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

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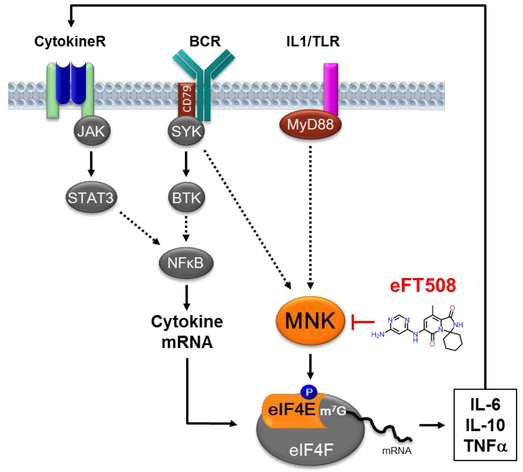
Introduction

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 Cmax, Tmax, $T_{1/2}$, 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: 1 Waldenstrom Macroglobulinemia (WM) 1 Mantle Cell (MCL) 1 Marginal Zone Lymphoma (MZL)	3 (25%)

Results (continued)

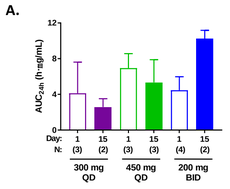
Table 2. Dose escalation

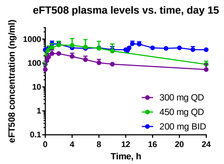
eFT508 dose	Patients Treated	Mean Days of eFT508 exposure (min, max)	Dose Limiting Toxicity (Patients)
300 mg QD*	3	91 (12-168)	
450 mg QD*	3	76 (37-152)	Grade 3 hypercalcemia (1)§
200 mg BID‡	6	30 (13-65)†	

*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





C.

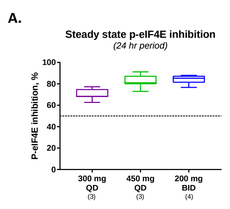
Dose (mg)	Regimen	Mean AUC_{24h} (h·µg/mL)		Mean C_{max} (µg/mL)	
		Day 1	Day 15	Day 1	Day 15
300*	QD	4.1	2.6	0.47	0.27
450*	QD	6.9	5.4	0.64	0.58
200‡	BID	4.5	10.9	0.28	0.65

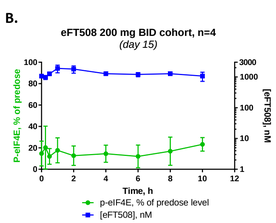
Note: For BID dosing AUC_{24h} is estimated by AUC_{12h} x 2; C_{max} is reported from the AM dose.
*oral suspension formulation; ‡capsule formulation

- **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_{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_{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 (rituxumab 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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