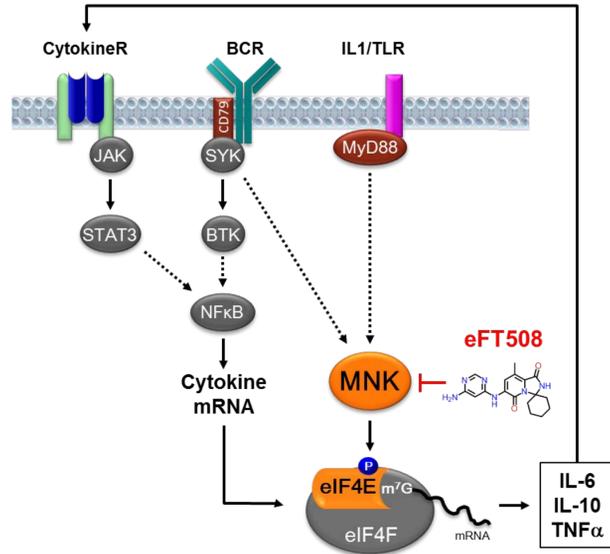


A Phase 1-2 Dose-Escalation and Cohort-Expansion Study of eFT508, a Selective, Orally Bioavailable Inhibitor of MNK1 and MNK2, in Patients with Hematological Malignancies 4624

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Introduction

Dysregulated translation of messenger RNA (mRNA) plays a role in the pathogenesis of multiple hematological and solid tumors. eFT508 is a potent and highly selective small molecule inhibitor of MNK-1 and 2 that blocks activation of eIF4E, a key regulator of mRNA translation, and thereby selectively regulates translation of a small set of mRNAs. Significant anti-tumor activity has been observed in preclinical models of diffuse large B-cell lymphoma (DLBCL), particularly in tumor models that have a mutation in MyD88. In addition to direct antitumor activity, eFT508 triggers an anti-tumor immune response and enhances responses to checkpoint inhibitors in preclinical models. The current study is a first-in-human dose escalation and cohort expansion trial of eFT508 in patients with advanced hematological malignancies.



- eFFECTOR Therapeutics has designed eFT508, a potent, orally bioavailable, highly selective, small molecule inhibitor of MNK1 and MNK2 activity
- MNK1 and MNK2 are S/T protein kinases that integrate signals from several oncogenic and immune signaling pathways, such as RAS and T-cell receptor (TCR), at the level of translational control
- MNK selectively controls the translation of key regulators of the anti-tumor immune response
- eFT508 modulates anti-tumor immunity and effectively synergizes with immune checkpoint blockade *in vivo* in pre-clinical models

Objectives

- Part 1**
Primary objective
- To determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of eFT508

- Secondary objectives**
- To characterize the safety profile of eFT508
 - To evaluate the anti-tumor activity of eFT508
 - To evaluate the pharmacokinetic (PK) profile of eFT508
 - To assess the effects of eFT508 on pharmacodynamic (PD) markers relating to drug mechanism of action

- Part 2**
Primary objective
- To evaluate the Objective Response Rate (ORR) in patients with non-GCB DLBCL (Diffuse Large B Cell Lymphoma)

Methods

- Study design and treatment**
- A phase 1-2, open-label dose escalation and cohort expansion study in adult patients with hematological malignancies
 - Phase 1:** 3+3 dose escalation scheme with eFT508 administered once daily by oral suspension or twice daily (BID) by capsule
 - Phase 2:** Expansion at the MTD/RP2D in patients with relapsed/refractory non-GCB DLBCL

Patient eligibility criteria

- Age ≥ 18 years
- ECOG Performance status 0 or 1
- Adequate bone marrow and organ function
- Phase 1 – Unselected B cell malignancy
- Phase 2 – Chemorefractory non-GCB DLBCL

Maximum tolerated dose (MTD)

- Highest dose level at which ≥ 6 patients have been treated and associated with a first cycle DLT rate of ≤ 17%

Dose limiting toxicity (DLT)

- Graded according to NCI CTCAE v4.03 during first cycle (21 days) of treatment and not clearly related to disease progression
 - Grade ≥ 3 neutropenia with Grade ≥ 2 fever or Grade 4 neutropenia lasting ≥ 7 days
 - Grade ≥ 2 thrombocytopenia with Grad ≥ 2 bleeding or Grade 4 thrombocytopenia lasting ≥ 7 days
 - Non hematological ≥ grade 3 toxicities excluding those not maximally treated, inability to deliver ≥ 14/21 doses due to drug related AEs

Pharmacokinetic assessment

- Non-compartmental methods to assess C_{max}, T_{max}, T_{1/2}, AUC

Response assessment

- Every 6 weeks based on modified Lugano criteria

Formulations

- Initial dose escalation by once daily oral suspension
- Transition to capsule formulation administered BID
 - MTD/RP2D will be determined with the capsule

Results

Table 1. Patient demographic and baseline characteristics

Characteristic	N = 12
Age, mean (range), years	64.5 (32-79)
Gender	
• Male	8 (67%)
• Female	4 (33%)
Race	
• White	11 (92%)
• Other	1 (8%)
Median number of prior therapies (range)	4 (2-7)
Stem cell transplant	4 (33%)
Tumor type	
• Diffuse Large B Cell Lymphoma (DLBCL)	4 (33%)
• Follicular Lymphoma (FL)	3 (25%)
• Hodgkin Lymphoma (HL)	2 (17%)
• Other:	3 (25%)
1 Waldenstrom Macroglobulinemia (WM)	
1 Mantle Cell (MCL)	
1 Marginal Zone Lymphoma (MZL)	

Results (continued)

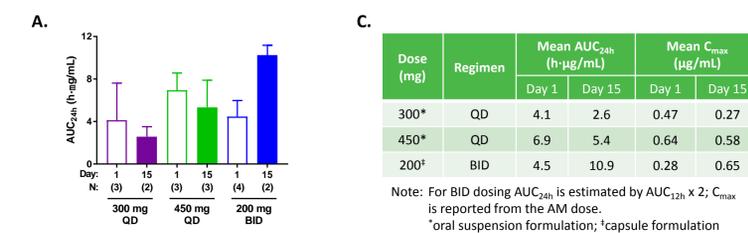
Table 2. Dose escalation

eFT508 dose	Patients Treated	Mean Days of eFT508 exposure (min, max)	Dose Limiting Toxicity (Patients)
300 mg QD*	3	91 (12-168)	
450 mg QD*	3	76 (37-152)	Grade 3 hypercalcemia (1) [§]
200 mg BID [‡]	6	30 (13-65) [†]	

*oral suspension; †capsule formulation
[§]Grade 3 hypercalcemia in a 75 year old female with DLBCL resolved with a single infusion of zoledronate
[†]Patients ongoing at time of data cut off

- Transition from oral suspension to capsule formulation after first 2 cohorts treated
- Recommended Phase 2 Dose (RP2D) from parallel solid tumor study was 450 mg QD oral suspension
- BID scheduling based on PK/PD data shows improved target coverage

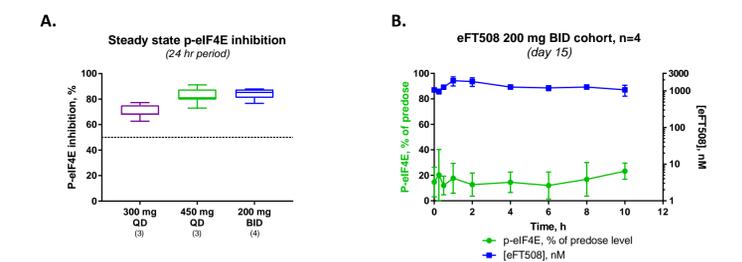
Figure 1. Preliminary pharmacokinetic analysis



- Mean exposure increase with dose from 300 to 450 mg (QD, oral suspension)
- No accumulation with repeat dose of oral suspension
- ~2-fold accumulation with repeat dose of BID capsule formulation
- Oral suspension: Median T_{max} 2h; Mean T_{1/2} 11h
- Capsule: Median T_{max} 4h; Mean T_{1/2} not determined

eFT508 levels were assessed in patient plasma samples. A) AUC_{0-24h} is plotted for each dose cohort with days 1 and 15, with number of patients denoted in parentheses. Bars, arithmetic mean; error bars, S.D. B) Average eFT508 plasma levels plotted (arithmetic mean) as a function of time for day 15. Error bars, S.D. C) Table of AUC_{0-24h} and C_{max} values (arithmetic means) for each dose cohort.

Figure 2. Pharmacodynamic analysis



- A 200 mg BID dose achieves a median inhibition of 85% during a 24h period
- This is in excess of the degree of inhibition required to deliver maximal efficacy in preclinical models

Patient PBMCs were isolated and assessed for p-eIF4E by flow cytometry on d15. Data from patients are plotted with number of patients denoted in parentheses. A) Box and whisker plot of the mean (arithmetic) values for p-eIF4E inhibition over 24h. Line, median p-eIF4E inhibition; whiskers, 5-95 percentile. B) PK/PD of p-eIF4E in the 200 mg BID cohort. Mean (arithmetic) levels of p-eIF4E (green) and eFT508 exposure (blue) are plotted; error bars, S.D.

Table 3. Patient disposition

Patient status	N = 12
Continuing on study therapy	3
Discontinued therapy	9
• Disease Progression	8
• Adverse Event	1
• Withdrawal of consent	0

Table 4. Treatment emergent adverse events (AEs)

MedDRA preferred term	AEs all causality N = 10			Treatment related N = 10	
	All grades	Grade 3	Grade 4	All grades	Grade 3
Fatigue	7	0	0	5	0
Hypercalcemia	4	2	0	3	1
Nausea	6	0	0	5	0
Anemia	3	0	0	2	0
Constipation	3	0	0	0	0
Gastro-esophageal reflux	3	0	0	3	0
Tremor	3	0	0	2	0
Diarrhea	2	0	0	2	0
Headache	2	0	0	1	0
Hypokalemia	2	1	0	0	0
Hyponatremia	2	1	0	0	0
Peripheral edema	2	0	0	0	0
Pyrexia	2	0	0	0	0
Vomiting	2	0	0	2	0
Creatine phosphokinase	2	0	0	2	0

Data for oral suspension and capsule formulations have been combined. Each patient is only counted once for each event, according to highest grade for that event. No patient experienced > grade 1 neutropenia or thrombocytopenia.

Table 5. Efficacy summary

Best Overall Objective Response	N = 12
CR/PR	1
SD*	4
PD	4
Not evaluable	1
*Durations of SD range, days	38 [†] - 168

- 32 year old HL patient (chemotherapy and stem cell transplant failure) experienced a 30% reduction in nodal disease and improvement in B symptoms
- 79 year old WM patient experienced a 22% reduction in M protein maintained for 152 days
- 59 year old FL patient (rituximab refractory) maintained SD for 168 days
- Post-data cut, a 68 year old DLBCL patient (relapsing post stem cell transplant) achieved a partial response at 12 weeks and continues on treatment

[†]Duration of SD is censored at 38 days for one active subject in the study. Two active subjects have not yet had a response assessment.

Summary

- eFT508 capsule formulation administered BID has an acceptable tolerability profile in this population.
- Common treatment related AEs are fatigue, hypercalcemia, nausea, anemia, gastro-esophageal reflux, tremor, diarrhea, and vomiting.
- The 200 mg BID capsule formulation shows approximately a 2-fold accumulation upon repeat dosing. The median T_{max} of the capsule formulation is 4 hours.
- Based on a pharmacodynamic assay, the well-tolerated 200 mg BID dose provides target coverage associated with maximal pre-clinical activity.
- Dose escalation continues and formal evaluation of efficacy at the RP2D will be initiated in a cohort of non-GCB DLBCL patients. Additional tumor types will be added based on emerging clinical data.

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