# PEMETREXED AND ZANUBRUTINIB COMBINATION IN RELAPSED/REFRACTORY CNS B-CELL LYMPHOMA: PRELIMINARY REPORT OF THE SAFETY LEAD-IN COHORT IN A SINGLE-CENTER PHASE 2 STUDY

T. KEHTARI [1], T. AL SAGHEER [2], A. PEREZ PEREZ [1,2], Y. ODIA [1,2], Z. CHEN [1,2], M. AHLUWALIA [1,2], A. STAROSCIAK [2], C. TORRALBAS [2], M. ABREU [2], G. KOEHNE [1,2] and Y. LINHARES [1,2]

1. Florida International University Herbert Wertheim College of Medicine, Miami, FL, USA.
2. Miami Cancer Institute, Baptist Health South Florida, Miami, FL, USA

## Introduction

- **R/R PCNSL and SCNSL** have a poor prognosis, with a median OS 6.8 months and 3.4 months, respectively
- Treatment options are limited
- **BCR/TLR pathway mutations** (e.g., *MYD88*, *CD79B*) drive **NF-κB** activation via BTK —> **BTK inhibition** is a key therapeutic target
- Ibrutinib shows activity in PCNSL with short-lived responses
- **Zanubrutinib** is a potent 2nd generation oral BTKi with highly selective target binding profile, excellent CNS penetration, and favorable toxicity profile
- **Pemetrexed** is a multi targeted folate metabolism inhibitor with known activity in R/R-CNSL and is administered in the outpatient basis
- We hypothesize that pemetrexed in combination with zanubrutinib (Pem-Zan) will produce a higher overall response rate than pemetrexed alone in R/R-CNSL

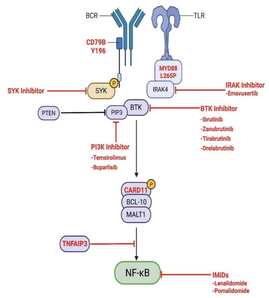
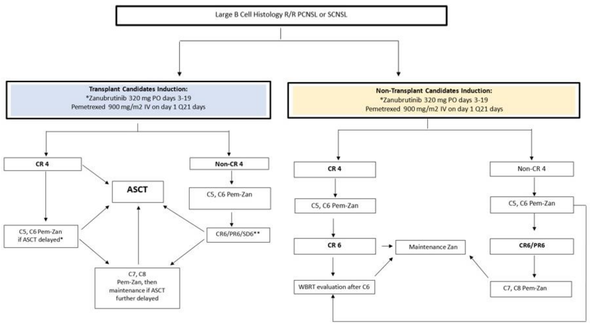



**Figure 1** Targeting NF-κB Signaling Network in Primary CNS Lymphoma. Original Figure: Mendez JS, Grommes C. Treatment of primary central nervous system lymphoma: from chemotherapy to small molecules. Am Soc Clin Oncol Educ Book. 2018;38:604-615. DOI: 10.1200/EDBK_200829.

## Objectives

- **Primary Endpoint**: best overall response rate (ORR) to Pem-Zan induction therapy using international PCNSL Collaborative Group's criteria
- **Key Secondary Endpoints**: CR rate post-induction, best CR and ORR rate post-transplant, WBRT followed by zanubrutinib maintenance, and Zanubrutinib maintenance, clinical benefit (CR, PR, SD) rate, duration of response, progression free survival, overall survival, and type/frequency of DLTs
- **Exploratory objectives**: Correlate cell of origin by Hans algorithm, chromosomal abnormalities, and tumor mutational profiles (BostonGene); with clinical outcomes, significance of circulating tumor DNA presence and quality in blood and CSF by next generation sequencing (ClonoSEQ, Adaptive)

## Methods




### Design

- Prospective, single-center, investigator-initiated phase II trial (NCT05681195)
- Safety lead-in Pocock-type stopping boundary
- Simon's two-stage MiniMax design for second phase (estimated n=15)

### Population

- Histologically confirmed R/R primary or secondary CNS large B-cell lymphoma
- Eligibility: KPS ≥ 30% (≥ 50% if ≥ 60 years old), adequate organ function, HIV allowed if viral load undetectable & CD4 > 400, non-viremic hepatitis B or C allowed

### Treatment

- Induction up to 8 cycles
  - Pemetrexed 900 mg/m² IV q3w
  - Zanubrutinib 320 mg PO daily, Days 3–19 of each 21-day cycle
  - Staggered scheduling to avoid antagonism with pemetrexed

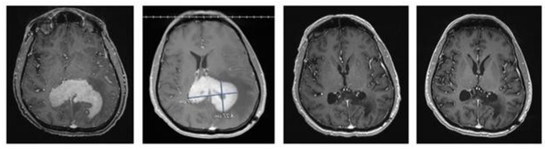
### Post-Induction Pathways

- ASCT candidates: proceed to transplant after CR, or after ≤ 8 cycles if PR
- Non-ASCT candidates: up to 8 cycles Pem-Zan → zanubrutinib maintenance
- Non-ASCT, CR after 6 cycles: option for consolidative WBRT → zanubrutinib maintenance

## Results

**Patient #1 — 60 y/o M w/ CLL and clonally related large B cell CNS lymphoma (CLL-MYD88 L265P, CNS-LBCL-CD79B Y196N) with progressive neurologic symptoms after 2 doses of HD-MTX**

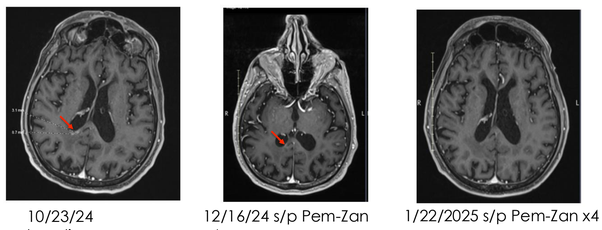
- **Efficacy:** Achieved PR after 2 cycles of Pem-Zan, CR after 4 cycles, underwent ASCT, with DOR 13.7 months (ongoing)
- **Safety:** Grade 1 LFT elevation



presentation | s/p HD-MTX x2 | s/p Pem-Zan x2 | s/p Pem-Zan x4

**Patient #2 — 76 y/o M with PCNSL (MYD88 V204F) with progressive disease after 2 cycles of MTX-Rituximab-Temozolomide**

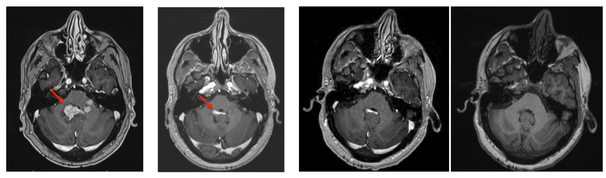
- **Efficacy**: Achieved PR after 2 cycles of Pem-Zan, CRu after 4 cycles, after cycle 6, zanubrutinib maintenance initiated, DOR 7.5 months (ongoing)
- **Safety**: Grade 1 diarrhea and hypomagnesemia



10/23/24 baseline | 12/16/24 s/p Pem-Zan x4 | 1/22/2025 s/p Pem-Zan x4

**Patient #3 — 33 y/o M Stage IV DLBCL with CNS relapse, progressed after 2 cycles of R-MTX-AraC (modified MATRIX)**

- **Efficacy**: Achieved PR after 2 cycles of Pem-Zan. After 6 cycles, CR by PET, CRu by MRI, planned for autoSCT, DOR 3.3 months (ongoing)
- **Safety**: No reported AEs



3/12/25 baseline | 4/30/25 s/p Pem-Zan x2 | 7/30/25 s/p Pem-Zan x6 [MRI] | 7/30/25 s/p Pem-Zan x6 [PET MR]

| Age/ Sex | ECOG | Dz Characteristics | Prior Tx | Prior Dz Status | # of Pem-Zan cycles | Best Response to Pem-Zan | DOR (months) | Post Pem-Zan Tx | Current Status |
|---|---|---|---|---|---|---|---|---|---|
| 60 M | 2 | CNS: ABC-LBCL CD79B Y196N GOF CLL: MYD88 L265P GOF | HD-MTX x2 cycles | Stable dz | 5 | CR (CLL-PR) | 13.7 | ASCT | CR (CLL-PR) |
| 76 M | 2 | GCB-DLBCL MYD88 V204F missense | MTX, Rituximab, Temozolomide x 6 cycles | Progressive dz | 6 | CR | 7.5 | Zan maintenance | CR |
| 33 M | 1 | CNS: ABC-DLBCL, DE (MYC+/BCL2+), DH-, MYD88 WT | R-MTX-AraC x 2 (PD) | Progressive dz | 7 | CR (PET), CRu (MRI) | 3.3 | Pending ASCT | CRu |

Median follow-up across the three patients was **9.3 months**.

## Conclusions

- 3 patients with R/R CNS lymphoma received Pem-Zan following failure of methotrexate-based regimens
- All harbored activating MYD88 and/or CD79B mutations, drivers of BTK/NF-κB signaling
- All achieved PR by cycle 2; 2 achieved CR and 1 CRu by cycle 6
- Treatment was well tolerated with no grade ≥3 AEs, even in older or heavily pretreated patients
- Implications:
  - **BTK inhibition plus antifolate therapy demonstrates promising activity in CNS lymphoma**
  - Objective responses in MYD88/CD79B-mutant cases support a **biomarker-driven therapeutic approach**
- The Pem-Zan phase II trial (NCT05681195) is ongoing and continues to accrue patients

**Corresponding Author:**
Yuliya Linhares, MD
Chief of Lymphoma Services, Miami Cancer Institute
yuliyal@baptisthealth.net

**References**