A Phase 1 Dose Escalation Study of eFT508, an Inhibitor of Mitogen-Activated Protein Kinase-Interacting Serine/Threonine Kinase-1 (MNK-1) and MNK-2 in Patients with Advanced Solid Tumors

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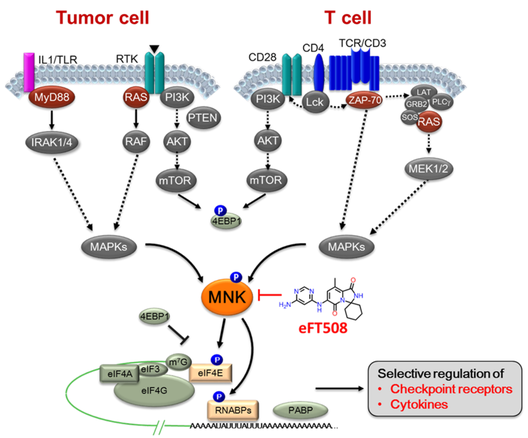
Abstract

Background: Dysregulated translation of messenger RNA (mRNA) plays a role in the pathogenesis of multiple solid tumors. eFT508, a potent and highly selective small molecule inhibitor of MNK-1 and 2 blocks activation of eIF4E, a key regulator of mRNA translation, and thereby selectively regulates translation of a small set of mRNAs. In addition to direct antitumor activity, eFT508 triggers an anti- tumor immune response and enhances responses to checkpoint inhibitors in preclinical models. **Methods**: Using a 3+3 dose escalation schema, cohorts of solid tumor patients (pts) were treated with eFT508 administered orally once daily at doses ranging from 50 mg to 600 mg. **Results**: 28 pts were treated, and the most common tumor types were colorectal cancer (8), prostate cancer (3), and soft tissue sarcoma (3). Median number of prior therapies was 4. The most common observed adverse events (AEs) included nausea (47%), vomiting (47%), dyspepsia (23%), fatigue (20%), and constipation (20%). Two pts treated at 600 mg experienced Gr 3 related AEs, including one pt with Gr3 nausea and vomiting (met criteria for dose limiting toxicity) and one pt with reversible Gr3 AST/ALT elevation. 6 pts achieved stable disease with duration ranging from 82 to 196 days. Pharmacokinetic analysis revealed that eFT508 is bioavailable and rapidly absorbed, with median Tmax of 2 hours and a mean $T_{1/2}$ of 12 hours. Minimal accumulation was observed between Days 1 and 14/15, with mean accumulation factor of 1.2-fold. Analysis of eIF4E phosphorylation in peripheral blood cells suggested that doses ≥ 300 mg achieved engagement sufficient for maximal efficacy as predicted by preclinical models. **Conclusions**: Preliminary results suggest that eFT508 is well tolerated, and dose escalation continues with a cohort of pts providing pretreatment and on treatment biopsies for evaluation of target engagement and immunomodulatory effects. After determination of the recommended phase 2 dose, further evaluation will include monotherapy cohorts in specific tumor types as well as cohorts to evaluate efficacy and tolerability in combination with checkpoint inhibitors.

Introduction



- **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 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 ORR of eFT508 in specific tumor types

Methods

Study design and treatment

- Open label study in adult patients with advanced solid tumors
- **Part 1**: 3+3 dose escalation scheme with eFT508 oral suspension administered once daily
- **Part 2**: Expansion at MTD or RP2D in the following cohorts
  - NSCLC after treatment with chemotherapy and a checkpoint inhibitor
  - Hepatocellular carcinoma (HCC) following failure of local and 1 systemic therapy

Patient eligibility – key inclusion criteria

Part 1

- Advanced solid tumor malignancy progressive after standard therapy or with no potential for cure
- Adequate bone marrow and organ function

Part 2

- Metastatic NSCLC following failure of chemotherapy and checkpoint inhibitor
- Advanced HCC following failure of 1 systemic disease
- Measurable disease

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 of treatment and not clearly related to disease progression
  - Grade ≥ 4 neutropenia or thrombocytopenia
  - 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

- Radiological tumor assessment at baseline and every 6 weeks
- Response assessment using modified RECIST 1.1

Results

Table 1. Patient demographic and baseline characteristics

Characteristic	N =32
Age, mean (range), years	60.1 (36-81)
Gender	
• Male	10 (31%)
• Female	22 (69%)
Race	
• White	27 (84.5%)
• African American	3 (9.5%)
• Other	2 (6%) – Asian (1); Unknown (1)
Median number of prior therapies (range)	4 (0-9)
Primary Tumor Type	
• Colorectal	9 (28%)
• Breast	3 (9.5%)
• Prostate	3 (9.5%)
• Sarcoma	2 (6%) Chondrosarcoma, Leiomyosarcoma
• Pancreas	2 (6%)
• Other (1-2 patients per tumor type*)	13 (41%)

*adrenal, appendiceal, cholangiocarcinoma, CNS, esophageal, fallopian, GIST, kidney, lung, myoepithelial, ovary, stomach, uterus

Results (continued)

Table 2. Dose escalation

eFT508 dose (mg QD)	Patients Treated	Mean Days of eFT508 exposure (min, max)	Dose Limiting Toxicity (Patients)
50	3	57 (42, 83)	None (0)
100	3	54 (36, 84)	None (0)
200	3	87 (35, 187)	None (0)
300	3	55 (42, 82)	None (0)
450	8	51 (20, 84)	None (0)
600	12	25 (4, 44)	Gr 3 Nausea/Vomiting (1) Gr 3 Tremor (1)

Figure 1. Pharmacokinetic analysis

C.

Dose (mg)	AUC_{24h} (h·µg/mL)		Cmax (µg/mL)	
	Day 1	Day 14/15	Day 1	Day 14/15
50	1.5	2.0	0.11	0.15
100	3.3	3.3	0.24	0.23
200	3.6	6.0	0.30	0.46
300	4.7	4.6	0.37	0.40
450	7.8	7.1	0.54	0.49
600	6.6	7.5	0.46	0.58

- **Exposure increases are less than dose proportional**
- **Minimal accumulation with repeat dosing**
- **Other key PK parameters:**

  Median Tmax ~ 3.7 h; Mean $T_{1/2}$ ~ 12 h

eFT508 levels were assessed in patient plasma samples. **A**) AUC_{24h} is plotted for each dose cohort with days 1 and 14/15 combined. Bars, arithmetic mean; error bars, S.D. **B**) Average eFT508 plasma levels plotted (arithmetic mean) as a function of time for day 1. Error bars, S.D. **C**) Table of AUC_{24h} and Cmax values (arithmetic means) for each dose cohort.

Figure 2. Pharmacodynamic analysis

- **A 450 mg dose achieves a median inhibition of 74% during a 24 hr 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 exceeding a 2-fold S/N threshold in the assay are plotted with sample size denoted in parentheses. **A**) Inhibition of p-eIF4E (%) at Cmax is plotted for each patient. Solid lines, mean (arithmetic) inhibition; dotted line, 50% inhibition. **B**) Box and whisker plot of the mean (arithmetic) values for p-eIF4E inhibition over 24 hrs. Box line, median p-eIF4E inhibition; whiskers, 5-95 percentile; dotted line, 50% inhibition. **C**) PK/PD of p-eIF4E in the 450 mg dose cohort. Mean (arithmetic) levels of p-eIF4E (green) and eFT508 exposure (black) are plotted; error bars, S.D.

Table 3. Patient disposition

Patient status	N=32
Continuing on study therapy	1 (3%)
Discontinued therapy	
• Disease Progression	27 (85%)
• Adverse Event	2 (6%)
• Withdrawal of consent	2 (6%)

Table 4. Treatment emergent adverse events (AEs)

MedDRA preferred term	AEs all causality N=32			Treatment related N=32	
	All grades	Grade 3	Grade 4	All grades	Grade 3
Vomiting	18 (56%)	1 (3%)	0	14 (44%)	1 (3%)
Nausea	17 (53%)	1 (3%)	0	16 (50%)	1 (3%)
Constipation	10 (31%)	0 (0%)	0	4 (13%)	0 (0%)
Fatigue	7(22%)	0 (0%)	0	7 (22%)	0 (0%)
Dyspepsia	7 (22%)	0 (0%)	0	5 (16%)	0 (0%)
Abdominal Pain	7 (22%)	1 (3%)	0	2 (6%)	0 (0%)
Tremor	6 (19%)	1 (3%)	0	6 (19%)	1 (3%)
Dyspnoea	5 (16%)	0 (0%)	0	1 (3%)	0 (0%)
Headache	5 (16%)	0 (0%)	0	3 (9%)	0 (0%)
Elevated Transaminases	5 (16%)	2 (6%)	0	5 (16%)	2 (6%)
Acute Kidney Injury	2 (6%)	1 (3%)	0	0 (0%)	0 (0%)
Arthritis	1 (3%)	1 (3%)	0	1 (3%)	1 (3%)

Note: Each patient is only counted once for each event, according to highest grade for that event. Four grade 5 events (not included) were all clinical disease progression leading to death after end of treatment.

All 12 patients treated at a dose of 600 mg experienced at least one TEAE and two patients experienced DLTs (grade 3 nausea/vomiting and grade 3 tremor)

- On the basis of these findings, the 450 mg dose level is the RP2D for the oral suspension

Table 5. Efficacy summary

Best Overall Objective Response	N =32
CR/PR	0
SD*	7
PD	22*
Not evaluable	3
Durations of SD range from 83-193 days	

* One subject who clinically progressed within 3 days of a scan showing SD is categorized as PD

Summary

- **eFT508 oral suspension administered at a dose of 450 mg QD has an acceptable tolerability profile in this population and is the recommended phase 2 dose**
- **Common treatment related AEs are nausea, vomiting, constipation, dyspepsia and fatigue**
- **Based on an *ex vivo* PD assay, the 450 mg dose provides target coverage associated with maximal pre-clinical activity**
- **Exposure increases are less than dose-proportional. Estimated terminal half life is 14 hours. There is minimal accumulation upon repeat dosing**
- **Data support evaluation of monotherapy and combinations in patients with advanced solid tumors**

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