R&D Day
– PROSPECT Study Data Presentation –

June 4, 2025

ONO PHARMA

Agenda

PROSPECT Study (10:30-10:45)

Vice President, Medical Affairs, ONO PHARMA USA

Thomas Lechner, MSc. Ph.D.

Closing (10:45-10:55)

Corporate Officer / Executive Director, Clinical Development

Tatsuya Okamoto

Q&A Session (10:55-11:15)

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Tirabrutinib for the treatment of relapsed or refractory primary central nervous system lymphoma: efficacy and safety from the phase II PROSPECT study

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PROSPECT: Key Takeaway Points

The PROSPECT study was a phase II, open-label, multicenter, US-based study of tirabrutinib in patients with r/r PCNSL

The first efficacy and safety findings from the PROSPECT study support tirabrutinib monotherapy as a potentially effective treatment option for patients with r/r 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]

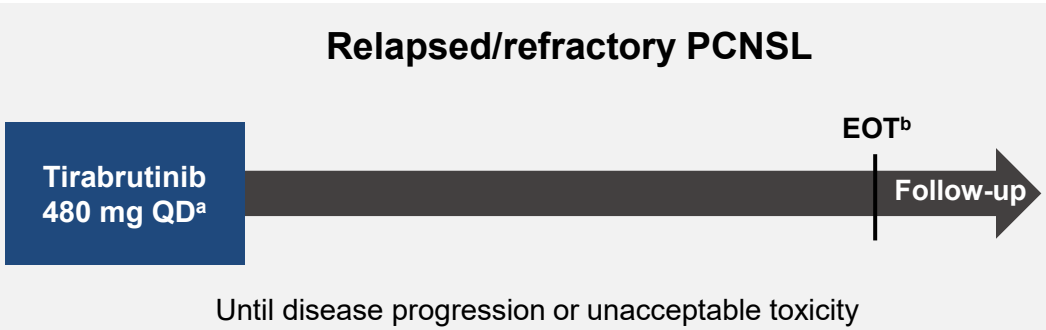
- Here we report results from the PROSPECT study (NCT04947319) conducted in the United States[6]

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

PROSPECT: Study Design and Methods

Eligibility

- Age ≥18 years
- ECOG PS 0-2
- Measurable brain lesion with a minimum diameter >1.0 cm
- Disease r/r status
- At least 1 prior HD-MTX based therapy
- Life expectancy of ≥3 months



Endpoints

Primary

- ORR per IPCG criteria, assessed by IRC

Secondary

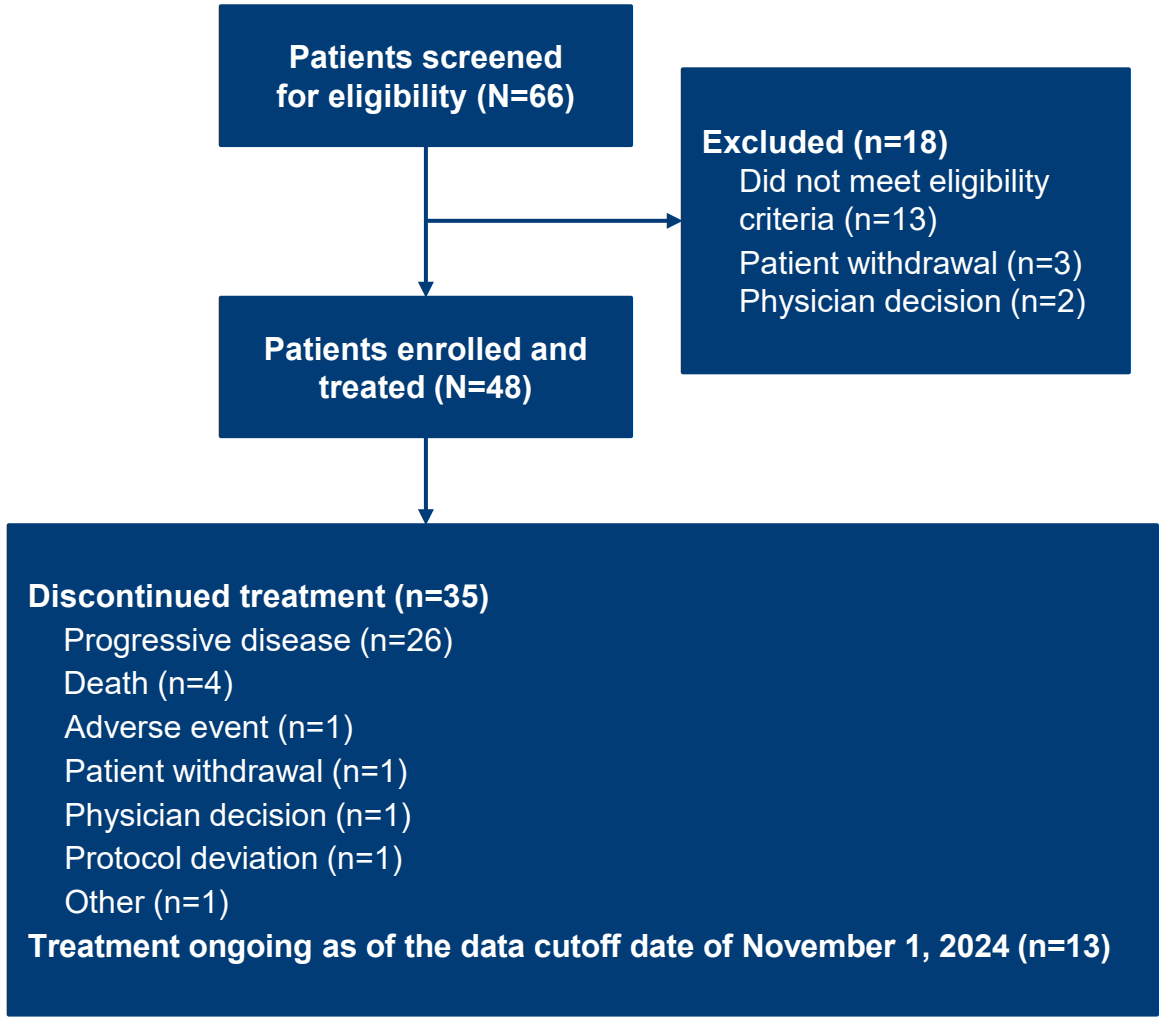
- DOR, TTR, BOR, safety

Exploratory

- OS, PFS

[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.

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.

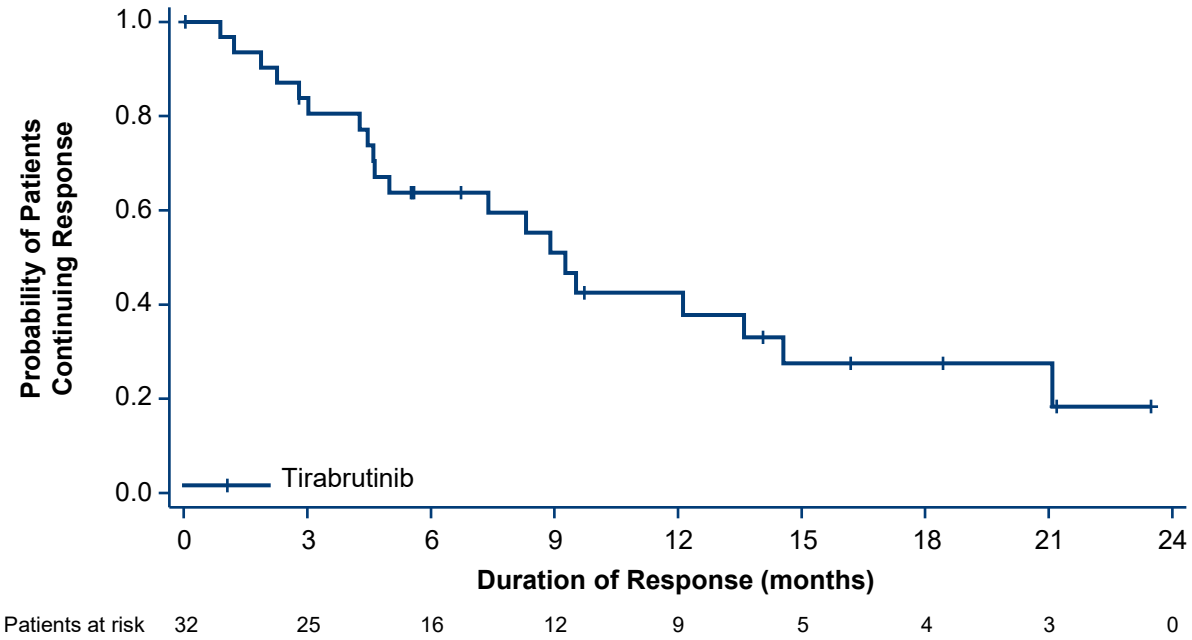
PROSPECT: Overall Response Rate and Duration of Response

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



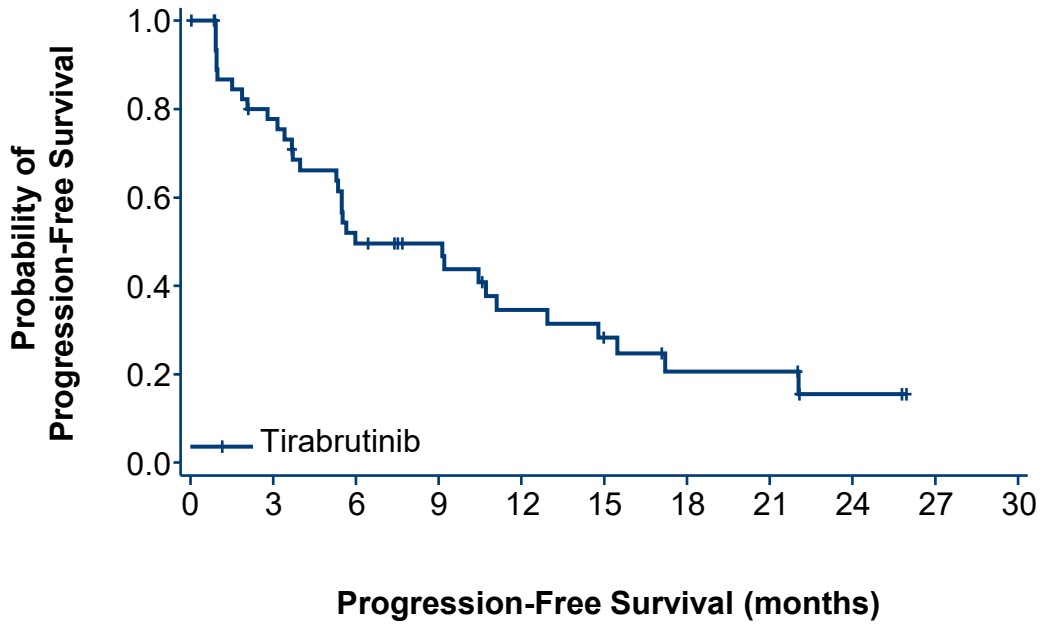
- Median DOR by IRC = 9.3 months (95% CI: 4.6, 14.6)

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.

PROSPECT: Progression-Free Survival and Overall Survival

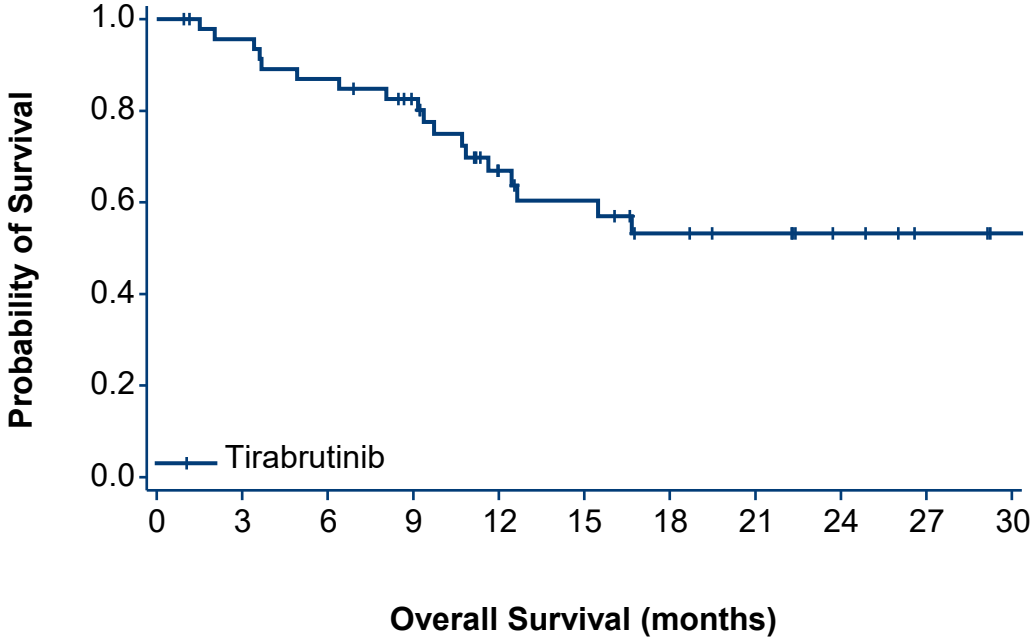
Progression-Free Survival by IRC



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



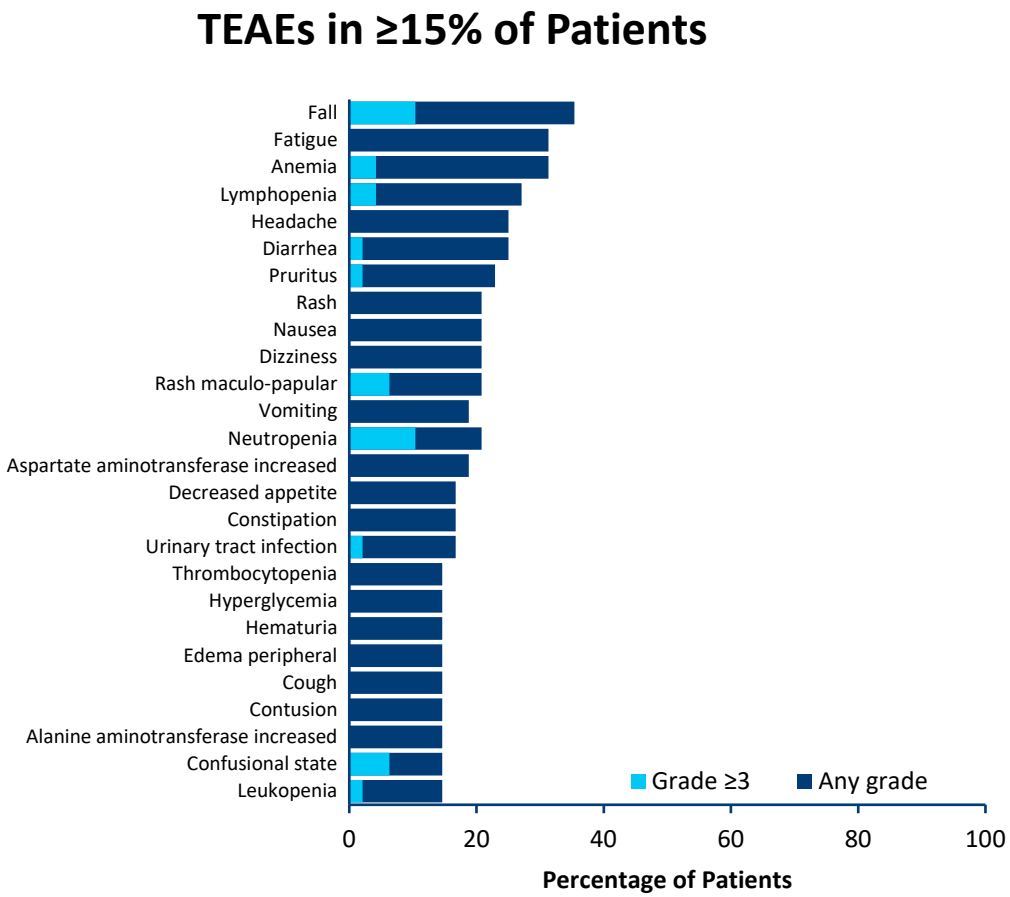
Patients at risk	48	44	40	34	21	18	13	11	7	4	2

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

NA, not available; NR, not reached.

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	



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

TEAE, treatment-emergent adverse event.

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

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

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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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