#7575: Open-Label, Dose Escalation and Expansion Trial of Emavusertib (CA-4948), in Combination with Ibrutinib in Patients with Relapsed or Refractory Hematological Malignances

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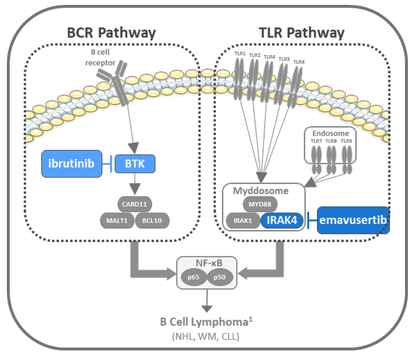
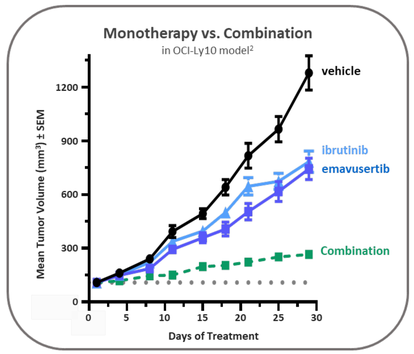
Background



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 forming multiprotein complexes causing inflammation and tumor growth [1, 2]

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

- Single agent activity in R/R non-Hodgkin Lymphoma patients [3]
- Demonstrated in preclinical studies to overcome tumor resistance to ibrutinib and PI3K inhibitors [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]
- Showed in-vivo synergy in B-cell NHL in combination with ibrutinib [6]

Study Design

TakeAim-Lymphoma (NCT03328078)

1. **Part A1**: dose escalation of emavusertib as monotherapy
2. **Part A2**: dose escalation of emavusertib in combination with ibrutinib
   - Endpoints of Part A1 and A2 include safety, tolerability, and RP2D
   - Treatment: Oral, once-daily (QD), or twice-daily (BID), dosing in continuous 21-day cycles
3. **Part B**: expansion cohorts of emavusertib in combination with ibrutinib (not yet initiated)

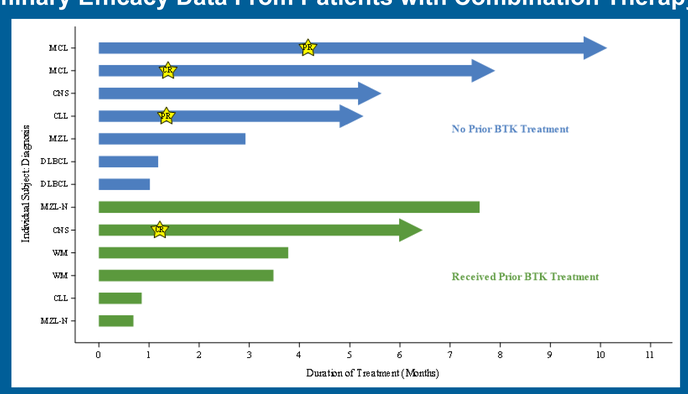
Abbreviations
Relapsed/Refractory (R/R), Marginal Zone Lymphoma (MZL), Diffuse Large B-Cell Lymphoma (DLBCL), Primary Central Nervous System Lymphoma (PCNSL), Non-Hodgkin Lymphomas (NHL), Mantle Cell Lymphoma (MCL), Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Recommended Phase II Dose (RP2D)

Baseline Characteristics

- 13 patients received emavusertib + ibrutinib combination therapy: 8 patients discontinued treatment due to adverse event (2), PD (3), and other (3)

Combination therapy	Total (N = 13)
Female n : Male n	6 : 7
Age (yrs): median (range)	66 (56, 92)
Diagnosis	
CLL	2
PCNSL	2
DLBCL	2
MCL	2
MZL	3
WM	2
Prior lines of therapy: median (range)	3 (1-8)
Prior BTK inhibitor	6

Preliminary Efficacy Data From Patients with Combination Therapy



★ Indicates time of response

- In prior clinical studies oral emavusertib monotherapy appeared to be well tolerated with an acceptable long term safety profile
- Preliminary data suggest that combination therapy may overcome ibrutinib resistance in hematological malignances
- Objective responses occurred at both 200mg and 300mg BID dose levels. All responding patients are presently being treated at 200mg BID of emavusertib with full dose of ibrutinib

Data extracted May 6th, 2022

Acknowledgment
We would like to thank the patients, their families and caregivers for their invaluable contribution and participation in this study

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TakeAim

SCAN ME

Safety

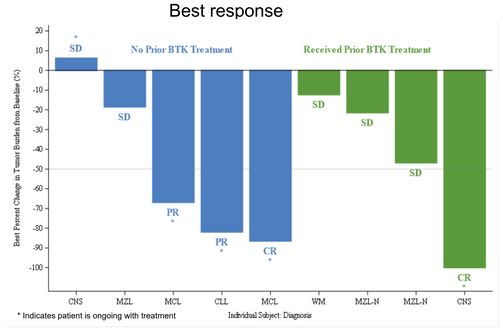
- 13 patients received emavusertib combination therapy
- Emavusertib in combination with ibrutinib is well tolerated
- No DLTs observed at 200mg, 2 DLTs observed at 300mg (Stomatitis and Syncope)

Grade 3+ Treatment-Related Adverse Event	Emavusertib 200 mg BID		Emavusertib 300 mg BID	
	Ibrutinib 420 mg QD (N = 1)	Ibrutinib 560 mg QD (N = 5)	Ibrutinib 420 mg QD (N = 3)	Ibrutinib 560 mg QD (N = 4)
# patients having grade 3+ TRAEs	1	4	1	3
Platelet count decreased		2	1	
Alanine aminotransferase increased	1			
Anaemia		1		
Aspartate aminotransferase increased	1			
Asthenia		1		
Blood alkaline phosphatase increased		1		
Diarrhea				1
Fatigue		1		
Hyponatraemia	1			
Lipase increased		1		
Muscular weakness				1
Pain				1
Stomatitis				1
Syncope			1	
Thrombocytopenia				1
Vomiting				1

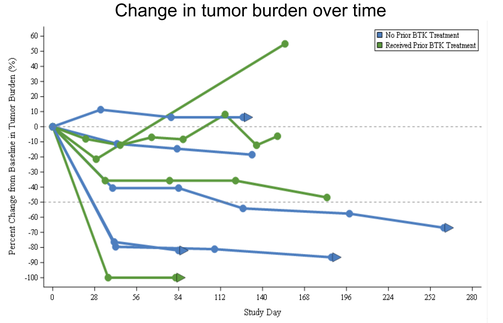
Results

Evaluable Patients treated with emavusertib + ibrutinib

- 4 patients that received prior BTK treatment show promising anti-cancer activity (SD/CR)
- 4/13 patients were not evaluable for tumor burden; 1 patient progressed without evaluable tumor burden; 3 patients had no response assessments prior to discontinuation from treatment (1 due to adverse event, 1 died, 1 other)



- Majority of patients had decreases In tumor burden or SD over time



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