Analysis of genetic mutation profile and CNS pharmacokinetics in relapsed/refractory primary CNS lymphoma patients responding to novel emavusertib (IRAK4i) and BTKi combination

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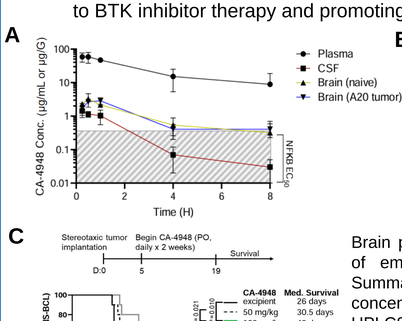
INTRODUCTION

NFκB Biology:
Two Pathways Drive NHL/CLL

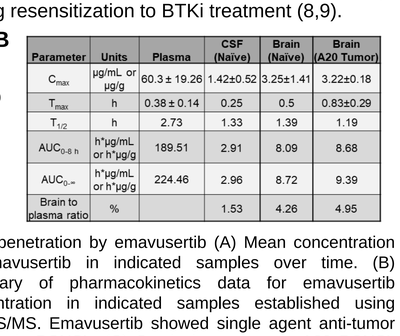
BCR and TLR Pathways independently drive NF-κB overactivity (and NF-κB drives NHL/CLL)



1) IMBRUVICA Package Insert. Rev 08/2018

Clinical Strategy:
Block both pathways with Combination Therapy

In preclinical testing, blocking both IRAK4 and BTK demonstrated better tumor reduction than blocking either one alone



2) Booher et al. Waldenström Roadmap Symposium 2019

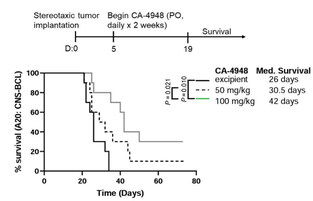
- Primary central nervous system lymphoma (PCNSL) is a rare and aggressive form of extranodal NHL in the CNS or vitreoretinal space, that represents approximately 4% of newly diagnosed malignant brain tumors (1). There are no approved treatments for R/R PCNSL, highlighting a significant unmet medical need.
- Interleukin-1 receptor associated kinase 4 (IRAK4), is highly expressed in PCNSL tumor microenvironment, and is essential for TLR and IL-1R signaling in B-cell proliferation. It forms a Myddosome complex with MYD88 adaptor protein and drives overactivation of NF-κB, causing inflammation and tumor growth (2,3). MYD88 mutations have been reported in about 70% of PCNSL tumors (4).
- Emavusertib, a first in class oral IRAK4 inhibitor, dosed twice daily has:
  - ✓ Demonstrated an acceptable long term safety profile in combination cohort of TakeAim Lymphoma trial in R/R NHL patients (5).
  - ✓ Demonstrated the ability to overcome tumor resistance to ibrutinib and PI3K inhibitors in preclinical studies (6).
  - ✓ Crossed the blood-brain barrier, reversed IRAK4 pathway activity and caused tumor regression, including cure in a murine PDX model with transplanted A20 NHL to the brain (7).
  - ✓ Shown in-vivo synergy in B-cell NHL in combination with multiple BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib), potentially enhancing patient sensitivity to BTK inhibitor therapy and promoting resensitization to BTKi treatment (8,9).

A

B

Parameter	Units	Plasma	CSF (Naïve)	Brain (Naïve)	Brain (A20 Tumor)
C_{max}	µg/mL or µg/g	60.3 ± 19.26	1.42±0.52	3.25±1.41	3.22±0.18
T_{max}	h	0.38 ± 0.14	0.25	0.5	0.83±0.29
$T_{1/2}$	h	2.73	1.33	1.39	1.19
$AUC_{0\text{-}8\ h}$	h*µg/mL or h*µg/g	189.51	2.91	8.09	8.68
$AUC_{0\text{-}\infty}$	h*µg/mL or h*µg/g	224.46	2.96	8.72	9.39
Brain to plasma ratio	%		1.53	4.26	4.95

C



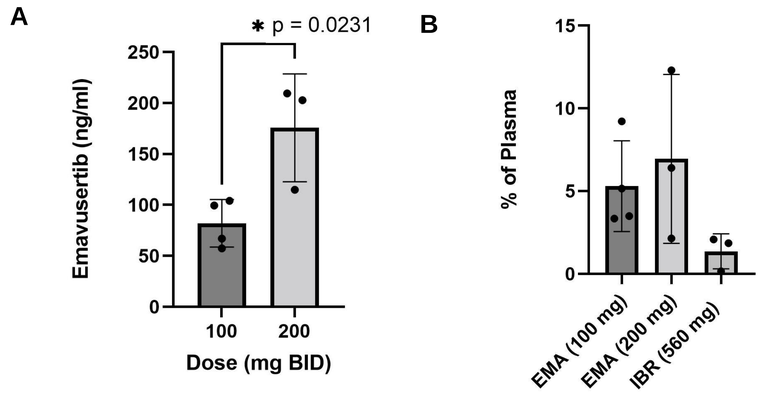
Brain penetration by emavusertib (A) Mean concentration of emavusertib in indicated samples over time. (B) Summary of pharmacokinetics data for emavusertib concentration in indicated samples established using UPLCS/MS. Emavusertib showed single agent anti-tumor efficacy in PCNSL. (C) Survival response in A20 PCNSL bearing mice treated with emavusertib. Treatment map included. P-values determined by Log-rank (Mantel-Cox) test, n=10 per group (7).

METHODS

- The safety, clinical activity, and potential biomarkers of emavusertib in R/R PCNSL are being investigated in the ongoing open-label, Phase 1/2 TakeAim Lymphoma trial (NCT03328078).
- Pre-dose and 1.5-hour post-dose plasma samples were collected on Cycle 3 Day 1, Cycle 5 Day 1 and Cycle 7 Day 1.
- Cerebrospinal fluid (CSF) samples from 7 patients were obtained via a lumbar puncture within 1.5 hrs of collection of the post-dose plasma pharmacokinetics (PK) sample on Cycle 3 Day 1. Mutation analysis of 9 patients, including sequencing of archival tissues, CSF, and plasma, was performed by Tempus.

RESULTS

Figure 1: Pharmacokinetic Profiling of Emavusertib in CSF and Plasma of 7 PCNSL Patients



A. CSF PK of emavusertib (ng/ml) at dose levels of 100 mg and 200 mg BID in PCNSL patients p = 0.0231.
B. Comparison of PK % of CSF/plasma emavusertib (EMA) (at dose levels of 100 mg and 200 mg BID) and ibrutinib (IBR) (560 mg QD). 4 out of 7 samples of IBR were below the level of detection.

Data are shown as mean ± standard deviation; Statistical analysis was performed using an unpaired t-test

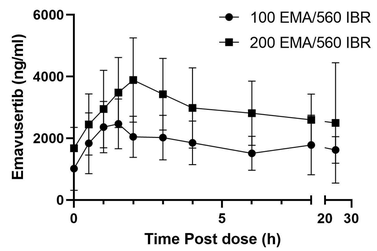


Figure 2: Plasma Pharmacokinetics of Emavusertib in Combination with Ibrutinib in PCNSL Patients (C2D1)

Plasma concentrations of EMA (ng/mL) were measured at multiple time points following administration of 100 mg or 200 mg BID emavusertib combined with 560 mg ibrutinib. Data are presented as mean ± standard deviation.

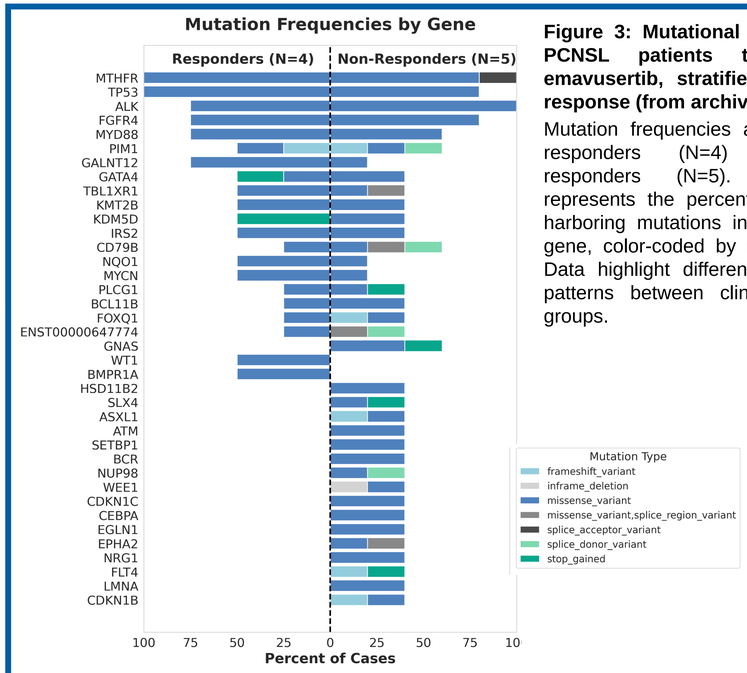


Figure 3: Mutational landscape in PCNSL patients treated with emavusertib, stratified by clinical response (from archival tissue)

Mutation frequencies are shown for responders (N=4) and non-responders (N=5). Each bar represents the percentage of cases harboring mutations in the indicated gene, color-coded by mutation type. Data highlight differential mutational patterns between clinical response groups.

CONCLUSIONS

1. Emavusertib levels in CSF were significantly higher in the 200 mg BID cohort compared to the 100 mg BID cohort (p = 0.0231).
2. Plasma concentrations increased after dosing and peaked between 2–3 hours post-dose for both dose levels. Higher plasma exposure was observed in the 200 mg cohort compared to the 100 mg cohort across all time points.
3. Targeted sequencing of PCNSL patients treated with emavusertib revealed distinct mutational profiles between responders and non-responders. Responders showed a higher prevalence of mutations in TP53, GALNT12, WT1, and BMPR1A. In contrast, non-responders demonstrated higher mutation rates in genes such as GNAS.

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