Preliminary safety and efficacy data on two patients with relapsed/refractory CNS lymphoma treated with emavusertib (CA-4948) and ibrutinib combination: a subset analysis of TakeAim Lymphoma trial

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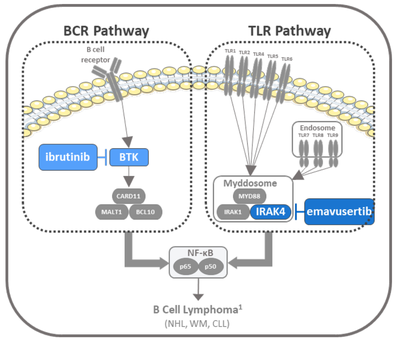
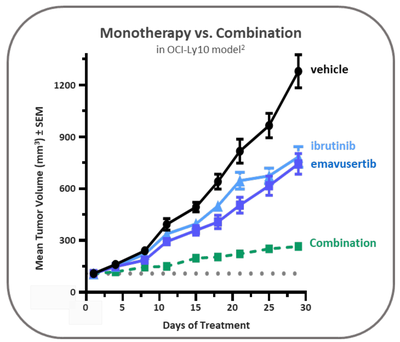
Background



BCR and TLR Pathways independently drive NF-κB overactivity (IMBRUVICA Package Insert. Rev 08/2018)



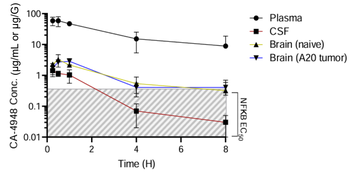
In preclinical testing, blocking both IRAK4 and BTK drove tumor reduction better than blocking either one alone (Booher et al. Waldenström Roadmap Symposium 2019)

IRAK4 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 [1,2]

Emavusertib, a novel oral IRAK4 inhibitor, dosed twice daily has:

- Demonstrated an acceptable long term safety profile in monotherapy cohort of TakeAim Lymphoma trial
- Shown single agent activity in R/R NHL patients [3]
- Demonstrated the ability to overcome tumor resistance to ibrutinib and PI3K inhibitors in preclinical studies [4]
- 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 [5]
- Shown *in vivo* synergy in B-cell NHL in combination with ibrutinib [6]

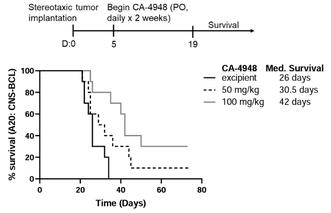
A



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 [5]

Study Design

TakeAim-Lymphoma (NCT03328078)

Part A2: dose escalation of emavusertib in combination with ibrutinib

Part A2 (continuous 21-day cycles)

Emavusertib 200mg (BID) + Ibrutinib dose per label (QD) → Emavusertib 300mg (BID) + Ibrutinib dose per label (QD)

- Endpoints include safety, tolerability, and RP2D
- As of October 12th, 2022, two patients with relapsed/refractory CNS lymphoma (CNSL) have been treated with emavusertib + ibrutinib combination therapy.

Baseline Characteristics

	Case 1	Case 2
Gender	Female	Male
Age (yrs)	66	65
Diagnosis	Primary CNSL	Secondary CNSL
MYD88 mutation	Yes (L265P)	NA
Prior BTK inhibitor / Best Response	Yes / PR	No / NA
# of measurable disease at baseline	2	1
Prior lines of anti-cancer therapy	2	4
Prior bone marrow transplant	No	Yes (autologous)

Safety Profile

Grade 3+ Treatment-Related Adverse Event	emavusertib (300 mg BID) + ibrutinib (560 mg QD)	
	Case 1	Case 2
Thrombocytopenia	Gr 3	-
Pain	Gr 3	-
Muscular weakness	Gr 3	-
Blood Bilirubin increased	-	Gr 3
Alanine aminotransferase increase	-	Gr 3
Aspartate aminotransferase increase	-	Gr 3

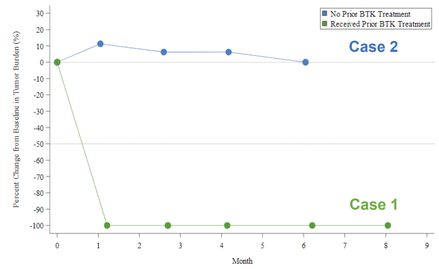
Data extracted October 12th, 2022

- No DLT and no treatment-related SAE was reported
- Majority of Gr 3 TRAEs were recovered or resolved

Results

- The preliminary efficacy data demonstrated one CR (**Case 1**) and one SD (**Case 2**).
- **Case 1** was originally intolerant to high-dose methotrexate-based chemoimmunotherapy and achieved PR after switching to ibrutinib. **Case 1** then achieved CR with emavusertib and ibrutinib combination therapy.
- **Case 2** achieved and maintained radiographic SD for ~5 months, with clinical resolution of associated symptoms.

Change in tumor burden over time



Data extracted October 12th, 2022

Summary

- Preliminary data provide early clinical evidence of CNS penetration and anti-tumor activity of emavusertib.
- In R/R CNSL, the preliminary data suggest that combination therapy has a tolerable safety profile with promising anti-cancer activity and may overcome ibrutinib resistance.
- Trial enrollment is ongoing to further evaluate the clinical efficacy of emavusertib + ibrutinib combination therapy in CNSL.

References

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