Preliminary safety and efficacy of emavusertib (CA-4948) in combination with ibrutinib in relapsed/refractory primary central nervous system lymphoma patients

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BACKGROUND

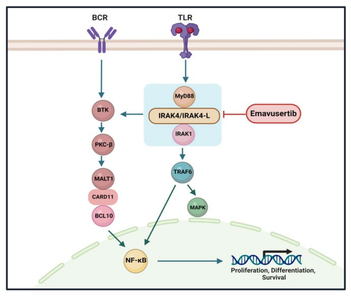


Figure 1. BCR and TLR Pathways independently drive NF-κB overactivity in B-cell lymphoma

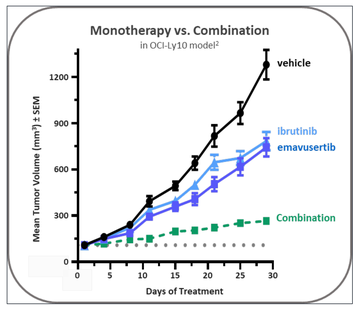


Figure 2. In preclinical testing, blocking both IRAK4 and BTK drove tumor reduction better than blocking either one alone[1]

- Primary central nervous system lymphoma (PCNSL) is a rare and aggressive form of extranodal Non-Hodgkins Lymphoma (NHL) in the CNS or vitreoretinal space that represents approximately 4% of newly diagnosed malignant brain tumors[2].
- Patients who have progressed on BTKi treatment have a poor prognosis and 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).
- Emavusertib is a first-in-class oral IRAK4 inhibitor, with blood-brain barrier penetration[3], a favorable long-term safety profile, and demonstrated efficacy in heme malignancies as both monotherapy and combination therapy[4, 5].
- 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[6].
- Preclinical testing demonstrated that the combination of ibrutinib and emavusertib is synergistic (Figure 2).
- Here we present promising efficacy and safety from CA-4948-101 (NCT03328078), Parts A2 and B of emavusertib in combination with ibrutinib in R/R PCNSL (data cut 01 May 2025).

STUDY DESIGN

CURRENTLY ENROLLING

COMPLETED
Parts A1 and A2

multiple NHL subtypes
dose escalation

A1: monotherapy
A2: emavusertib + ibrutinib

Part B

PCNSL
in BTKi-experienced patients

- emavusertib + ibrutinib

single-arm design
intended to support Accelerated Approval

Part C

PCNSL
in BTKi-naïve patients

- emavusertib monotherapy
- ibrutinib monotherapy
- emavusertib + ibrutinib

randomized design
intended to support Confirmatory Study

Note: Part C is designed to demonstrate the contribution of components in the emavusertib + ibrutinib combination.

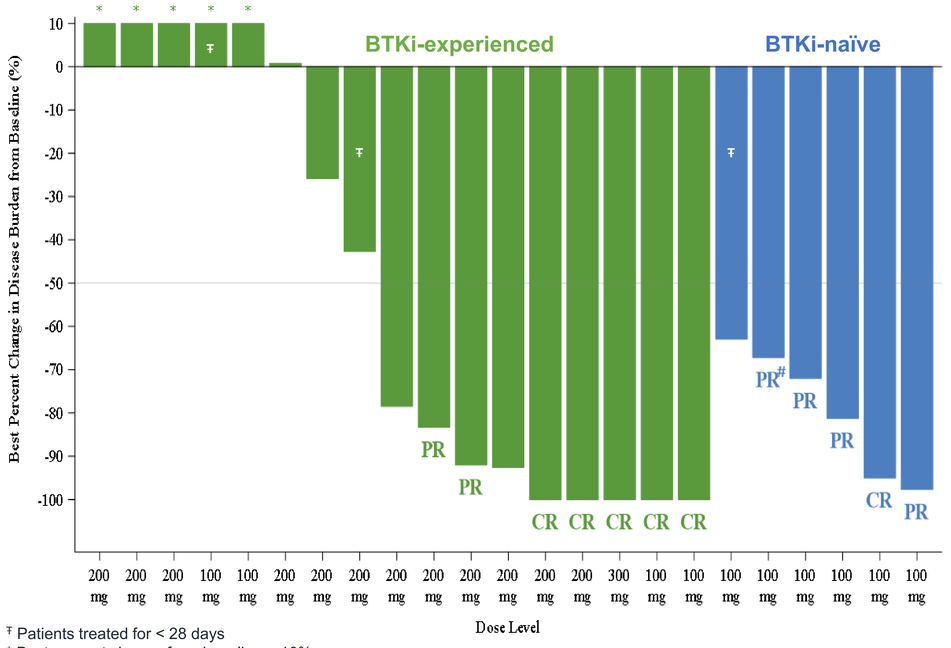
BASELINE CHARACTERISTICS

PCNSL Part A2/B in Combination with Ibrutinib	100 mg BID +IBR (N=13)	200 mg BID +IBR (N=19)	300 mg BID +IBR (N=1)	Total (N=33)
Female n (%) : Male n (%)	7 (53.8) : 6 (46.2)	9 (47.4) : 10 (52.6)	1 (100) : 0 (0)	17 (51.5) : 16 (48.5)
Median age, years (range)	60 (43,79)	63 (44,81)	66 (66,66)	63 (43,81)
Prior lines of therapy, median (range)	2 (1,3)	2 (2,5)	2 (2,2)	2 (1,5)
Prior BTKi use , n (%)	6 (46.2)	19 (100)	1 (100)	26 (78.8)
Disease status at entry, Refractory, n (%): Relapse, n (%)	2 (15.4) : 11 (84.6)	7 (36.8) : 12 (63.2)	1 (100): 0 (0)	10 (30.3) : 23 (69.7)

SAFETY PROFILE

Grade 3+ Treatment-Related Adverse Event (TRAE)	100 mg BID +IBR	200 mg BID +IBR	300 mg BID +IBR	Total
N (%)	(N=13)	(N=19)	(N=1)	(N=33)
# patients having grade 3+ TRAEs	5 (38.5)	5 (26.3)	1 (100.0)	11 (33.3)
Neutropenia	4 (30.8)	1 (5.3)	0	5 (15.2)
Amylase increased	2 (15.4)	0	0	2 (6.1)
Leukopenia	2 (15.4)	0	0	2 (6.1)
Lipase increased	2 (15.4)	0	0	2 (6.1)
Acute respiratory failure	0	1 (5.3)	0	1 (3.0)
Alanine aminotransferase	0	1 (5.3)	0	1 (3.0)
Asthenia	0	1 (5.3)	0	1 (3.0)
Blood Creatine phosphokinase increased	0	1 (5.3)	0	1 (3.0)
Covid-19 pneumonia	0	1 (5.3)	0	1 (3.0)
Muscular weakness	0	0	1 (100.0)	1 (3.0)
Syncope	0	1 (5.3)	0	1 (3.0)
Thrombocytopenia	0	0	1 (100.0)	1 (3.0)

PERCENT CHANGE IN DISEASE BURDEN (PART A2/B): EMAVUSERTIB PLUS IBRUTINIB[1]



ŦPatients treated for < 28 days
* Best percent change from baseline > 10%
# Patient achieved PR on May 6, 2025 (data extraction was May 1, 2025)

BTKi Experience	Yes	No
Patients who received emavusertib for ≥ 28 days	19	5
CR	5	1
PR	2	4[2]
ORR[3]	37%	100%
Combined ORR[3]	50% 6 CR and 6 PR	

[1] 9 BTKi experienced patients and 1 BTKi naïve patient had no calculable post-baseline tumor burden at data cutoff.
[2] 1 patient achieved PR on May 6, 2025 (data extraction was May 1, 2025)
[3] Response rates in the above table were based on patients who received emavusertib for ≥ 28 days

DURATION OF TREATMENT (PART A2/B)

- 3 BTKi-experienced patients with CR on treatment for ≥ 10 months (10-26mos)
- 2 patients with CR remain on treatment as of data cutoff (ongoing at 18 months and 26 months, respectively)
- Median treatment duration was 51 days (5-798)
- 9 of 33 (BTKi experienced and BTKi naïve) patients were unable to complete 28 days of treatment due to rapid disease progression and went to hospice, consistent with the aggressive clinical course typically observed in R/R PCNSL[7, 8, 9]
  - 7 of 26 patients with prior BTKi experience discontinued treatment prior to receiving a full cycle of emavusertib for the following reasons: hospice (n=4), non-related death (COVID, septic shock; n=2), and physician decision (n=1)
  - 2 of 7 BTKi-naïve patients discontinued treatment prior to receiving a full cycle of emavusertib for the following reasons: non-related adverse event; GI perforation; n=1), and death (cause of death was unknown; n=1)

CONCLUSIONS AND CLINICAL SIGNIFICANCE

- The combination of emavusertib and ibrutinib in R/R PCNSL patients:
  - Demonstrated promising clinical activity with an acceptable safety profile
  - Demonstrated ability to overcome resistance to prior BTKi therapy, offering a significant advancement in the treatment of R/R PCNSL
- Patients with R/R PCNSL have limited options after they progress on BTKi treatment, often progressing rapidly and/or proceeding to hospice[7, 8, 9]
- Here we report promising response rates in both BTKi-experienced (37%) and BTKi-naïve (100%) patients who were able to complete at least 28 days of treatment
- Patient enrollment is ongoing

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