Emavusertib (CA-4948) in Combination with Ibrutinib in Relapsed/Refractory Primary Central Nervous System Lymphoma (R/R PCNSL) Patient

Christian Grommes, MD[1], Han W. Tun, MD[2], Christopher D'Angelo, MD[3], Adolfo de la Fuente MD[4], Anna Dabrowska-Iwanicka, MD[5], Lucia Regales, PhD[6], Wanying Zhao, PhD[6], Dora Ferrari, BS[6], Meaghan Fowles, BS[6], Maureen Lane, PhD[6], Catherine Wang, MD[6], Reinhard von Roemeling, MD[6], Michael Taszner, MD[7] and Grzegorz Nowakowski, MD[8].

[1]Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Division of Hematology/Oncology, Department of Internal Medicine, Mayo Clinic-Florida, Jacksonville, FL;[3] Division of Hematology and Oncology, University of Nebraska Medical Center, Omaha, NE; [4]Department of Hematology, MD Anderson Cancer Center Madrid, Madrid, Spain; [5]Maria Sklodowska-Curie Memorial Cancer Center, Institute of Oncology, Warsaw, Poland: [6]Curis Inc., Lexington, MA; [7]Department of Hematology, University Clinical Center, Medical University of Gdańsk, Gdańsk, Poland; [8]Divisionof Hematology, Department of Internal Medicine, Mayo Clinic-Minnesota, Rochester, MN

BACKGROUND

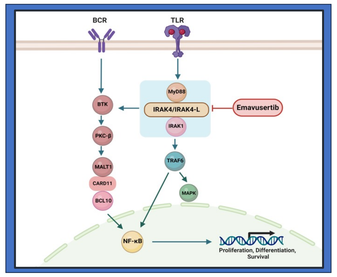


Figure 1. BCR and TLR Pathways independently drive NF-κB overactivity in B-cell lymphoma

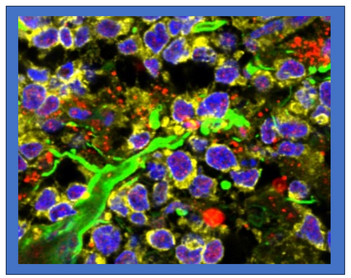


Figure 2. Human PCNSL express high levels of IRAK4: Section of a brain tumor biopsy from a PCNSL patient showing immune infiltration (CD45 yellow) characterized by high phosphor IRAK-4 expression (red), interspersed with tumor reactive astrocytes (green) (1).

- Primary central nervous system lymphoma (PCNSL) is a rare and aggressive form of extranodal NHL in the CNS or vitreoretinal space, that represents approximately 4% of newly diagnosed malignant brain tumors (2).
- There are no approved treatments for R/R PCNSL, highlighting a significant unmet medical need.
- Interleukin-1 receptor associated kinase 4 (IRAK4) is an essential protein kinase downstream of TLR and IL-1R signaling, with a key role in the innate immune system (figure 1).
- IRAK4 is highly expressed in PCNSL tumor microenvironment (figure 2) and forms a myddosome complex with MYD88 adaptor protein which drives overactivation of NF-κB, causing inflammation and tumor growth (3,4). *MYD88* mutations have been reported in about 70% of PCNSL tumors (5).
- Emavusertib is a first in class oral IRAK4 inhibitor, with blood-brain barrier penetration (2), demonstrated acceptable long term safety profile and efficacy in monotherapy and combination with ibrutinib in R/R NHL patients, including PCNSL patients (6, 7).
- Emavusertib's targeting of TLR signaling is synergistic with small molecules targeting BCR signaling and improves the sensitivity to BTK and PI3K inhibitors in BTK-resistant models (8).

SAFETY PROFILE

Grade 3+ Treatment-Related Adverse Event Ocurred in >1 Patient	100 mg BID+IBR	200 mg BID+IBR	300 mg BID+IBR	Total
N (%)	(N=2)	(N=10)	(N=7)	(N=19)
# patients having grade 3+ TRAEs	1 (50)	7 (70)	6 (86)	14 (74)
Platelet count decreased		2 (20)	1 (14)	3 (16)
Alanine aminotransferase increased		1 (10)	1 (14)	2 (11)
Aspartate aminotransferase increased		1 (10)	1 (14)	2 (11)
Fatigue		1 (10)	1 (14)	2 (11)
Hyponatraemia		2 (20)		2 (11)
Lipase increased	1 (50)	1 (10)		2 (11)

Abbreviations
Primary Central Nervous System Lymphoma (PCNSL), Non-Hodgkin Lymphomas (NHL), Toll Like Receptor (TLR), Blood-Brain Barrier (BBB), Once a day (QD), Two times a day (BID), IBR Ibrutinib, Complete Response (CR), Stable Disease (SD), Bruton's Tyrosine Kinase inhibitor (BTKi).

CASE PRESENTATION

Case study

- 53-year-old male PCNSL patient whose disease progressed following two prior lines of treatment, including ibrutinib.
- Patient enrolled in the TakeAim lymphoma study, receiving emavusertib (100 mg BID) in combination with ibrutinib (560 mg QD) in a 21-day cycle.
- At baseline, the patient presented one target lesion (13x12mm size). After cycle 2, the patient presented stable disease. By the end of cycle 4, the target lesion was absent (patient achieved CR).
- Emavusertib dose was interrupted for seven days due to grade 4 lipase increase, then resumed at the same dose level after resolution.
- Patient is ongoing and has maintained CR > 1yr without the use of steroids.

RESULTS

Study Design **TakeAim-Lymphoma (NCT03328078)-** Part A2: Dose escalation of emavusertib in combination with ibrutinib

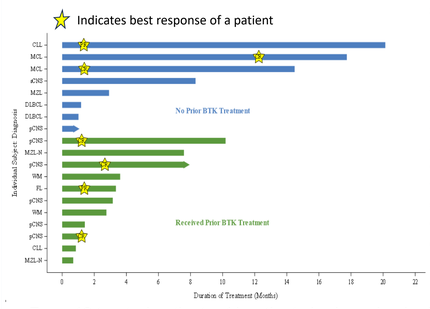
Patient Population
- Relapsed/Refractory Hematologic Malignancies (except leukemia)
- Absence of residual grade ≥2 toxicity from prior therapy

Study Treatment
Emavusertib 100-200 mg BID
+
Ibrutinib 420-560 mg QD

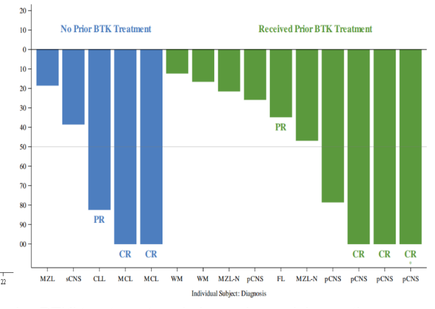
Endpoints
Primary:
- Safety (AEs)

Secondary:
- ORR, DOR, DCR, PFS, OS, PK

Duration of treatment



Best percent change in tumor burden



- From 19 treated patients, 11 patients had received prior BTKi treatment and showed promising anti-cancer activity with 5 CRs.
- Median treatment duration was 96 days (range 21-613 days), suggesting acceptable safety and tolerability.
- Majority of patients had decreases in tumor burden or stable disease over time.
- The preliminary efficacy data of 16 evaluable patients in combination with ibrutinib showed 5 CR (2 MCL, 3 PCNSL).

CASE STUDY EFFICACY

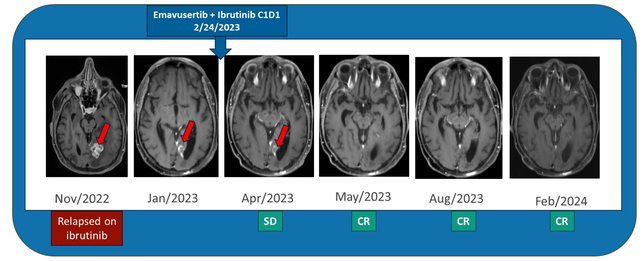


Figure 3. Axial Magnetic Resonance images (MRI) showing pre-treatment and post-treatment PCNSL brain images from one R/R PCNSL patient. After two cycles of emavusertib+ ibrutinib, the patient showed stable disease (SD). Complete responses (CR) with absent lesions have been seen after cycle 4.

CONCLUSIONS AND CLINICAL SIGNIFICANCE

- Emavusertib in combination with ibrutinib continues to show promising efficacy, including complete responses, along with a manageable and acceptable safety profile, in heavily pretreated patients, including BTKi-naïve and BTKi-experienced patients.
- Here we describe a case of a patient who, after receiving emavusertib in combination with ibrutinib for 2.7 months, achieved CR. Further, there is no clinical evidence of disease progression 13 months after initial treatment.
- Consistent with our previous findings, these data support the hypothesis that emavusertib can re-sensitize patients to BTKi therapy, marking a significant advancement in R/R PCNSL treatment.
- The trial continues to enroll with the addition of 17 sites in seven countries.

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CONTACT INFORMATION

Reinhard von Roemeling, MD
SVP, Clinical Development, Curis
rvonroemeling@curis.com

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