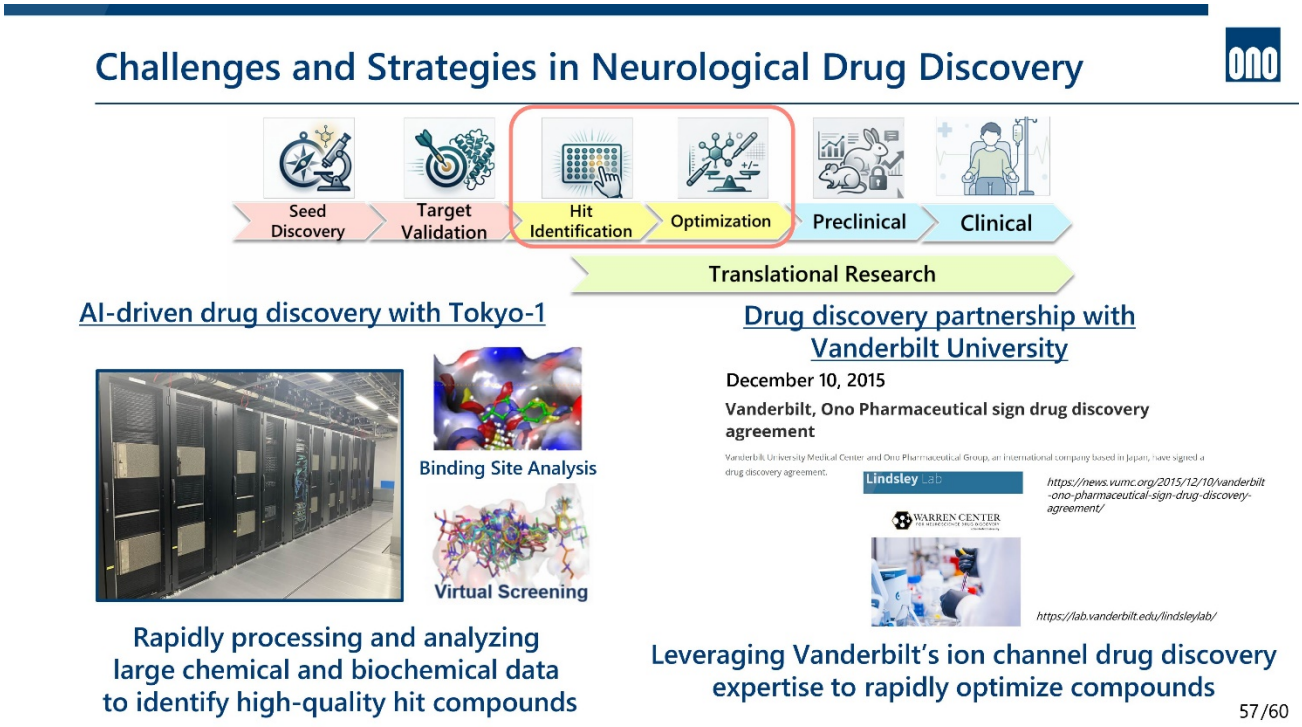
Next is the validation of identified targets.

Through collaborations with academia and biotech companies, we use various iPS cell models. We also utilize an automated two-armed robot system called “Mahoro,” and we induce the differentiation of difficult-to-handle iPS cells, confirm their differentiation into target cells, and provide them to the project.

In addition, we are also exploring the use of brain organoids that reproduce intercellular interactions.



Next is drug discovery.

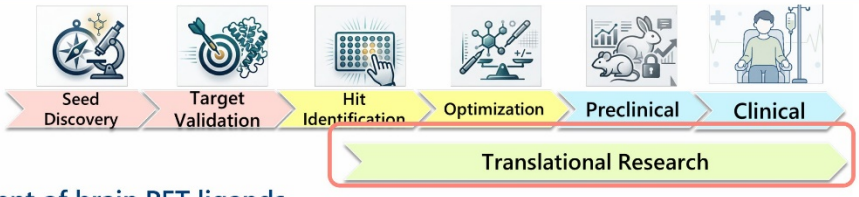
Most drug candidates targeting the central nervous system are small molecules. However, many of the targets are difficult to control. The use of AI becomes important. We have long been actively promoting open innovation and co-creation with a wide range of partners, advancing drug discovery by leveraging computational chemistry and simulations.

Recently, as shown on the left, the ultra-high-speed analytical environment of Tokyo-1 has enabled us to analyze massive volumes of data, making it possible to conduct large-scale screening and simulations—previously difficult due to time constraints—within a feasible time frame.

In addition, through long-term collaboration with Vanderbilt University, we have developed expertise in ion channel drug discovery. This allows us to move more efficiently from hit compounds to clinical candidates in a short time frame.

In this way, we have established a system that enables us to select appropriate control methods and create new drug candidates for targets that cannot be controlled by conventional methods in the area of small molecule drug discovery.

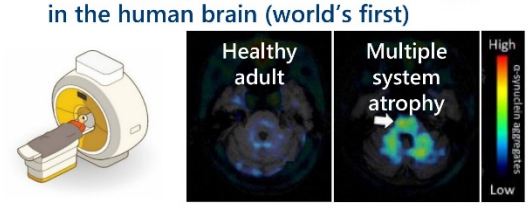
Challenges and Strategies in Neurological Drug Discovery



Co-development of brain PET ligands (CNS drug discovery alliance)

Co-development of α-synuclein pathology PET

Successful imaging of α-synuclein pathology in the human brain (world's first)



'22/8/31 QST PR (https://www.qst.go.jp/site/news/20220831.html)

Longitudinal clinical study of the disease (investigator-initiated observational study)

Disease Progression in Multiple System Atrophy: The ASPIRE Multi-Modal Biomarker Study

Ann Neurol. 2026 Jan;99(1):96-113.

Partnership with University of Toulouse in France

Identification of clinical biomarkers for multiple system atrophy

▼

Utilized in the clinical trial for ONO-2808

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Finally, translational research.

If we have biomarkers that reflect clinical endpoints, we can use them to guide drug discovery and early clinical decisions. However, such biomarkers are still limited.

The use of biomarkers is also important to identify the right patient populations suitable for the new drug candidates. At ONO PHARMACEUTICAL, we are working to acquire these biomarkers through initiatives such as brain disease alliances shown left and investigator-initiated observational studies shown right, and these biomarkers are already being used in clinical trials of ONO-2808.

Development Pipeline (Neurology)

Code	Target Indication	P I	P II	P III	Filed	Approval
ONO-2017	Partial-onset seizures	■	■	■	■	
	Partial-onset seizures (pediatric)	■	■	■		
	Primary generalized tonic-clonic seizures	■	■	■		
ONO-2808	Mutiple system atrophy	■	■			
ONO-1110	Postherpetic neuralgia	■	■			
	Fibromyalgia	■	■			
	Hunner-type interstitial cystitis	■	■			
	Major depressive disorder	■	■			
	Social anxiety disorder	■	■			
ONO-2020	Alzheimer's disease (AD)	■	■			
	Agitation associated with dementia due to AD	■	■			
ONO-2416	Psychiatric disorders	■				

⋮ Coming soon

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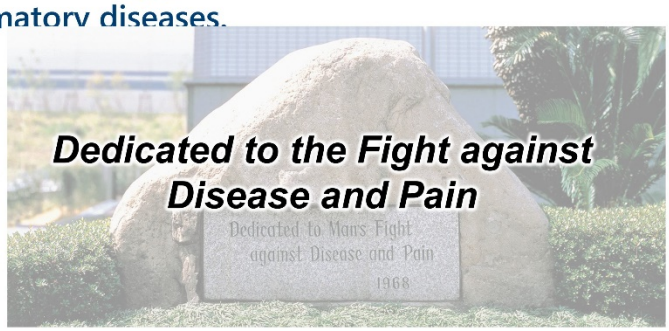
Through these efforts which I have just described, we have built our pipeline.

The slide shows our current clinical pipeline in neurology. This year, we also initiated a Phase I study of ONO-2416 for psychiatric disorders. We expect more candidates to continue to enter the clinic going forward, and we hope for your continued interest.

Summary

- Ono is strengthening our pipeline by integrating internal and external expertise across the stage of the drug discovery process.
- Ono leverages cutting-edge technologies and open innovation to deliver innovative new drugs as quickly as possible to patients worldwide, addressing unmet medical needs not only in neurology but also in oncology, immunology, and inflammatory diseases.



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ONO PHARMACEUTICAL has been a pioneer in open innovation through industry–academia collaboration. By combining internal and external expertise at each stage of drug discovery, we are strengthening our pipeline.

We will continue to fully apply advanced technologies and open innovation not only in neurology, but also in oncology and immunology/inflammation, to address unmet medical needs. Our goal is to deliver innovative medicines to patients worldwide as quickly as possible.

That is all.

Question & Answer

Imura: We would now like to take your questions.

Mr. Seki from UBS Securities, please.

Seki : ONO-4578, congratulations on the very good data. In the negative L1 group, the hazard ratio exceeded 1, indicating worse outcomes compared with OPDIVO plus chemotherapy. Why does this happen? What are your thoughts on this area so far, including whether it is a coincidence?

Okamoto : Regarding the point you just raised, our current view is that interpretation is difficult given the small sample size of 33 versus 19. In addition, although I did not touch on this earlier when discussing patient characteristics, imbalances in prognostic factors tend to arise in small populations. In fact, such imbalances were observed even within the CPS-negative group.

Taking all that into account, while the placebo group appears to have performed better on the surface, we believe that there was no real difference between the groups. In other words, although clear efficacy was not observed compared with the CPS-positive group on the left side, we do not believe the treatment worsened outcomes.

Seki : The second point is that ONO-2808 also targets a very difficult and heterogeneous disease, so thank you for the very interesting data.

I think that reproducibility will be very important in the Phase 3 study, and I was wondering if you have any ideas at the moment on how to improve the reproducibility of the Phase 2 findings.

Okamoto : I cannot answer in detail because this is the core part of our development strategy. What we said today is that while our competitors are developing treatments for MSA, we are going will focus on MSA-P for Phase 3, based on the fact that both imaging and UMSARAS showed consistent trends. I think this is the message I can provide today.

Imura : Mr. Yamaguchi from Citigroup Securities, please.

Yamaguchi : Regarding ONO-4578, looking at OS the curves appear to cross early on. Given that this is a PD-1-based treatment, that kind of pattern is sometimes seen, but how do you interpret this?

Okamoto : We do not interpret this as the curves crossing.

As we mentioned in the safety section, although we omitted the details, there are gastrointestinal side effects when it acts on EP4, but this can be managed by prophylactic administration of PPIs, etc., and we do not believe there are safety issues the OS.

On the other hand, the fact that there is a 20% increase in response rate means that we do not accept at least what you have just pointed out with this Kaplan-Meier.

Yamaguchi : I see. Does this mean that PPI will be used more and more already?

Okamoto : In short, based on the same pharmacological effects as so-called COX inhibitors, regarding ONO-4578, ulcers in the digestive system may occur, etc. If they are treated prophylactically with PPIs, it is known that this can be prevented.

However, that is a matter of development strategy as to whether or not to take such measures from the beginning, so I will refrain from answering your question.

Imura : Mr. Wakao from JP Morgan Securities, please.

Wakao : First, I also would like to ask about ONO-4578. I would like to know about the subgroup analysis.

I think you mentioned earlier about the CPS-negative , but I would like you to comment on the data for those between 1 and 5 of the CPS, and together with the CLDN 18.2 positive, which does not seem to be working for those who are positive, can you comment on these as well?

Okamoto : We understand that you have seen the forest plot and have asked us questions.

For 1 through 5, we have also allocated CPS, but we have not allocated them strictly from 1 through 5, so there is inevitably an imbalance in patient distribution. Therefore, while it is true that the 95% confidence interval is greater than 1, we do not consider this to be a wide range. We understand that it is an accidental, accidental exceedance.

As for CLDN, I was talking only about CLDN univariate, and as I mentioned earlier in my presentation, the data for CPS-positive and CLDN positive are not disclosed, I am afraid. Regarding your point, we do not consider that it doesn't work because CLDN is positive.

Wakao : Have you already looked at the data for the double positive subanalysis?

Okamoto : Including seeing and not seeing, it’s undisclosed.

Wakao : The second question is about ONO-2808. I would like to know the scientific background of this, or rather a discussion of why it works, as it worked better for MSA-P. I think that Lundbeck did not see the efficacy, or at least there was no difference, and this was partly because the number of patients was small; however, how should I see your results?

Okamoto : As you just mentioned, I have also read the Lancet Neurology and Lundbeck's data, which were published this year, and Lundbeck saw the data that it was more pronounced and effective in patients with less severe baseline disabilities among patients with MSA-C.

It is difficult to make a direct comparison because neither we nor Lundbeck have disclosed everything, but our understanding is that, when looking at all enrolled patients, the degree of disability was the same. However, we did not observe a difference in patients with MSA-C.

One possibility is that, for example, the treatment worked well for Lundbeck patients with mild MSA-C. Although we do not disclose the data, the original baseline UMSARAS for MSA-P and MSA-C are naturally different, so I wonder if this might also be a factor.

The other thing I would like to mention is in the imaging evaluation section, can we see the MRI section? This is the one I just mentioned, this is the P, and the C is the next one, or there is no difference in 24 weeks. In short, MSA-P and MSA-C are very difficult diseases, and there are various reports, from the neurology literature, but as far as I can tell, I believe that MSA-P is reported to have faster disease progression. I wonder if this data of MSA-C represents that point. It is difficult to identify the difference in short period. So we interpreted it as not that it was not working, but that we could not find any difference.

So, although we are not completely stopping the development of MSA-C at this point, we would like to choose MSA-P first, which has a high degree of certainty.

Wakao : I see. I was wondering if your company's baseline UMSARS is not being provided.

Okamoto : Yes. We do not disclose that information.

Imura : Next, Mr. Wada of SMBC Nikko Securities, please.

Wada : I would like to ask your thoughts on ONO-4578 when the case was CLDN and PD-L1 double positive.

I'm wondering if it is quite characteristic that when we look at Kaplan-Meier for ONO-4578, the immune drugs seem to cause what is called pseudoprogression and don't seem to work very well for about three months at first. I was wondering if a molecularly targeted drug like CLDN might look more like it is starting to work from the beginning.

So the question I would like to ask is, leaving ONO-4578 aside at the moment, whether there is such a thing that CLDN is more likely to be selected when using OPDIVO and CLDN, where it is easier to see the beginning of the efficacy of the drug. I would like to ask you about something like that.

Okamoto : It would be good to see data on response rates.

First of all, regarding your question, the recommendations in the guidelines are as I mentioned earlier. In cases of CPS-positive or CLDN-positive, when both are positive, the choice of treatment should be taken into consideration. As I understand it, in many cases where a patient is CLDN-positive, CLDN is prioritized even if the patient is also CPS-positive.

The reason for this is not that the drugs you just mentioned for tumor immunity are ineffective in how they work initially, but rather that zolbetuximab, a molecularly targeted therapy for CLDN-positive tumors, can only be used as a first-line treatment.

On the other hand, nivolumab can be used in third-line and later settings under insurance coverage in Japan, and when considering treatment options, we have heard from specialists that zolbetuximab, a molecularly targeted agent for CLDN, is being used when considering which treatment option to choose.

On the other hand, it is objectively said that PD-1 antibodies, in combination with chemotherapy, and zolbetuximab in combination with chemotherapy, zolbetuximab does not have an additive effect on the response rate. In fact, in their Phase 3 trial called SPOTLIGHT, which was limited to the population with the target disease, the response rate remained the same at 61% even when zolbetuximab was added to the chemotherapy group.

On the other hand, for PD-1 antibodies, whether it's OPDIVO or pembrolizumab, they provide addition to response rate. So I believe that it is used not because the initial efficacy is poor due to immunotherapy, but only because if it is not used that point, there will be no opportunity to use it later.

If we can add another 20% to the response rate, we will be able to meet the needs of patients such as those who have transit problems or pain caused by tumors by controlling the tumors early. We believe that we can fully respond to such needs.

Wada : Just one more point.

On the other hand, when combining EGFR inhibitors and Keytruda, it is said that if molecular targeted drugs are used first, it could cause a lot of toxicity, such as interstitial lung cancer. So I think there was some discussion that it would be better to use immunotherapy first. Isn't that also the case with CLDN and OPDIVO?

Okamoto : As I mentioned earlier, the fundamental question is whether to conduct a head-to-head trial comparing PD-1 plus chemotherapy versus zolbetuximab plus chemotherapy.

In colorectal cancer, the standard first-line treatment is FOLFOX or FOLFIRI, but regarding this specific comparison—whether FOLFOX/FOLFIRI is better, or FOLFIRI/FOLFOX is better—trials examining this sequence are currently underway, and I think we won't be able to reach a conclusion without going that far.

Currently, both OPDIVO/chemotherapy and zolbetuximab/chemotherapy are subject to restrictions under the guidelines for optimal use, meaning that neither can be used unless it is for first-line treatment. Therefore, even if we were to suggest continuing the current chemotherapy regimen while switching from zolbetuximab to OPDIVO—since we did not see a response from the combination of zolbetuximab and chemotherapy—it is currently not possible to do so. As for the current point, I don't think we'll be able to reach a conclusion anytime soon.

I just think that, mechanically speaking, it might be a little different from the case of EGFR in lung cancer.

Imura : We've run out of time, I'd like to wrap up the R&D meeting for now.

Thank you very much.

[END]