BACKGROUND

ENMD-2076 is a novel, orally-active molecule that inhibits Aurora A kinase and FLT3, as well as multiple receptor tyrosine kinases that drive tumor vasculatization, including VEGFR2 (KDR), PDGR, and FGFR. A phase I study was conducted to determine the maximum tolerated dose (MTD) and toxicities of ENMD-2076 in patients with refractory hematological malignancies.

METHODS

Patients (cohorts of 6 evaluable patients per dose level) received escalating doses of ENMD-2076 administered orally daily [225 mg (n=7), 375 mg (n=6), or 325 mg (n=7)]. Plasma levels of ENMD-2076 were measured on Days 1, 8, & 29 of cycle 1 and at end of study. Peripheral blood and/or bone marrow were obtained at baseline for ex vivo drug sensitivity testing, and on Days 8 & 29 of cycle 1 for pharmacodynamic (PD) monitoring to measure the effects of ENMD-2076 on cell signaling pathways. This flow cytometry-based assay uses combined labeling of pERK, pAkt, pSTAT5, and pS6 as the readout, and tests the effects of acute stimulation with the ligands SCF and FLT3L, in the presence or absence of pathway inhibitors, including ENMD-2076.

RESULTS

SUMMARY OF TOXICITY

No other drug-related DLTs were observed. 

PERIPHERAL BLOOD

30% change from baseline in hematological parameters, for Cycle 1 (n=20)

Non-hematologic: Grade 3/4

Side effects: 4 (27) 0 4 (27)

Fatigue: 6 (40) 3 (20) 9 (60)

Diarrea: 5 (33) 0 5 (33)

Decreases in the ability to stimulate ERK, Akt, STAT5, and S6 activity.

Complex flow cytometry protocol developed to study multiple potential drug targets:

1) analysis baseline signaling in leukemic blast cells; 

2) ex vivo drug effects on c-KIT activation. Cells were stimulated with the ligands SCF and FLT3L, in the presence or absence of pathway inhibitors (i.e. U0126 (MEK inhibitor), LY294002 (PI3 kinase inhibitor), rapamycin (mTOR inhibitor), and sorafenib (FLT3 and Raf kinase inhibitor) and ENMD-2076).

monitor pharmacodynamic effects during treatment. 

Peripheral blood or bone marrow were fixed with 4% formaldehyde. 

OBJECTIVES

To define MTD and DLT of oral daily ENMD-2076 in patients with relapsed or refractory hematological malignancies. 

- To determine MTD and DLT of oral daily ENMD-2076 in patients with relapsed or refractory hematological malignancies 
- To determine safety & toxicity of repeated oral dosing of ENMD-2076 
- To assess for anti-cancer effects of ENMD-2076

- To determine the PK profiles & PD effects of ENMD-2076 on signaling pathways, and on Aurora A kinase and cell cycle in the cancer cells

PHARMACODYNAMIC MONITORING

Functional assessment of complete cytorotation pathway inhibition in leukemia blasts cells, including inhibition of ERK, Akt, STAT5, and S6 activity. Enrollment, as well as PK and PD monitoring of this study, is ongoing. 

The Table shows that single agent ENMD-2076 has activity in a heavily pre-treated group of AML patients that may correlate with inhibition of ERK, Akt, STAT5, and S6 activity.

EVALUATION OF RESPONSE

The Table shows overall responses by IWG criteria (2003) (n=15)

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Additional flow cytometry monitoring of effects of ENMD-2076 on Aurora kinases and the cell cycle is being performed using combined staining for cyclin A2, pHistone H3 (Ser 10), and DNA content.

CONCLUSIONS

- Single agent ENMD-2076 has activity in patients with relapsed or refractory AML
- Enrollment as well as PK and PD monitoring of this study, is ongoing
- Additional flow cytometry monitoring of effects of ENMD-2076 on Aurora kinases and the cell cycle is being performed using combined staining for cyclin A2, pHistone H3 (Ser 10), and DNA content