A Single-Center, Open-Label, Dose-Escalation, Safety, and Pharmacokinetic Study of ENMD-1198 Administered Orally to Patients with Advanced Cancer

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ABSTRACT (UPDATED)

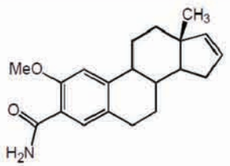
Background: ENMD-1198 (2-methoxyestra-1, 3, 5, (10) 16-tetraene-3-carboxamide), an analog of 2-methoxyestradiol (2ME2), has both antiangiogenic and antiproliferative effects in various tumor types. ENMD-1198 inhibits microtubule polymerization by binding to β-tubulin at the colchicine-binding site and inhibits HIF-1alpha. This Phase 1 study is evaluating the safety of ENMD-1198 to determine the maximum tolerated dose.

Materials and Methods: Eligible pts had advanced cancer for which no effective therapy exists that is either evaluable by RECIST criteria or tumor markers that could be monitored for clinical benefit. Phase 1 dose escalation in 3+3 design for first 5 cohorts; modified to 1 pt cohorts for subsequent cohorts until Grade 2 treatment related toxicity, and then standard 3+3 design. The initial low starting dose for the first cohorts was driven by a lower MTD in rats than in dogs. All pts treated with once daily oral ENMD-1198 in 28-day cycles (with post-treatment drug-free observation period of 14 [Cohorts 1-5] or 7 [Cohorts 6-12] days in Cycle 1 only). Pts are treated until the appearance of significant treatment-emergent toxicities or disease progression occurs.

Results: To date, 29 pts have been enrolled in 12 dose cohorts (range 5 to 550 mg/m^2/d). Median age and performance status was 60 and 1. Most common treatment-related toxicities of all grades were fatigue (55%), nausea and vomiting (37%), and constipation (34%). Two pts experienced dose limiting toxicity with Grade 4 neutropenia in the 550 mg/m^2/d cohort. Following a drug holiday, pts restarted at 425 mg/m^2/d and continued for at least 1-2 more cycles before being removed from study for progressive disease. ENMD-1198 was absorbed rapidly after oral administration. There was a linear relationship between dose and drug exposure as measured by AUC across all doses (5 - 550 mg/m^2/day). The mean elimination half-life of ENMD-1198 averaged 15 hours after a single dose. There have been no objective responses to date. Five pts have experienced stable disease (SD) for more than 2 cycles. One pt (neuroendocrine ca pancreas) is experiencing prolonged SD at 60 mg/m^2/d > 20 cycles and a second pt (prostate ca) experienced SD at 30 mg/m^2/d for 10 cycles.

Conclusions: ENMD-1198 appears orally bioavailable in humans with PK parameters compatible with once daily dosing. Dose escalation was continued up to 550 mg/m^2/d where two patients developed DLTs of neutropenia. 425 mg/m^2/d was determined to be the maximum tolerated dose. There is early evidence of clinical activity in prostate and neuroendocrine cancers.

INTRODUCTION



- ENMD-1198 (2-methoxyestra-1, 3, 5, (10) 16-tetraene-3-carboxamide), an analog of 2-methoxyestradiol (2ME2), has both antiangiogenic and antiproliferative effects in various tumor types.
- ENMD-1198 inhibits microtubule polymerization by binding to β-tubulin at the colchicine-binding site and inhibits HIF-1a.
- The *in vitro* IC_{50} for ENMD-1198 is in the range of 0.13 - 0.44 μM.

PATIENTS & METHODS

Primary Objective

- To identify the maximum tolerated dose (MTD) of ENMD-1198 administered orally over a range of doses in patients with advanced solid tumors.

Secondary Objectives

- To determine the safety and tolerability profile of ENMD-1198 in patients with advanced solid tumors
- To determine the plasma pharmacokinetics (PK) of ENMD-1198 administered orally over a range of doses
- To determine any early evidence of clinical benefit of ENMD-1198 in advanced cancer patients

Eligibility

Key Inclusion Criteria

- Adult patients with advanced cancer that can be monitored by RECIST or tumor markers
- ECOG performance status 0-1
- Adequate hematologic, hepatic, and renal function - standard parameters

Key Exclusion Criteria

- Have participated in any clinical trial involving conventional or investigational drugs within 30 days prior to initiation of ENMD-1198 dosing
- Sensory neuropathy of Grade 2 or greater according to the NCI CTCAE v3.0
- Not recovered from prior chemotherapy, radiotherapy, surgery

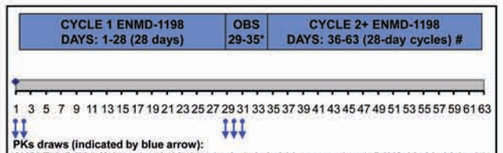
Treatment

Drug administration

- ENMD-1198 given orally as a NanoCrystal® Dispersion (NCD) once daily in 28-day cycles (First cycle includes a 7- or 14-day observation period)
- Treatments continue until DLT, progressive disease or unacceptable toxicities

Safety Monitoring

- Physical examination, vital signs, PS and laboratory assessments are performed at Day 1, 8, 15, 22 and 29 of each cycle
- ECGs at Screening, Cycle 1, Day 29, and final visit
- Adverse events (AEs) recorded according to NCI CTCAE v 3.0



PKs draws (indicated by blue arrow):
CYCLE 1, DAY 1 (0 (pre-dose), 30, 60 min, 2, 4, 6, 8, 24 hrs post-dose), DAYS 29, 30, 31 (at 24, 48 and 72 hours following the last dose of ENMD-1198 on Day 28); DAY 1 trough level in each subsequent cycle

* 14-day observation period (Cohorts 1 through 5); 7-day observation period (Cohorts 6 through 12)
# Tumor assessments performed every 8 weeks (2 treatment cycles)

Dose-Limiting Toxicities (DLTs)

- Determined during the first cycle of administration of ENMD-1198, utilizing NCI CTCAE version 3.0
- Any treatment-related Grade 3 or greater nonhematological AE
- Any treatment-related Grade 4 or greater hematological AE
- Nausea, vomiting and diarrhea, unless adequate supportive care is given, and alopecia are excluded from the determination of DLT

PATIENT CHARACTERISTICS

Demographics

Gender	**N**
Male	14
Female	15
Age	**Years**
Median (range)	60 (35-77)
ECOG Performance Status	**(N=26)**
0	9
1	17
Race	**N**
White	26
Others	3
Prior Therapies	**N**
Chemotherapy	26
Radiotherapy	19
Hormonal	9
Immunotherapy	4
Investigational Agent	5

RESULTS

Dose Cohorts, Number of Pts, and Cycles

Dose cohort	ENMD-1198 (mg/m^2/d)	N	Completed cycles (mean)
1	5	4	1.5
2	10	3	1.7
3	20	3	1.7
4	30	3	4.3
5	40	3	1.3
6*	60	1	20 (continues on study)
7	120	1	2
8	180	1	2
9	240	1	2
10	320	1	1
11#	425	5	1.6
12	550	3	3.7

* Amendment 02 (version date 06 Jun 2007) to proceed with single-patient cohorts until Grade 2 or greater toxicities seen in Cycle 1 (then return to 3+3 design)
# Expanded as recommended Phase 2 dose cohort

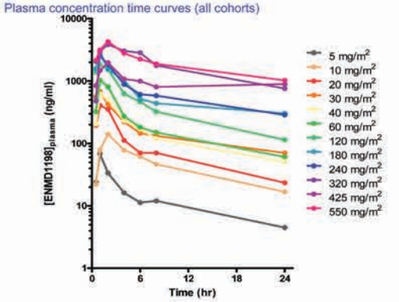
Adverse Events by Dose Cohort (N=29)

Dose Level (N)	5 mg/m^2 (4)		10 mg/m^2 (3)		20 mg/m^2 (3)		30 mg/m^2 (3)		40 mg/m^2 (3)		60 mg/m^2 (1)		120 mg/m^2 (1)		180 mg/m^2 (1)		240 mg/m^2 (1)		320 mg/m^2 (1)		425 mg/m^2 (5)		550 mg/m^2 (3)	
Grades	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4	G1/2	G3/4
Fatigue	3	--	1	--	2	--	2	--	2	--	--	--	--	--	1	--	1	--	--	--	2	--	2	--
Anorexia	2	--	--	--	--	--	--	--	--	--	--	--	--	--	1	--	--	--	--	--	1	--	1	--
Anemia	2	--	1	--	1	--	1	--	1	--	--	--	--	--	--	--	--	--	--	--	1	--	1	--
Neutropenia	--	--	1	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	2
Thrombocytopenia	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	1	--
Nausea/Vomiting	2	--	1	--	--	--	1	--	1	--	--	--	--	--	1	--	--	--	--	--	3	--	--	--
Diarrhea	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	1	--
Alopecia	1	--	--	--	1	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	2	--
LFTs	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	1	--	1	--
Facial Flushing	1	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
GERD	2	--	1	--	1	--	1	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Change in Taste	1	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Neuropathy	--	--	3	--	1	--	--	--	--	--	--	--	--	--	1	--	--	--	1	--	--	--	1	--
Hypotension	--	--	--	--	--	--	--	--	1	--	--	--	--	--	--	--	--	--	--	--	--	--	--	--
Constipation	3	--	--	--	3	--	1	--	2	--	--	--	--	--	--	--	1	--	1	--	1	--	1	--

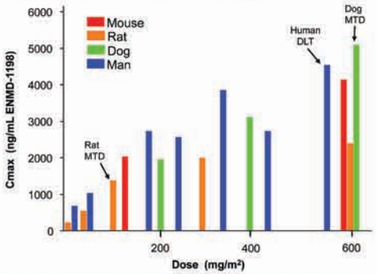
Pharmacokinetics

- The mean half life value in patients is ~15 hrs, justifying daily dosing.
- Exposure to ENMD-1198 in humans increases linearly with dose as determined by AUC.
- C_{max} is also dose-proportional, although at higher doses there is a trend towards absorption becoming non-linear.
- CL and $t_{1/2}$ are dose invariant.
- PK is predictable across a wide range of doses in multiple species (rat, dog, mouse, and human). Both C_{max} (figure below) and AUC (not shown) indicate similar pharmacokinetic behavior of ENMD-1198 when doses are adjusted for surface area.
- Human MTD (425 mg/m^2/d) is consistent with results of preclinical toxicokinetic studies in dogs, but not in rats. The reason for the enhanced toxicological impact in rats is not known, but is not related to drug exposure.

Plasma concentration time curves (all cohorts)



Cross-species comparison of ENMD-1198 PK (C_{max})

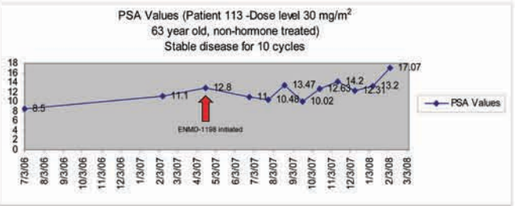


Efficacy

Dose Level (mg/m^2/d)	Tumor type	Prior drug regimens	No of cycles	Best response (PD – Progressive disease SD – Stable disease)
5	Ovarian Colon Melanoma Prostate	2 3 3 3	2 <1 2 1	PD PD PD PD
10	Prostate Ovary Breast	3 8 5	2 2 1	PD PD PD
20	Ovarian Prostate Prostate	8 3 5	1 2 2	PD PD PD
30	Breast Colon Prostate	8 5 2	2 1 10	PD WC (withdrew consent) SD (10 cycles)
40	Kidney Melanoma NSCLC	3 2 3	1 1 2	PD PD PD
60	Neuroendocrine - Pancreas	0	20	SD (25% shrinkage) Continues on study
120	Prostate	7	2	PD
180	Ovarian	5	2	PD
240	Prostate	4	3	SD for 2 cycles
320	Adenocystic carcinoma	0	1	PD
425	Colon Pancreas Bladder Anal Mesothelioma	4 2 3 2 4	2 1 1 1 3	PD PD PD PD SD for 2 cycles
550	Ovarian Colon Adrenal	3 4 3	8 2 2	SD for 8 cycles PD PD

Case Report of Prolonged Stable Disease

PROSTATE CANCER PATIENT WITH STABLE DISEASE FOR 10 CYCLES



CONCLUSIONS

- ENMD-1198 is orally bioavailable in humans.
- Pharmacokinetic profile is compatible with once daily dosing.
- Exposure to ENMD-1198 increases linearly with dose as determined by AUC.
- 425 mg/m^2/day has been determined as the maximum tolerated dose; two DLTs (2/3 pts) of neutropenia were identified in the 550 mg/m^2/d cohort.
- Stabilization of disease (range 2-20 cycles) has been noted in 5 of 29 patients treated across a range of doses, with particular promise in prostate and neuroendocrine tumors.
- Phase 2 clinical development plan is pending.