ONO PHARMACEUTICAL CO., LTD.

R&D Day / ASCO PROSPECT Data Presentation

June 4, 2025

[Number of Speakers]	3	
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	Ryuta Imura	Senior Director of Corporate Communications

Presentation

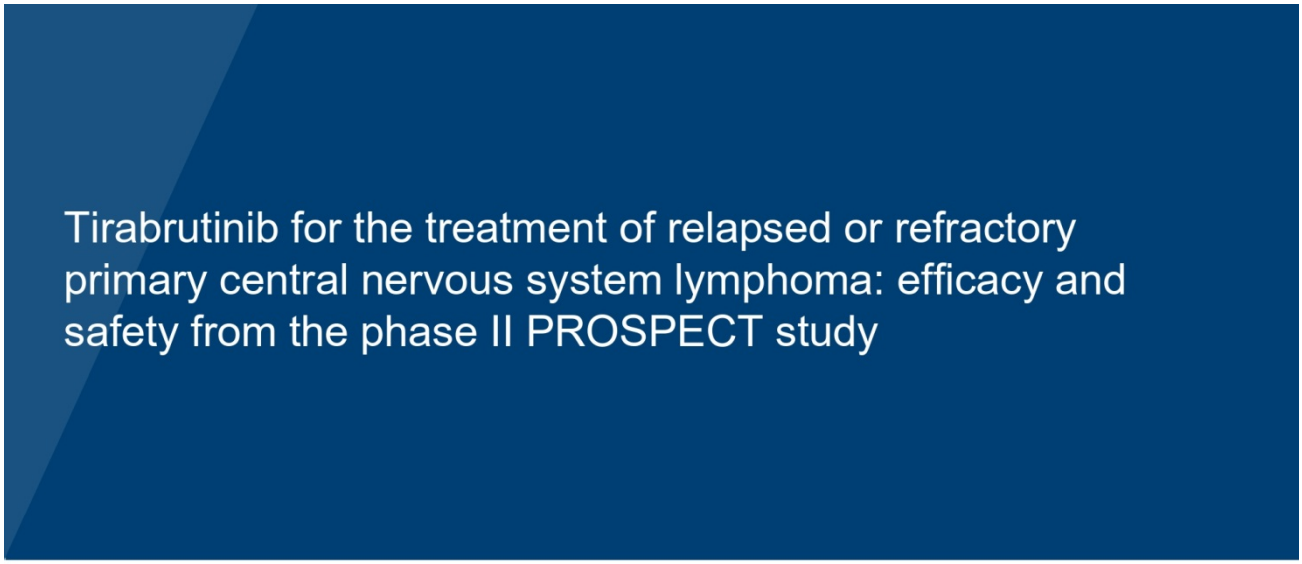
Imura: Let us now begin ONO PHARMACEUTICAL CO., LTD.'s R&D Day. I am Imura from the Corporate Communications Dept.

Today, we have the presentation about the tirabrutinib PROSPECT Study that was announced at the ASCO annual meeting the other day.

Let me introduce the attendees. From our headquarters in Osaka, we have Mr. Okamoto, the Executive Director of Clinical Development. From ONO PHARMA USA, INC., we have the Vice President of Medical Affairs, Mr. Thomas Lechner.

This is the agenda for today. First, we have the presentation about the PROSPECT study by Mr. Lechner. After that, Mr. Okamoto will talk about tirabrutinib data in Japan. As for the materials for today's session, Thomas Lechner's presentation was sent to you by email this morning. Please have a look at it.

Now, we'd like to have the presentation on the PROSPECT study, which was announced at ASCO by Mr. Lechner. Thomas-san, the microphone is yours.



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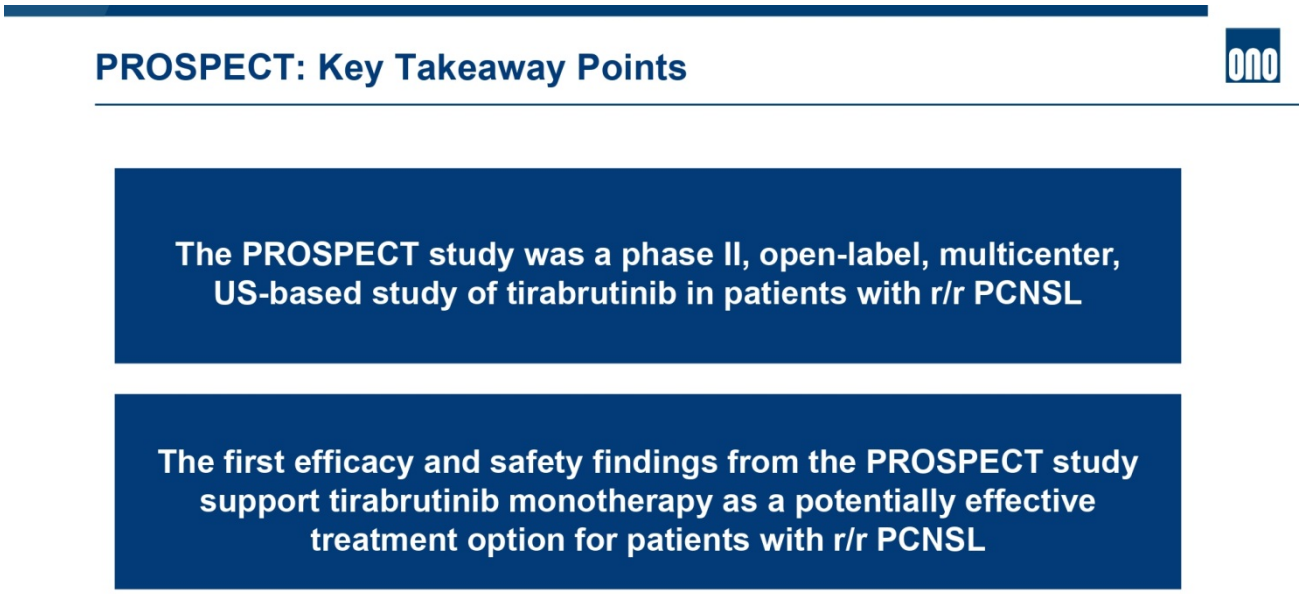
Lechner*: I hope you can all see my slides now. Good morning, ladies and gentlemen. It is my great pleasure to present the data from the pivotal PROSPECT study, as it was recently presented at the 2025 annual meeting by Dr. Lakshmi Nayak.



First, I want to go over some key takeaways from this study. The PROSPECT study was an open-label, multicenter study in patients with relapsed and refractory primary central nervous system lymphoma and was conducted solely in the United States. The efficacy and safety findings reported support tirabrutinib monotherapy as a potential effective treatment option for patients with PCNSL.

PROSPECT: Background

- Primary central nervous system lymphoma (PCNSL) is a rare, aggressive form of non-Hodgkin lymphoma localized to the central nervous system[1,2]
- In the relapsed/refractory setting, treatment options are limited, standard of care is not well established, and prognosis is poor[1,2]
  - There are no currently approved drug therapies for PCNSL in the United States or European Union
- Bruton's tyrosine kinase (BTK) is a regulator of the B-cell receptor pathway, and BTK inhibitors (BTKi) have been investigated for the treatment of B-cell lymphomas[2,3]
- Tirabrutinib is a potent, highly selective second-generation BTKi[4,5]
  - Approved for PCNSL in Japan, Taiwan, and South Korea based on a phase I/II study conducted in Japan[2,4,5]
- Here we report results from the PROSPECT study (NCT04947319) conducted in the United States[6]

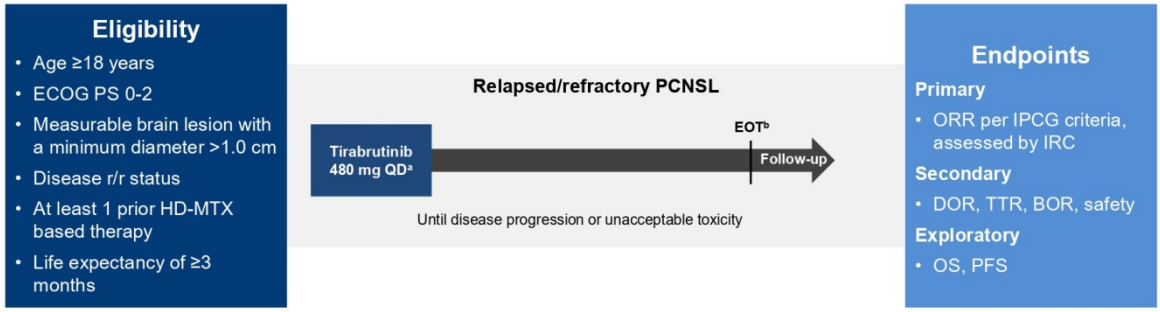
1. Grommes C, DeAngelis LM. *J Clin Oncol*. 2017;35:2410-2418. 2. Schaff L, et al. *Leuk Lymphoma*. 2024;65:882-894. 3. Shirley M. *Target Oncol*. 2022;17:69-84. 4. Narita Y, et al. *Neuro Oncol*. 2021;23:122-133. 5. Yonezawa H, et al. *Neurooncol Adv*. 2024;6(1):vdae037. 6. ClinicalTrials.gov. Accessed March 31, 2025. https://clinicaltrials.gov/ct2/show/NCT04947319

Please allow me to provide a little bit more background before I proceed to the study data.

Primary central nervous system lymphoma, or PCNSL, is a rare and aggressive form of non-Hodgkin's lymphoma, which is localized mainly to the central nervous system. In the relapsed and refractory setting, treatment options are limited, standard of care is not well established, prognosis is poor, and most importantly, there are currently no approved therapies for PCNSL in the United States or the European Union.

Bruton's tyrosine kinase, BTK, is a regulator of the B-cell receptor pathway, and BTK inhibitors (BTKi), have been investigated for the treatment of B-cell lymphomas. Tirabrutinib is a potent, highly selective second-generation BTKi and is approved for PCNSL in Japan, Taiwan, and South Korea, based on a Phase I/II study that was conducted in Japan.

PROSPECT: Study Design and Methods



[a]Tirabrutinib is administered on an empty stomach at least 1 hour prior to eating or 2 hours after eating.
[b]EOT is defined as the date the investigator decides to discontinue tirabrutinib for each patient.
BOR, best overall response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; HD-MTX, high-dose methotrexate; IPCG, International PCNSL Collaborative Group; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; QD, once daily; r/r, relapsed or refractory; TTR, time to response.

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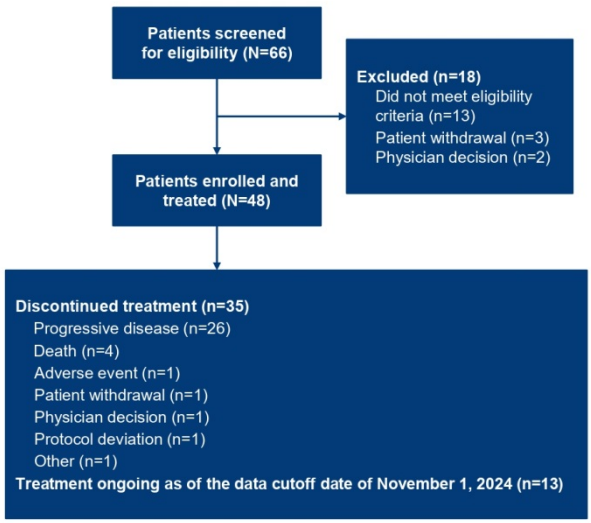
Now, I would like to review the study design.

As you can see here, eligible patients who had a confirmed diagnosis of relapsed or refractory PCNSL, had received at least one prior therapy with a high-dose methotrexate-containing regimen, and fulfilled other criteria as outlined on this slide, were allowed on the study.

Those patients then received tirabrutinib at 480 mg QD, meaning once daily in a faster state until disease progression or unacceptable toxicity. The primary endpoint of the study was overall survival rate. Secondary endpoints included duration of response and exploratory endpoints and included overall survival and progression-free survival.

PROSPECT: Patient Disposition and Characteristics



Characteristic	Tirabrutinib (N=48)
Age, median years (range)	65.5 (34-87)
Sex, male, n (%)	21 (44)
ECOG PS, n (%)	
0	9 (19)
1	30 (63)
≥2	9 (19)
KPS, median (range)	85 (50-100)
Prior treatment for PCNSL, n (%)	
Any medication	48 (100)
Methotrexate	48 (100)
Rituximab	43 (90)
Cytarabine	25 (52)
Radiotherapy	16 (33)
Hematopoietic stem cell transplant	5 (10)
R/R status at most recent treatment, n (%)	
Refractory	23 (48)
Relapsed	22 (46)
Unknown	3 (66)
Number of prior treatments for PCNSL, n (%)	
1	30 (63)
2	10 (21)
≥3	8 (17)

KPS, Karnofsky performance status; R/R, relapsed or refractory.

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Please allow me to briefly review the patient disposition and characteristics.

As you can see here on the left side of this slide, overall, 66 patients were screened. 18 were excluded as they did not meet eligibility criteria, patients withdrew, or physicians made the decision not to enroll the patient. Ultimately, 48 patients made it onto the study.

As of the data cutoff from November 1, 2024, 35 patients discontinued treatment due to progressive disease, death, adverse events, patient withdrawal, physician decision, protocol deviation, or other reasons. But most importantly and also very encouraging, as of data cutoff, 13 patients were still on treatment.

Now, if you look at the patient characteristics, the median age was 65.5 years, which is quite characteristic for a relapsed and refractory patient population in PCNSL, as it mostly inflicts elderly patients. The distribution between genders was also as expected.

Looking at ECOG performance status and Karnofsky performance scale, you can see here the range for ECOG; most patients had an ECOG performance status of one, and Karnofsky was at 85. Prior treatments, any medication that was received by 100% of patients, methotrexate by 100% as this was, of course, an inclusion criterion, 90% received rituximab, which is also very often given together with high-dose methotrexate.

Cytarabine and radiotherapy were received by 52% and 33% of patients, respectively, and 10% actually had a hematopoietic stem cell transplant. Unfortunately, these patients relapsed, and for that reason, were included in the study.

The distribution between refractory and relapse is also almost 50-50. As for the number of prior treatments, 63% received one prior treatment, 21%, 2, and 17%, 3 or more, respectively. This constitutes a fairly high pretreated patient population.

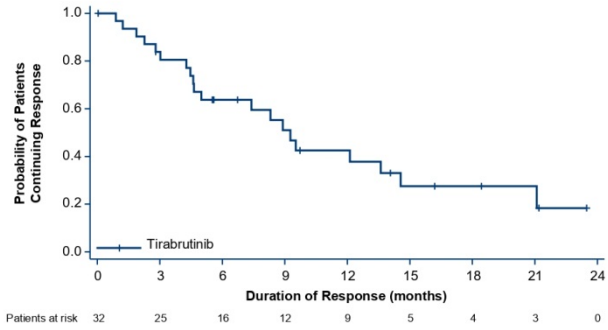
PROSPECT: Overall Response Rate and Duration of Response

Primary Endpoint: ORR by IRC[a]

		ORR by IRC	
		n (%)	95% CI
ORR (CR+CRu+PR)		32 (67)	52, 80
CRR (CR+CRu)		21 (44)	29, 59
BOR	CR	13 (27)	15, 42
	CRu	8 (17)	7, 30
	PR	11 (23)	12, 37
	SD	9 (19)	9, 33
	PD	6 (13)	5, 25
	NE	1 (2)	0, 11

- ORR by IRC = 67% (95% CI: 52, 80)
- CRR by IRC = 44% (95% CI: 29, 59)

Duration of Response by IRC



- Median DOR by IRC = 9.3 months (95% CI: 4.6, 14.6)

Median time to response by IRC = 1.0 months (range, 0.9-3.7)

[a]Response determined per IPCG criteria.
CR, complete response; CRR, complete response rate; CRu, unconfirmed complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

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Next, let me highlight the primary endpoint, overall response rate.

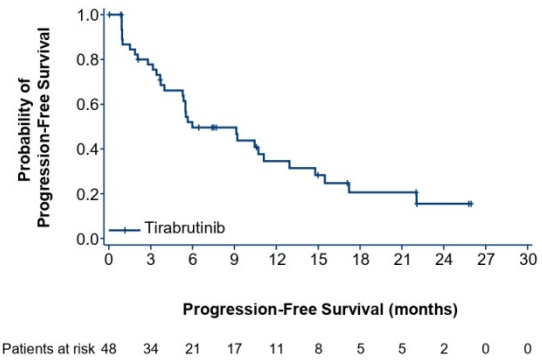
As you can see here in the table, 67% of patients had an objective response (ORR: 67%). That is constituted of complete response (CR), unconfirmed complete response (CRu) and PR. Most importantly, and I want to highlight that number, the complete response (CRR) was 44%, which we believe is quite remarkable.

If you look now to the right-hand side, you can see the Kaplan-Meier curve for the duration of response. The median duration response assessed by an independent review committee was 9.3 months, which is also quite remarkable.

Another important clinical parameter depicted here is the median time to response, which was one month. This indicates that patients who actually had a response to tirabrutinib could be evaluated fairly quickly, which is also important for clinicians as it determines the next steps in terms of treatment management.

PROSPECT: Progression-Free Survival and Overall Survival

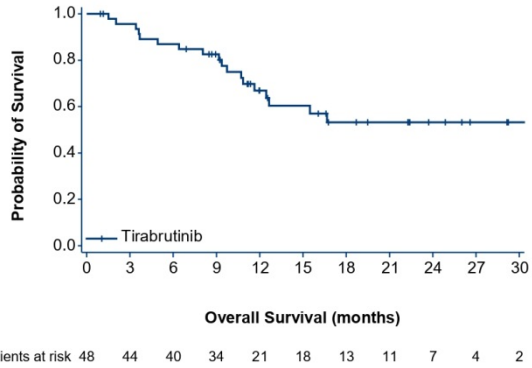
Progression-Free Survival by IRC



Patients at risk 48 34 21 17 11 8 5 5 2 0 0

- Median PFS by IRC = 6.0 months (95% CI: 5.3, 11.1)

Overall Survival



Patients at risk 48 44 40 34 21 18 13 11 7 4 2

- Median OS = NR (95% CI: 12.5, NA)

NA, not available; NR, not reached.

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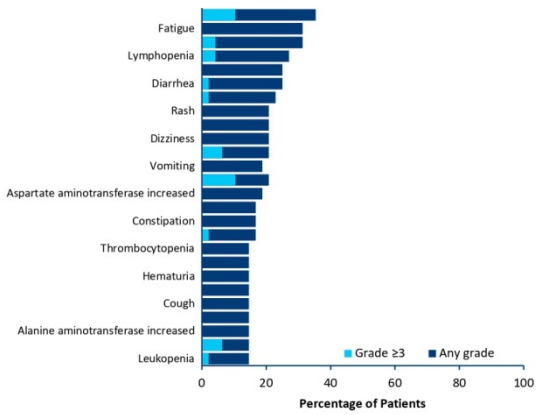
Now, I move to the two exploratory endpoints, progression-free survival and overall survival.

In the PROSPECT study, the median PFS was six months, and the overall survival was not reached yet. Both these endpoints are quite encouraging. Of course, the safety of tirabrutinib was also evaluated, and I will go over some of the key treatment-emergent adverse events.

PROSPECT: Adverse Events

TEAEs	Tirabrutinib (N=48)	
	Any grade, n (%)	Grade ≥3, n (%)
Patients with ≥1 TEAE	47 (98)	27 (56)
Patients with ≥1 treatment-related TEAE	36 (75)	13 (27)
Patients with TEAEs leading to dose interruption Treatment-related	24 (50) 16 (33)	15 (31) 8 (17)
Patients with TEAEs leading to dose reduction Treatment-related	5 (10) 3 (6)	0 0
Patients with TEAEs leading to study withdrawal Treatment-related	5 (10) 1 (2)	4 (8) 1 (2)
Patients with serious TEAEs Treatment-related	21 (44) 5 (10)	17 (35) 5 (10)
	Any grade, n (%)	
Patients with fatal TEAEs Treatment-related	2 (4) 0	

TEAEs in ≥15% of Patients



- Tirabrutinib was well tolerated in this population, with a low incidence of cardiac events (<10%, all grade 1-2)

TEAE, treatment-emergent adverse event.

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As you can see here in this table, patients with more than one treatment-emergent adverse event, which includes treatment-related, were any grade 98% and grade 3 or higher 56%. Patients with one or more treatment-related TEAE were 75%, and grade 3 or higher at 27%, respectively.

If you look at the patients with treatment-emergent adverse events that were treatment-related leading to dose interruption, which was one of the mechanisms for physicians and clinicians treating these patients to manage adverse events. These were any grade 33%, grade 3 or higher, 17%.

TEAEs leading to dose reductions, treatment-related was fairly low with any grade 6%, grade 3 or higher, 0%. Leading to study withdrawal, treatment-related, again, any grade, or grade 3 or higher was 2%, 2%, respectively, which was also very low. Patients with serious treatment-emergent TEAEs that were treatment-related were 10% each for any grade and grade 3 or higher. Patients with fatal TEAEs were 4%, but none of those were related to treatment, i.e., tirabrutinib.

Now, looking over here at TEAEs that emerged in 15% or more of patients such as fatigue, lymphopenia, diarrhea, rash, dizziness, vomiting, constipation, thrombocytopenia, leukopenia, etc. They all occurred at a fairly low incidence, and most importantly, grade 3 or higher were low in incidence.

Also important to note here, there was a low incidence of cardiac events, which can be concerning for clinicians at a rate of less than 10%, all grades 1 and 2. Based on this safety analysis, the PROSPECT study investigators concluded that tirabrutinib is well-tolerated.

PROSPECT: Conclusions

- PROSPECT was a phase II, open-label, multicenter, US-based study of tirabrutinib in patients with relapsed or refractory PCNSL
- Tirabrutinib demonstrated a high ORR, prolonged DOR, and reasonable PFS with a well-tolerated side effect profile
- Expanding on experience in Japan, these first efficacy and safety findings from the PROSPECT study further support tirabrutinib monotherapy as a potentially effective treatment option for patients with relapsed or refractory PCNSL

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In conclusion, tirabrutinib demonstrated a high overall response rate, prolonged duration response, a reasonable progression-free survival, with a well-tolerated side effect profile. The PROSPECT investigator thought by expanding on the experience in Japan, these first efficacy and safety findings from the PROSPECT study further support tirabrutinib monotherapy as a potentially effective treatment option for patients with relapsed or refractory PCNSL.

Acknowledgments

We thank the patients and their families for making the PROSPECT study possible

We also thank the investigators and clinical trial teams who participated in the study

This study was funded by Ono Pharmaceutical Co. Ltd

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We would like to thank all the patients and their families for making the PROSPECT study possible. We, of course, want to thank all the investigators and their clinical trial teams that participated in the study, and the study was funded by ONO PHARMACEUTICAL.

PROSPECT: Lay Summary

- Primary central nervous system lymphoma (PCNSL) is a rare tumor that occurs in the brain, spinal cord, and other parts of the central nervous system
- This kind of cancer can be treated with chemotherapy, but the cancer commonly comes back
- The PROSPECT study tested tirabrutinib, an experimental new medicine designed to treat PCNSL, in people whose cancer had come back after chemotherapy
- Two thirds of patients with PCNSL responded to tirabrutinib
- For patients experiencing side effects, their doctors managed these by lowering the amount of tirabrutinib or pausing the treatment with tirabrutinib
- The PROSPECT study showed that tirabrutinib may be a good treatment option for people with PCNSL

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I would like to end by putting these findings into layman's terms. Primary PCNSL is a rare tumor that occurs mostly in the brain. It can be treated with chemotherapy, but the cancer commonly comes back or does not respond to initial chemotherapy.

This study tested tirabrutinib, which is an experimental new medicine in people whose cancer had come back after chemotherapy or did not have an initial response to chemotherapy. Remarkably, 2/3 of patients with PCNSL responded to tirabrutinib.

For those patients who experienced side effects, their physicians manage these by lowering the amount of tirabrutinib or pausing treatment. It was, as I mentioned before, very well-tolerated. The PROSPECT study showed that tirabrutinib may be a good treatment option for people with PCNSL. I believe this was my last slide, and I thank you very much for your attention.

Imura: Thank you very much. Now, let me go on to the production and presentation on tirabrutinib, including the data in Japan. Let me invite Okamoto-san.

Okamoto: Good morning and good afternoon to you all. I'm Okamoto.

We'd like to share with you the number of PCNSL patients in the US, currently available treatment options, and current status of the treatment of PCNSL, as well as the long-term follow-up data from the Phase II trial, ONO-4059-02, which served as the basis for approval in Japan. Based on this information, I will explain the results of the PROSPECT trial, which is a Phase II trial in the United States.

This slide shows the excerpt from the epidemiologic and treatment information on PCNSL publicized by our US subsidiary, OPUS. Please find this on the homepage later.

The positioning of PCNSL as a disease in the US is that PCNSL is a kind of highly malignant non-Hodgkin lymphoma, which accounts for 2% to 3% of non-Hodgkin lymphoma, or about 4% of brain tumors. 0.45% per 100,000 people develop this disease. It is a rare cancer. Every year, about 1,900 people are newly diagnosed with this disease.

This page is about the currently available treatments.

What you see here now are the guidelines from NCCN. The patients eligible for the PROSPECT study, which were recently published, are indicated in the blue box on the right side. These are relapsed and refractory PCNSL patients. The relevant part is what I will focus on today.

For newly diagnosed patients, in most cases, monotherapy with methotrexate, or combination chemotherapy based on methotrexate, are treatments. But it has been reported, unfortunately, that about 60% of the patients had a relapse of the disease.

As a treatment for the patients who relapse, as you see here in the blue box, the rechallenge with high-dose methotrexate or whole-brain radiation or a different drug therapy from the first-line treatment such as Temozolomide, are options.

It seems there are several options available. As you see at the very top, there are clinical trials. Clinical trials are one of the options. There is no established standard treatment at this moment. There is no drug treatment approved by the FDA for use in this treatment line. We believe there are very high unmet needs.

Next is about the result of the PROSPECT trial. At ASCO in 2023, the results of the ONO-4059-02, the 3-year follow-up of Phase II in Japan, were made. Let me make some additional explanations, including the comparison between the two trials.

First is about the primary endpoint for the PROSPECT study and Phase II in Japan, that is the response ratio by the primary endpoint. On the left side is the PROSPECT study, and right side is the domestic Phase II study. As you see here, response ratio and CR ratio from PROSPECT are equivalent or better or very similar. But the response ratio from the PROSPECT study or CR ratio from PROSPECT study are equivalent or better than the one achieved in Phase II in Japan.

The Phase II study in Japan had 17 patients enrolled, which was very limited. But this time with the PROSPECT study, 48 patients were enrolled, and an evaluation was made. The results of the efficacy from PROSPECT

study that we reproduced the results from the trial in Japan. We are happy to see that consistent results were shown about the efficacy of Velexbru on relapsed and refractory PCNSL.

Next is PFS, progression-free survival. For PROSPECT, as was mentioned earlier, the median figure was six months and a study in Japan has shown 5.8 months. Numerically, the equivalent level was achieved. About items such as PFS and OS, which depend on time for evaluation, a comparison of these studies are not possible. But based on the facts, there is no big difference in the patient background, except for race. As a result of the response ratio as primary endpoint a consistent result was shown with PFS.

Next is the OS, overall survival results. As was already mentioned, OS from PROSPECT has a very short follow-up period. At this moment, the OS results are still immature. But in Japan, as a result of the long-term follow-up of three years, the data is available. But still, the median OS was not achieved. Favorable results were achieved with 64.7% OS in the first year and 52.9% in the third year.

Today, we are not showing relevant data, but as a result of a long-term follow-up in trial in Japan, the acquired safety profile was consistent with the one gained before the filing, and it was manageable. With the absence of a difference in response ratio and in the safety profile between Japan and abroad, we believe US can be expected to experience the same long-term survival benefits as Japanese patients.

This is my last slide. As I mentioned earlier, there is no established treatment for relapsed and refractory PCNSL in the United States at present. Because PCNSL is a rare disease, not many active clinical studies were carried out in the past, which is the background of this current situation.

This table is quite busy, with a bit of old data from 2018, sorry about this. But please pay attention to the data in the blue box at the bottom, which shows a list of the active clinical trials reported. Some of them hadn't established the median value of OS at the time of the report. But in general, the OS results were not satisfactory.

On the right side, highlighted in blue, are the unsatisfactory OS results. There’s a very high unmet need in the US. Based on the results of the US and Japan, we believe tirabrutinib will become a new treatment option to meet the unmet need in the United States.

That's all from me. Thank you very much.

Imura: Thank you very much, Mr. Okamoto.

Questions & Answers

Imura : Now that we have had the presentations, I want to open the floor for the Q&A session from now. First, Mr. Wakao from JPMorgan.

Wakao : I am Wakao from JPMorgan. We are very happy to hear the very favorable results. I have some questions.

The first one is, as you explained, compared to Japan, the study in the US had a very favorable result. I think the increase in the number of patient enrollments can be the background of the several results you have. Are there any factors? In the profile of the side effects in Japan, 30% of patients have shown a rash, and a smaller number of patients in the US trial have shown a rash as a side effect. Is there any cause for that? These are the two questions I have.

Okamoto : Thank you very much for your questions. In case of the US PROSPECT study, the overall data has a favorable result over the one in Japan. As you mentioned, the patient enrollment in Japan was smaller. 95% CI is between 27.8 and 77 for the range in Japan, and 52 to 80 in the US. The small number of patients enrolled in Japan resulted in the difficulty to determine the capability of tirabrutinib with figures. In case of the US PROSPECT study, we have a greater number of enrollments. The actual capability of tirabrutinib on PCNSL was shown.

As for the side effects, I haven't made a detailed analysis of each patient case. As for the question about the smaller number of patients with rash as a side effect, please let me refrain from making a comment on that point.

Wakao : I understand. My next question is about the number of patients that you mentioned. I believe the maximum of 1,900 represents the annual newly diagnosed patients or annual incidence rate. How many patients are actually eligible patients for tirabrutinib when it is approved? Based on the results shown here, there is no other favorable or effective treatment available. When tirabrutinib is approved, can we expect a smooth entry into the market? Or do you expect any barriers for tirabrutinib to enter the market?

Okamoto : First about the number of patients. Thank you for your question. 1,900 is the number of the newly diagnosed patients. On the other hand, in the second line and later, for recurrent or refractory disease, it's a rare disease and it's currently difficult to fully grasp the exact numbers. But as I mentioned earlier, about 60% of the patients had a relapse of the disease. In case of the naïve patients, the OS is not so short. At least 0.6 multiplied by 1,900 patients definitely exist.

Wakao : Next question is about market entry barriers?

Okamoto : We don't have a person in charge of market entry, so let me answer your question. At present, we do not see any specific barriers for market entry.

Imura : Next is Mr. Sakai from UBS.

Sakai : I'm Sakai from UBS. I have two questions. One is about Japan. JPY11 billion per year is your forecast. Could you please provide a breakdown of this figure, such as the number of patients receiving treatment and the length of treatment, given that the drug has been on the market for about two years?

Imura : Thank you for your question. In Japan, for the number of patients administered, we have two indications approved in Japan. Approximately half of the sales comes from PCNSL as a result of our analysis. I

am sorry about the number of patients, but I don't have the information to answer your question right now, so we will respond to that question later.

Sakai : My second question is what is average duration of treatment for patients currently undergoing treatment.

Imura : As for the administration period, let me check to answer your question. I'll respond to that question later.

Sakai : Okay. I will wait for the answers.

Imura : I'd like to come back with the answers to your questions within this session.

Sakai : Okay. I have another question. High-dose MTX is an option for patients who develop symptoms for the first time, along with radiation. According to some information, with this treatment, without any treatment, patients last only for a few months. But with this high-dose MTX, 50% of the patients can live up to five years.

Given that treatment, the PROSPECT study, as was explained by Thomas, it seems to be heavily pre-treated. For the patients who first develop the disease, I think tirabrutinib will be an option, or replace, the high-dose MTX. It will depend on the guidelines by NCCN, but do you expect that tirabrutinib will replace the currently available treatment with MTX? Are you going to have a discussion with the FDA? Please tell us about the points of discussion with the FDA.

Okamoto : As you mentioned, for the patients who first developed the symptom or disease, yes, the current available treatment has some efficacy, and the overall survival from that point is long. But our target patients are the ones who had a relapse after the first treatment. We made the filing for approval for patients with R/R. Regarding the initial onset, we are currently exploring the combination with other chemotherapies in a separate cohort of the PROSPECT study. This is the answer to your first question.

Second, regarding the points of discussion with the FDA, we currently have no particular concerns regarding efficacy or safety, and we have already discussed the trial design with the FDA prior to the start of the trial. Specifically, we have conducted the trial after discussing matters such as the number of participants, so at this point, there are no major points of discussion.

Sakai : That means you already have an agreement with the FDA. You can bring this data for the filing. I think you will have another discussion with FDA before the filing.

Okamoto : We plan to apply based on this data.

Sakai : So, these 1,900 newly diagnosed patients in the US, 60% of them will be relapsing patients. This is the initial target patient group for you?

Okamoto : Yes. These 1,900 newly diagnosed patients, almost all of them have done the fast treatment and have a good response, and the short-term prognosis is not significantly poor. But 60% of them had a relapse, and so it is difficult to make a cumulative estimate on total patients. In the longer term, though at least 60% of these 1,900 patients will have a relapse of the disease. Over time we can expect a large patient group eligible for tirabrutinib.

Sakai : How about Japan?

Imura : Let me answer your question about Japan. We estimate 1,500 patients per year in Japan are newly diagnosed with this disease, of which Velexbru is prescribed for about 630 patients. 8.3 months is the median period for the treatment.

Sakai : Understood. 630 patients are treated with tirabrutinib.

Imura : Yes.

Sakai : Thank you.

Okamoto : Let me add one thing to that information. Based on the three-year follow-up data, the median PFS is 5.8 months, so when considering the overall results, 5.8 months can be the treatment period. But when you see the 12-month PFS, it is 31.7%, meaning that about 30% of patients have the treatment for 1 year, and 19% of those patients stay in remission for 36 months. So, about 20% of the patients continue to receive treatment for three years, indicating long-term benefits for these patients.

Imura : Next is Yamaguchi-san from Citi group.

Yamaguchi : I have one question. As you mentioned, you are targeting first-line treatment. I think this can be used as a monotherapy without chemo or other agents. Did you consider the possibility of using a BTK inhibitor as a monotherapy?

Okamoto : Thank you for your question. The effects of high-dose methotrexate therapy plus so-called combination chemotherapy are quite high, and I think it would be a little difficult to replace it with a single agent. As a result of repeated discussions within the company, we are currently exploring combination therapy. The data on combination therapy itself is not yet available, so we will consider various options once the data becomes available.

Yamaguchi : Is the MTX dosage usually reduced a little when used in combination with other drugs, or is it the same?

Okamoto : You're talking about the first line?

Yamaguchi : Yes.

Okamoto : We combine the tirabrutinib with the standard overall dosage of MTX.

Yamaguchi : It's an additional amount.

Okamoto : Yes.

Imura : Next is Muraoka-san from Morgan Stanley.

Muraoka : This is Muraoka from Morgan Stanley. Let me summarize the information I've received. In Japan, for PCNSL, I think tirabrutinib is used for the first-line treatment. Are the patients who are indicated to use tirabrutinib, 30% for one year, 20% for three years, mainly patients receiving the first-line treatment? What I want to ask is that in the United States, the success with the first-line treatment will be a kind of important factor for increasing the number of eligible patients and the duration of treatment. Sorry, if my understanding is not correct, would you please clarify it for me?

Okamoto : Thank you for your question. In Japan, efficacy is for the relapsed and refractory PCNSL, not for the first-line treatment. In the US, with the PROSPECT study as background, it is same as that of Japan. This time, this is for the other PCNSL, relapsed refractory PCNSL only.

Regarding future developments for first-line treatment, as with the previous question, we are currently exploring this area and are not yet at a stage where we can provide anything specific.

Muraoka : I understand that the data for the first-line treatment of the PROSPECT study are expected to be available around 2027. Is that correct? According to the information from ClinicalTrials.gov, it says 2027.

Okamoto : Thank you. As I mentioned earlier, the results that were explained this time are from Part A of the PROSPECT study. Part B of the same study is being conducted for the first-line treatment of patients who have not yet received treatment.

Muraoka : Can we expect the data coming in 2027? Is this understanding correct?

Okamoto : Yes.

Muraoka : In the second line, the PFS average is six months, but there are the patients who continue to use it one year or three years. There are many long-tail patients. Is this the kind of business model you can expect?

I found the discontinuation ratio is quite high, with 35 patients out of 48 discontinuing. There are the patients who use it for just a short period of time, and there are the others who continue to use for quite a long time. These patients who continue to use it for a long time will make a greater contribution to your sales?

Okamoto : It is difficult to analyze actual sales and the study results at the same time. Other than this study, in Japan, we have three-year follow-up data, and duration of response is available from the three-year follow-up. 56% for 12 months and 33% for three years. Many patients had efficacy for quite a long time. Response rate is over 60%. That means a little more than 30% of the patients witnessed the progress of disease and had to switch to the other treatments. How this will be reflected in the market and actual clinical practice is complex, so it is hard to make a definitive answer.

Muraoka : I understand the situation. You have made an application for the second line. Do you see any possibility of a breakthrough therapy?

Okamoto : We have traditionally refrained from responding to questions regarding strategic aspects of approval applications, both domestically and internationally. We appreciate your understanding.

Imura : Next, Wada-san from SMBC.

Wada : This is Wada from SMBC. I have a question about the expansion of indication to other types of lymphoma. What were the factors that led you to consider this PCNSL as an indication first, and why did you not consider applying it to other lymphomas at that time? Do you also see the other lymphoma as a candidate indication?

Okamoto : First, the reason we began development in the US focusing on PCNSL, particularly in cases of recurrent and refractory disease, is as I have mentioned before, we have never developed or marketed a product overseas on our own. In Japan, the product is already approved and considered to be well-established. We selected this disease and treatment line as our first step in the US because we were able to conduct trials and sufficiently evaluate the efficacy and safety benefits.

In Japan, we also have approval for WM, but regarding expansion into other lymphomas, as you are aware, BTK inhibitors have a very large market size overall, but it is a highly competitive field with many competitors. At least at this point, we are focusing specifically on PCNSL.

Wada : So, you are working on a clinical study of pemphigus? You are also focusing on the auto-immune aspect?

Okamoto : We have disclosed information about pemphigus, and we are conducting Phase 3 trials in Japan.

Imura : Thank you very much for your questions. I would like to close the Q&A session now and conclude the R&D briefing regarding the PROSPECT study of Tirabrutinib, which was presented at ASCO.

Thank you very much for joining us today despite your busy schedules. We will now conclude the session.