SOHO ANNUAL MEETING 2024

TRIAL IN PROGRESS: PHASE I STUDY WITH DOSE EXPANSION OF ACALABRUTINIB AND DURVALUMAB (MEDI 4736) IN PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

I. NIZAMUDDIN[1], B. KAHL[1], N. BARTLETT[1], N. EPPERLA[2], N. MEHTA-SHAH[1]

[1]Siteman Cancer Center, Washington University School of Medicine in St. Louis, Missouri, USA
[2]The James Cancer Hospital, The Ohio State University Wexner School of Medicine, Ohio, USA

Washington University in St. Louis SCHOOL OF MEDICINE

THE OHIO STATE UNIVERSITY WEXNER MEDICAL CENTER

BACKGROUND

- Primary central nervous system lymphoma (PCNSL) is difficult to treat due to limited effective therapies that cross the blood-brain barrier
- Up to 50% of patients will experience refractory or relapsed disease following first-line treatment with high-dose methotrexate (HD-MTX)-based regimens. Prognosis is dismal, with **median overall survival less than 12 months**[1]

STUDY RATIONALE

- PCNSL is often non-germinal center phenotype and has aberrancies in PD-1/PD-L1 pathway[2-3]
- Bruton's tyrosine kinase (BTK) inhibitors have shown activity in CNS lymphoma with **dose-dependent concentrations of ibrutinib detected in cerebrospinal fluid (CSF) pharmacokinetic (PK) studies**[4-5]
- Small studies have demonstrated efficacy of checkpoint inhibitors, such as nivolumab, in primary CNS lymphoma[6]
- Preclinical models and clinical studies in other B-cell lymphomas showed **synergy** between BTK and checkpoint inhibition, suggesting a role for combination therapy[7-8]

STUDY TIMELINE

June 2020	PRMC approval
Oct. 2020	IRB approval
Apr. 2021	Open to accrual*
Nov. 2023	Accrual of first patient to **dose expansion cohort**

*To date, 19 patients consented to screening and 18 patients enrolled

STUDY DESIGN

Open at Siteman Cancer Center (Washington University in St. Louis) & The James Cancer Hospital (Ohio State University)

NCT04462328

ELIGIBLE PATIENTS

Patients with primary CNS lymphoma who have relapsed after initial high-dose methotrexate-based therapy, or patients who are not candidates for high-dose methotrexate

See full criteria below

PHASE 1 COHORT

Treatment:

- Acalabrutinib 100-200 mg BID on days 1-28

- Durvalumab 1500 mg IV on day 1 of 28-day cycle

- 3+3 design with enrollment beginning at Dose Level 1
- Monitor for DLTs
- Treatment continued until progression or unacceptable toxicity
- CSF collected between C1D8 and C2D1
- Response assessment with MRI every 3 cycles from C3-C15, then every 6 cycles thereafter

EXPANSION COHORT (n=12)

Treatment:

- Acalabrutinib 100-200 mg BID on days 1-28 (based on tolerable dose)

- Durvalumab 1500 mg IV on day 1 of 28-day cycle

- Treatment continued until progression or unacceptable toxicity
- CSF collected between C1D8 and C2D1
- Response assessment with MRI every 3 cycles from C3-C15, then every 6 cycles thereafter

DLT defined as:

- Grade ≥3 non-hematologic toxicity
- Grade ≥4 hematologic toxicity (excluding lymphopenia)
- Neutropenic fever
- Grade ≥3 thrombocytopenia with bleeding
- Grade ≥2 immune-mediated pneumonitis, neuropathy, myositis
- Grade ≥3 rash or any bullous rash
- Toxicities leading to treatment delay of >21 days

Assessed during first 12 weeks of treatment in Phase I portion

The tolerable dose is defined as Dose Level 2 if 0 or 1 DLTs are seen in patients at that dose level, or Dose Level 1 if 2+ DLTs are seen in Dose Level 2 but only 0 or 1 DLTs are seen in patients at Dose Level 1. If 2 or more DLTs are seen in patients at Dose Level 1 during the phase I portion of the study, the study will be suspended.

Dose Escalation Schedule

Dose	Durvalumab	Acalabrutinib
Level 1	1500 mg IV q4w	100 mg PO BID
Level 2	1500 mg IV q4w	200 mg PO BID

OBJECTIVES

	Objective(s)	Endpoint(s)
Primary	Determine safety and tolerability of combination of durvalumab with acalabrutinib	Define safe and tolerable dose of acalabrutinib and durvalumab
Secondary	Evaluate preliminary efficacy of combination	Overall response rate, time to response, duration of response, progression-free survival, overall survival
Exploratory	Evaluate PK of acalabrutinib in CSF Evaluate characteristics of brain PET/MRI	Concentration of acalabrutinib and ACP-5862 in CSF + plasma during cycle 1 Image characteristics (SUVmax) vs brain MRI

PATIENT SELECTION

Inclusion:

- Biopsy-proven primary CNS lymphoma after >1 prior CNS-directed therapy (or ineligible for HD-MTX)
- Age ≥18, ECOG 0-2
- Adequate bone marrow and organ function

Exclusion:

- Secondary CNS lymphoma or primary vitreoretinal lymphoma
- Prior BTK inhibitor or checkpoint inhibitor use
- Use of dexamethasone ≥8 mg daily or equivalent for control of CNS symptoms

STATISTICS

- This is a safety study and thus no formal sample size calculation will be done
- Estimated total of 18 patients will be treated with study drug (6 in phase I portion, 12 in dose expansion)
- 95% CI for CR rate of 44% (8/18 patients) would be (21.5%, 69.4%)
- 95% CI for CR rate of 11% (2/18 patients) would be (1.4%, 34.7%)
- If all cohorts are filled, maximum number of patients will be 24
- If 0 responses are seen in first 8 patients in expansion cohort, enrollment will stop for futility

REFERENCES

1. Shiels MS, et al. Trends in primary central nervous system lymphoma incidence and survival in the US. *Br J Haematol*. 2016;174(3):417-24.
2. Chapuy B, et al. Targetable genetic features of primary testicular and primary central nervous system lymphomas. *Blood*. 2016;127(7):869-81.
3. Soussain C, et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: Final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network. *Eur J Cancer*. 2019;117:121-30.
4. Grommes C, et al. Ibrutinib unmasks critical role of Bruton tyrosine kinase in primary CNS lymphoma. *Cancer Discov*. 2017;7(9):1018-29.
5. Nayak L, et al. PD-1 blockade with nivolumab in relapsed/refractory primary central nervous system and testicular lymphoma. *Blood*. 2017;129(23):3071-3.
6. Sagiv-Barfi I, et al. Therapeutic antitumor immunity by checkpoint blockade is enhanced by ibrutinib, an inhibitor of both BTK and ITK. *Proc Natl Acad Sci U S A*. 2015;112(9):E966-72.
7. Younes A, et al. Safety and activity of ibrutinib in combination with nivolumab in patients with relapsed non-Hodgkin lymphoma or chronic lymphocytic leukaemia: a phase 1/2a study. *Lancet Haematol*. 2019;6(2):e67-78.

ACKNOWLEDGEMENTS

- Funding: AstraZeneca (ESR-18-14234)
- Acknowledgments: Anne Fischer, Chaz Moreno, Emily Vukadinovic (Washington University) and Anna Krivenko, Ilays Aden (The Ohio State University)