Trial in progress (IGNITE): a phase 3, multiregional, open-label, randomized study of tirabrutinib vs rituximab and temozolomide in relapsed/refractory primary central nervous system lymphoma

Poster: ABCL-086

Lakshmi Nayak[1]*, Christian Grommes[2]*, Charles Psoinos[3], Akira Takazawa[4], Tracy Batchelor[5]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Deciphera Pharmaceuticals, LLC, Waltham, MA, USA; [4]ONO PHARMA USA, INC., Cambridge, MA, USA; [5]Brigham and Women's Hospital, Boston, MA, USA

*These authors contributed equally to this work.

Introduction

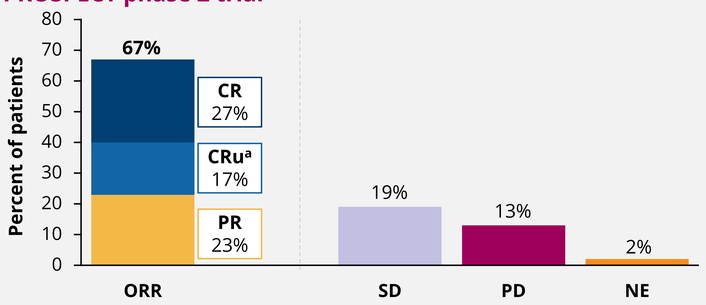
Unmet need in R/R PCNSL

- Primary central nervous system lymphoma (PCNSL) is a rare, highly aggressive form of non-Hodgkin lymphoma localized to the brain, spinal cord, cerebrospinal fluid, and/or eyes[1,2]
- Although patients with PCNSL generally respond to guideline-recommended first-line high-dose methotrexate induction, 10%–30% of patients have refractory disease and up to 45% relapse within 5 years[3-5]
- The prognosis for patients with relapsed or refractory (R/R) PCNSL is poor, with a median overall survival ranging from 5 to 20 months[6,7]
- Treatment options for R/R PCNSL are limited in the US and none are approved in the European Union
- Bruton tyrosine kinase (BTK) is a pivotal mediator of the B-cell receptor signaling pathway, making it an attractive therapeutic target for blocking the constitutive activation of key oncogenic pathways in PCNSL[8]
- The first-generation BTK inhibitor ibrutinib is often used as an off-label treatment option[9]
  - Despite high response rates, ibrutinib monotherapy has a relatively short duration of response of ~6 months, and adverse events such as atrial fibrillation, bleeding, and fungal infections remain a concern[9,10]

Tirabrutinib in R/R PCNSL

- Tirabrutinib is a highly selective and potent second-generation BTK inhibitor
- The demonstrated efficacy and safety of tirabrutinib in an open-label phase 1/2 trial conducted in Japan[11] served as the basis of its approval for R/R PCNSL in Japan, Taiwan, and South Korea
- The primary results from the PROSPECT phase 2 study (NCT04947319) conducted in the US reported an overall response rate of 67% (32/48) and duration of response of 9.3 months in patients with R/R PCNSL (**Figure 1**)[12]

Figure 1. Best overall response with tirabrutinib in the PROSPECT phase 2 trial



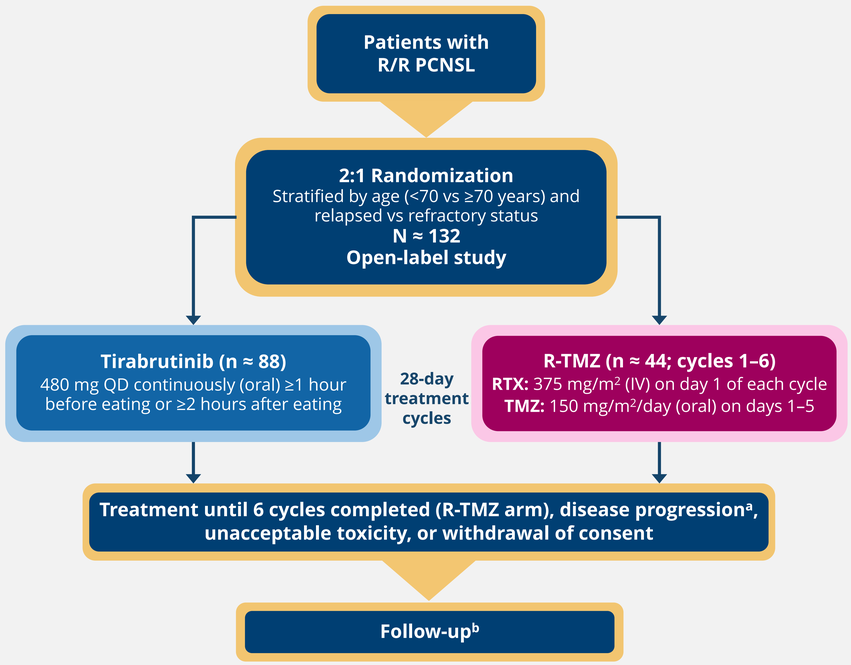
Assessed by blinded independent review committee per International PCNSL Collaborative Group Criteria.
Percentages may not add up to 100% because of rounding.
[a]Any patient who fulfills all criteria for CR but continues to require corticosteroid therapy at any dose, and patients with a persistent minor abnormality on follow-up ophthalmologic examination (if the abnormality is unlikely to represent ocular lymphoma).
CR, complete response; CRu, unconfirmed CR; NE, not evaluable; ORR, overall response rate; PCNSL, primary central nervous system lymphoma; PD, progressive disease; PR, partial response; SD, stable disease.

- Patients in the PROSPECT study achieved rapid response with tirabrutinib, and most were able to reduce or discontinue corticosteroid use[12]
- Tirabrutinib was generally well tolerated in this population without major cardiac toxicity; the most frequent treatment-emergent adverse events (≥25%) were fall, fatigue, anemia, lymphopenia, headache, and diarrhea[12]
- Here, we describe an ongoing phase 3 trial: IGNITE (NCT07104032) evaluating the efficacy and safety of tirabrutinib monotherapy compared with rituximab and temozolomide combination therapy in patients with R/R PCNSL

Study Design

- This multiregional, open-label, randomized, phase 3 study will enroll approximately 132 adult patients with R/R PCNSL (**Figure 2**)

Figure 2. IGNITE study design



[a]Progressive disease as determined by a blinded independent review committee assessment according to International PCNSL Collaborative Group criteria.
[b]Includes safety follow-up 28 days after last dose and survival follow-up every 3 months thereafter.
IV, intravenous; PCNSL, primary central nervous system lymphoma; QD, once daily; R/R, relapsed or refractory; R-TMZ, combination therapy with RTX and TMZ; RTX, rituximab; TMZ, temozolomide.

Key Eligibility Criteria

INCLUSION
Age ≥18 years at the time of informed consent
Pathologically confirmed diagnosis of R/R B-cell PCNSL
Must have received ≥1 prior HD-MTX–based therapy for PCNSL
Must have ≥1 bi-dimensionally measurable brain lesion with a diameter ≥1 cm × ≥1 cm using gadolinium-enhanced MRI
ECOG PS ≤2 at screening
Adequate bone marrow, renal, and hepatic function per central lab values
Must agree to comply with all defined contraceptive requirements

ECOG PS, Eastern Cooperative Oncology Group performance status; HD-MTX, high-dose methotrexate; MRI, magnetic resonance imaging; R/R, relapsed or refractory; PCNSL, primary central nervous system lymphoma.

EXCLUSION
Isolated intraocular PCNSL or spinal PCNSL with no brain lesions
Non–B-cell PCNSL
Systemic presence of lymphoma
Refractory to TMZ with or without RTX-containing regimens in the last PCNSL treatment
Concomitant systemic corticosteroid exposure within 14 days before starting study drug per investigator assessment, except for: • Equivalent of ≤10 mg/day of prednisone for a disease other than PCNSL • Equivalent of ≤50 mg/day of prednisone (8 mg/day dexamethasone) for patients with lesions of the brain and/or spinal cord
Active malignancy other than PCNSL requiring systemic therapy
Poorly controlled comorbidity or history of medical conditions contraindicated per investigator assessment
Unable to swallow oral medication
Prior BTK inhibitor treatment

BTK, Bruton tyrosine kinase; PCNSL, primary central nervous system lymphoma; RTX, rituximab; TMZ, temozolomide.

Outcome Measures

Primary outcome measure

- The primary outcome measure is progression-free survival based on blinded independent review committee (BIRC) assessment per International PCNSL Cooperative Group (IPCG) criteria

Secondary outcome measures

- Overall response rate based on BIRC per IPCG criteria
- Overall survival
- Complete response rate based on BIRC per IPCG criteria
- Best overall response rate based on BIRC per IPCG criteria
- Time-to-response based on BIRC per IPCG criteria
- Time-to-complete response based on BIRC per IPCG criteria
- Duration of response based on BIRC per IPCG criteria
- Disease-free survival based on BIRC per IPCG criteria
- Change from baseline in corticosteroid dose

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CORRESPONDING AUTHOR

Lakshmi Nayak, MD
Lakshmi_Nayak@dfci.harvard.edu

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