
A Phase I Study of ENMD-2076, a Unique Aurora A, Angiogenic Kinase Inhibitor, Administered Orally to Patients with Advanced Cancer

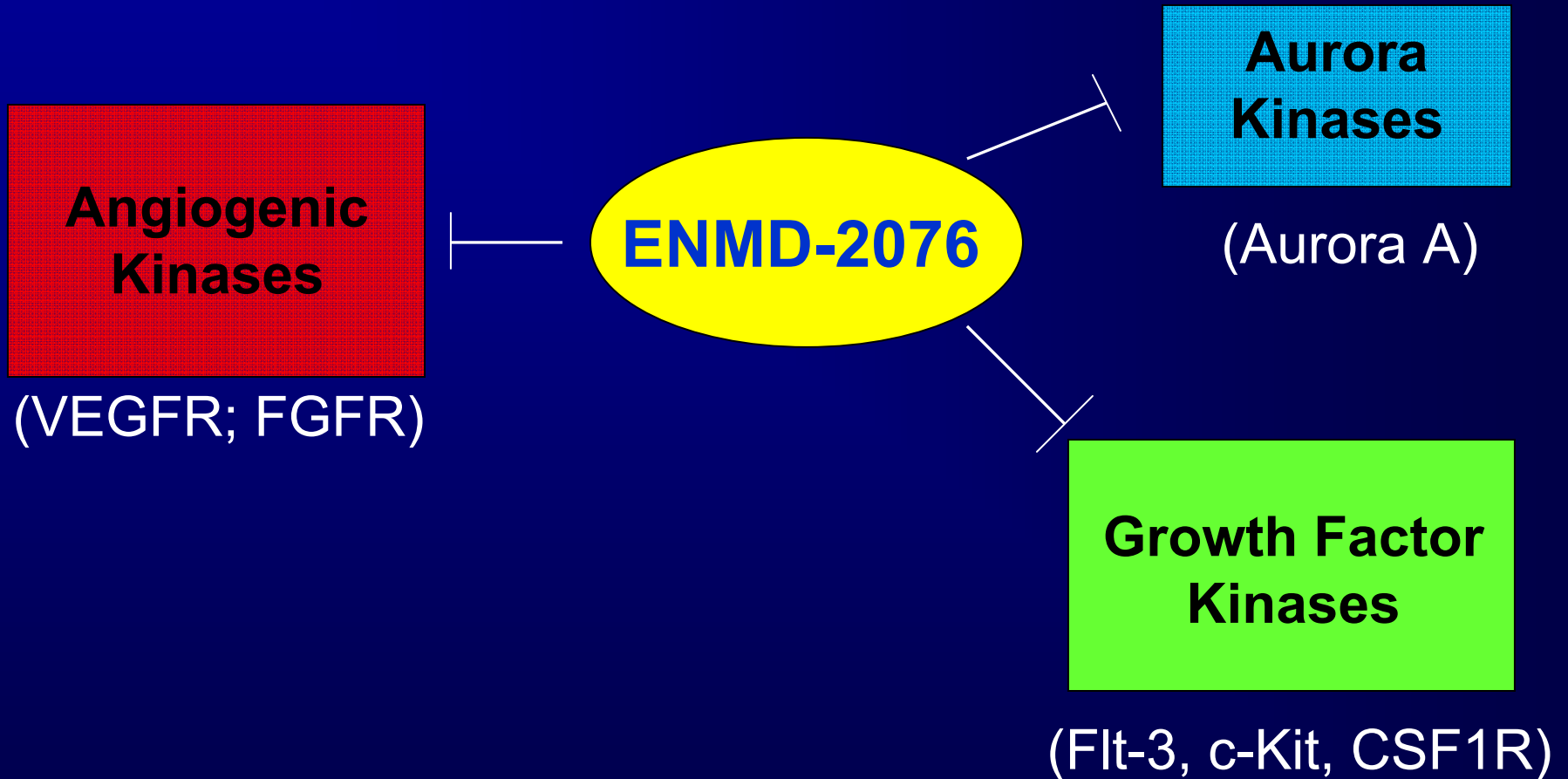
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ENMD-2076 – A Kinase Inhibitor With a Unique Target Profile

- **Orally active, multi-kinase inhibitor currently in Phase 1 clinical trials**
- **Unique combination of target activities**
 - **Angiogenic Kinases (VEGFRs, FGFRs)**
 - **Cell Cycle Kinases (Aurora A)**
 - **Growth Factor Kinases (c-Kit, Flt-3, CSF1R)**
- **Excellent preclinical antitumor activity as single agent or in combination**
- **Acceptable/manageable toxicity profile**

ENMD-2076 is an Orally Available Aurora A and Angiogenic Kinase Inhibitor

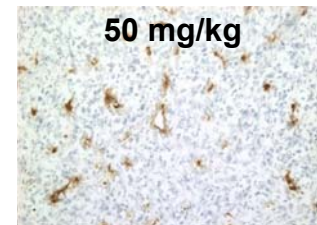
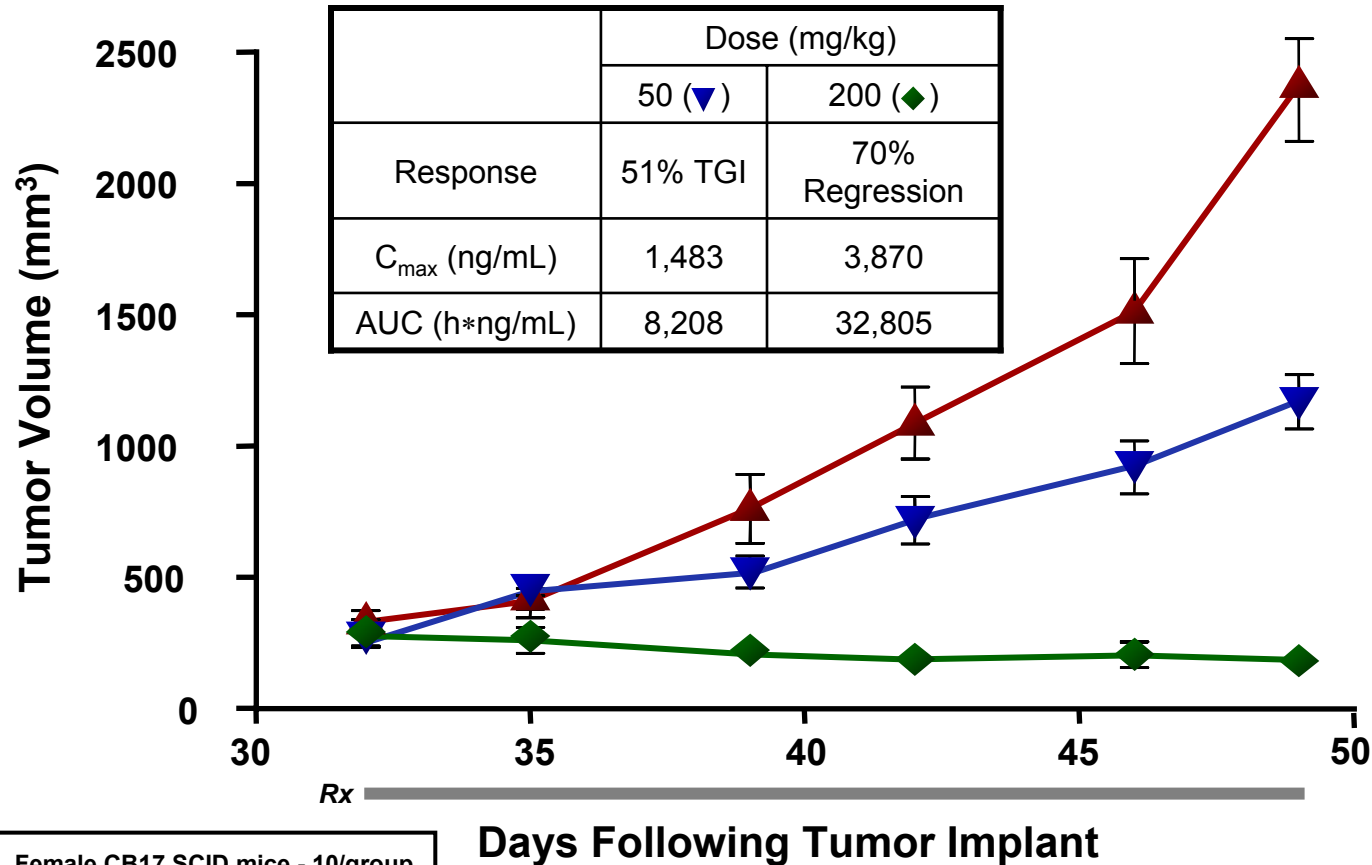


ENMD-2076 Experimental Results Consistent with Selective Inhibition of Aurora A *In Vitro* & *In Vivo*

- ENMD-2076 is selective for the Aurora A isoform
 - Recombinant enzyme IC_{50} s: Aur A = 14 nM, Aur B = 290 nM
 - Cellular enzyme IC_{50} s: Aur A = 130 nM, Aur B/C = 450 nM
- ENMD-2076 induces G2/M cell cycle arrest & apoptosis rather than endoreduplication/aneuploidy characteristic of Aur B/C inhibition
- ENMD-2076 induces abnormal mitosis, dose-dependent decrease in centrosomal distance, & monopindle phenotype characteristic of Aur A inhibition
- ENMD-2076 induces dose dependent increase in phospho-histone H3, decrease in anaphase profiles & inhibition of Aur A & TACC3 co-localization in treated tumors

ENMD-2076 Pharmacology

MDA-MB-231 Human Tumor Xenograft Model

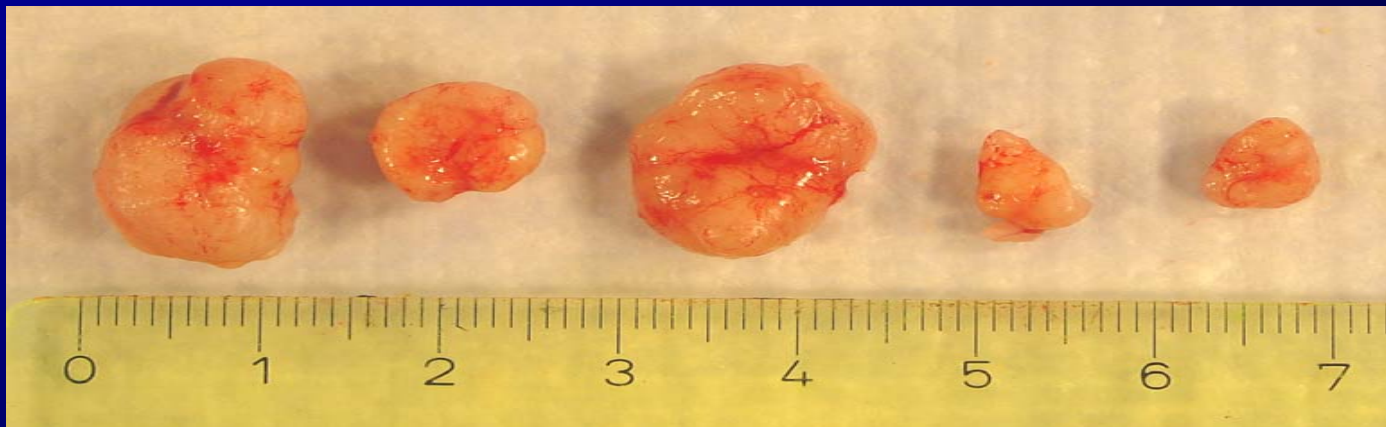


CD31 (Day 49)

Female CB17 SCID mice - 10/group
 Tumor implanted mfp on Day 0
 Rx initiated on Day 32

Tumor Regression and Inhibition of Angiogenesis in ENMD-2076 Treated HT-29 Xenografts

HT-29 Colon Cancer Xenograft
Vehicle Control Day 28

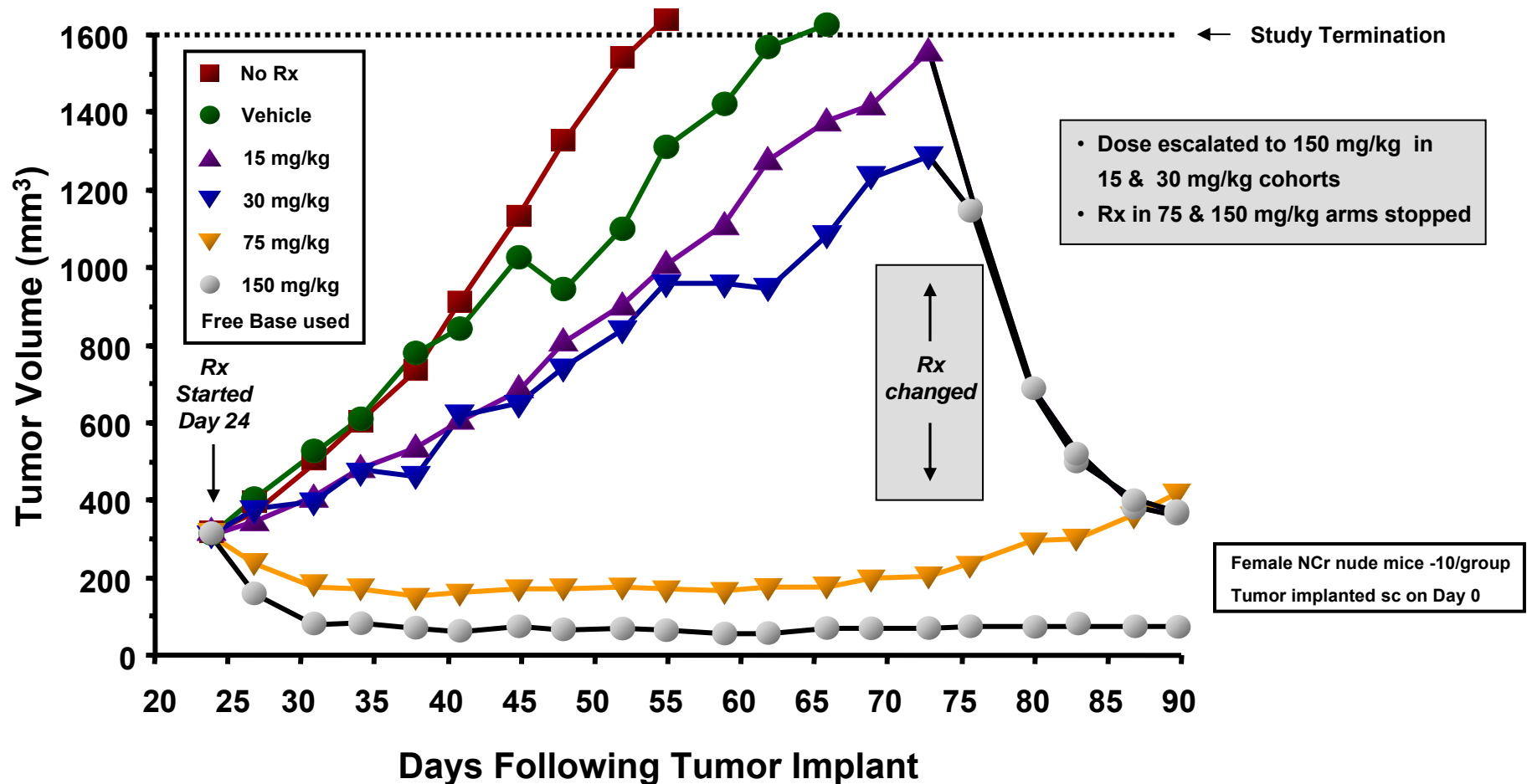


ENMD-2076 200 mg/kg/d PO Day 28

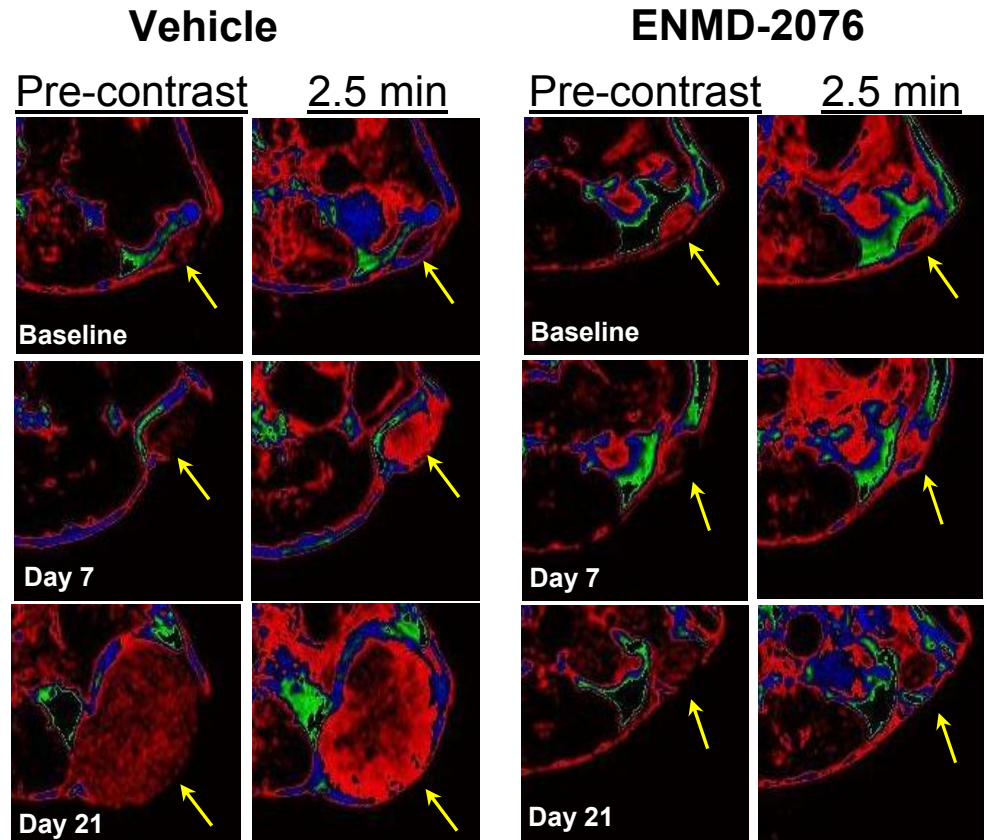
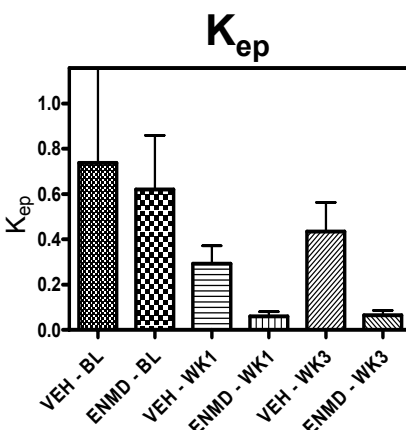
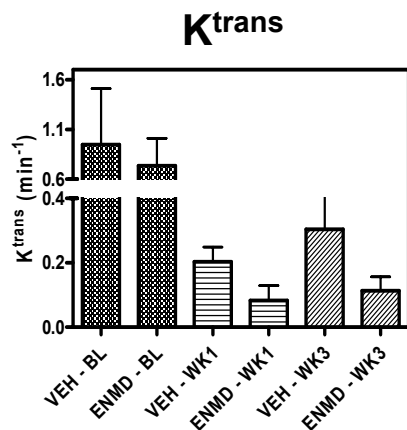
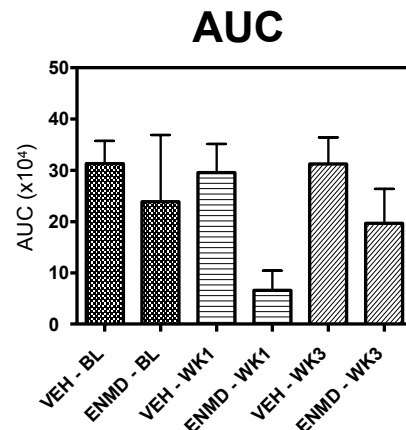
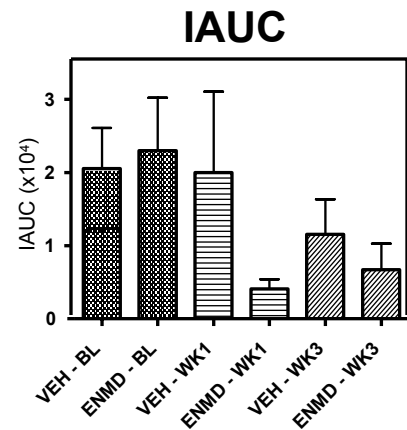


ENMD-2076 Induces Regression of MV4;11 AML (Flt-3-ITD) Tumor Xenografts

75 & 150 mg/kg doses of ENMD-2076 produce regressions; large tumors grown under lower exposures respond rapidly to increased dose



Antiangiogenic Effects Demonstrated with DCE-MRI Analysis of HT-29 Tumor Xenografts In Mice Treated With ENMD-2076



ENMD-2076 – Toxicology Results

- Toxicology
 - 28-day continuous oral dosing (rats & dogs)
 - Dose-proportional increases in C_{max} & AUC
 - GI effects observed in both rats & dogs
 - Reversible hard tissue effects in rats suggestive of kinase & antiangiogenic activities
 - Reversible LFTs & hematological effects in rats
- Safety Pharmacology
 - IC_{50} hERG channel = 300 nM
 - Telemetry study in non-anesthetized dogs demonstrated no effects on cardiovascular or respiratory system
- *In vitro* mutagenicity studies negative

A Phase I Study of ENMD-2076, a Unique Aurora A, Angiogenic Kinase Inhibitor, Administered Orally to Patients with Advanced Cancer

- Objectives

- To assess safety and tolerability and to determine the maximum tolerated dose (MTD) of ENMD-2076 administered orally in patients with advanced cancer over a range of doses
- To determine plasma pharmacokinetics of ENMD-2076 administered orally
- To investigate clinical efficacy in patients with advanced cancer

- Primary Eligibility Requirements

- Advanced cancer with progression on current therapy or for which no curative therapy exists
- ECOG PS 0-1
- Adequate organ function
 - No uncontrolled severe heart failure, Afib, \uparrow QTc
 - No uncontrolled severe hypertension
 - No $> 2+$ proteinuria or nephrotic syndrome
- Modified RECIST criteria or clinically evaluable disease
- Age ≥ 18 years
- Signed informed consent

Demographics and Dose Escalation

Enrolled	25
Male: Female	12:13
Median Age	61
Tumor Type	Colorectal = 8 Ovarian = 7 Renal cell = 3 Pancreatic = 2 Thyroid = 1 Neuroendocrine = 1 Urachal = 1 Melanoma = 1 Cervical = 1

3 (or 4) + 3 (or 2) dose
escalation design

60 mg/m²

80 mg/m²

120 mg/m²

200 mg/m²

160 mg/m²

ENMD-2076 given orally once daily in 28-day cycles

Dose-Limiting Toxicities (DLT)

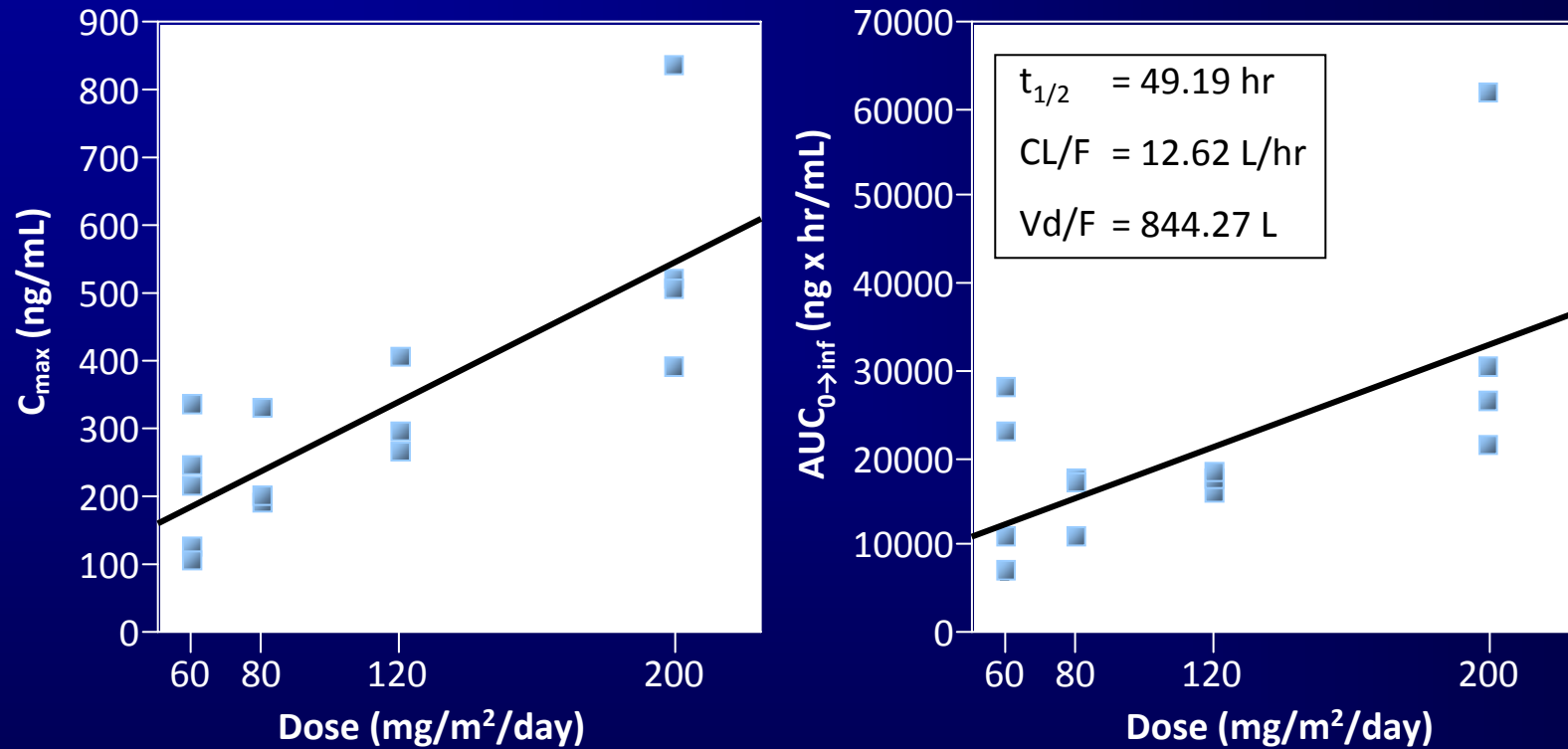
ENMD-2076 Dose	Enrolled	Evaluable	DLT (#)	DLT
60 mg/m ²	7	6	1	Grade 3 Cholecystitis Grade 4 HTN
80 mg/m ²	4	4	0	
120 mg/m ²	3	3	0	
200 mg/m ²	7	7	2	Grade 3 HTN Grade 3 Neutropenia
160 mg/m ²	4	Pending	Pending	

Treatment-Related Toxicities (n=22)

Toxicity	Grade 1/2	Grade 3	Grade 4	Total*
Hypertension	5 (22%)	2 (9%)	1 (5%)	8 (36%)
Diarrhea	5 (22%)			5 (22%)
Fatigue	3 (14%)			3 (14%)
Headache	3 (14%)			3 (14%)
Neutropenia		2 (9%)		2 (9%)
Nausea	2 (9%)			2 (9%)
Pruritus	2 (9%)			2 (9%)
Mucositis	2 (9%)			2 (9%)
Proteinuria	2 (9%)			2 (9%)
Pain		1 (5%)		1 (5%)
Elevated SGOT			1 (5%)	1 (5%)
Elevated SGPT		1 (5%)		1 (5%)
Cholecystitis		1 (5%)		1 (5%)

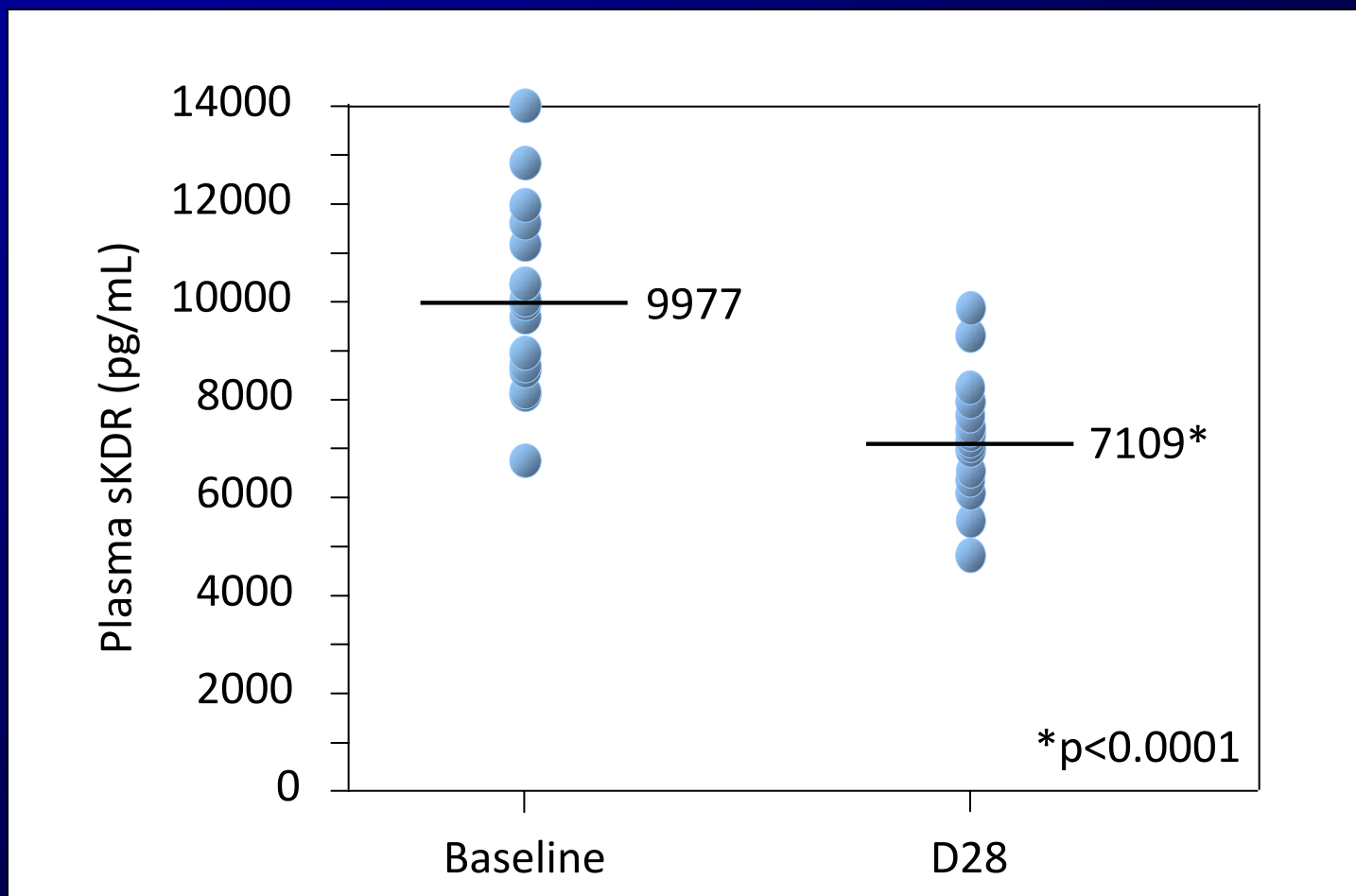
*Grade 1 or 2 treatment-related AEs in ≥ 2 patients and all Grade 3 or 4 treatment-related AEs

Pharmacokinetic Results (Day 28)



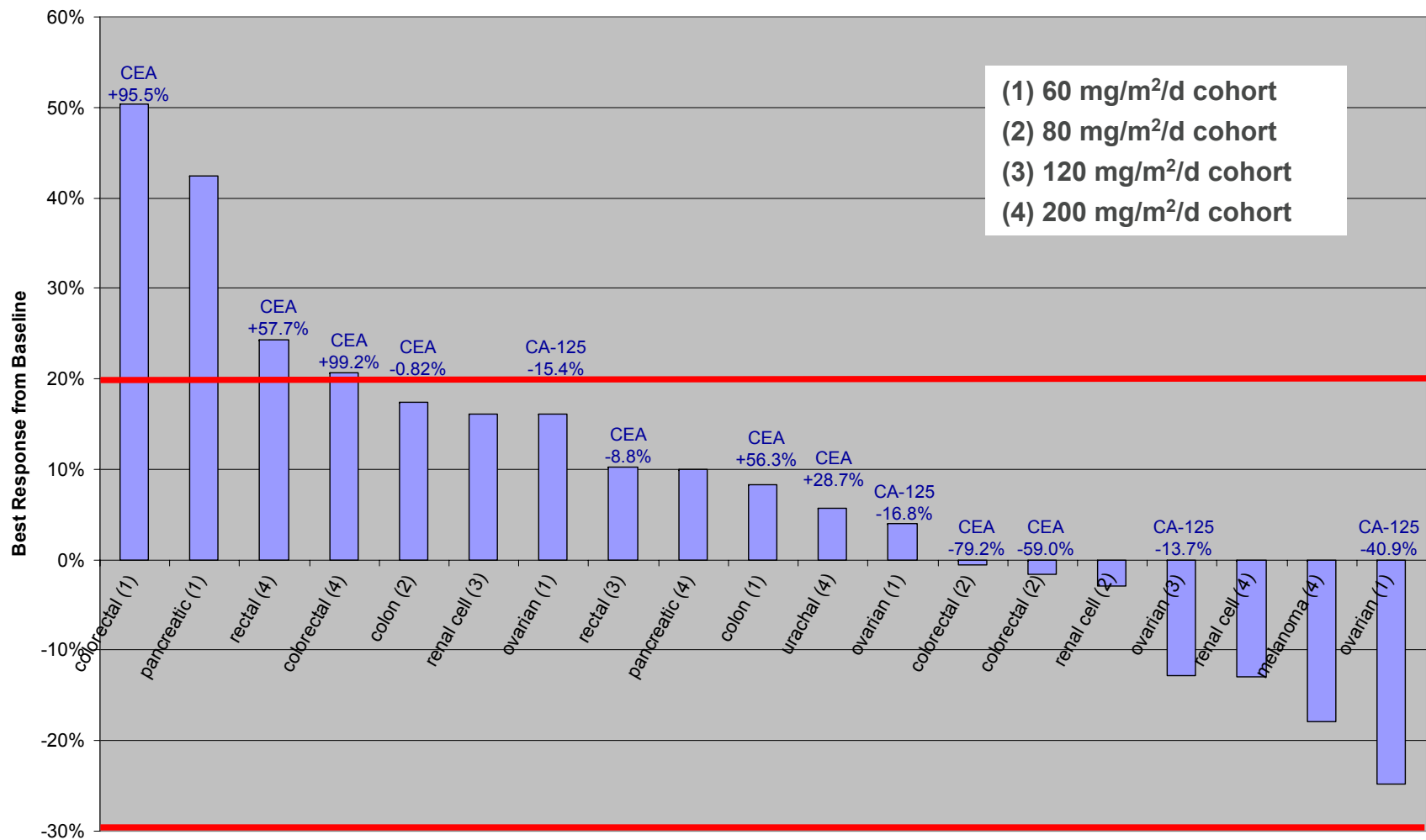
Steady state concentrations of ENMD-2076 approached or exceeded $1\mu M$ (375 ng/mL) with a half-life of 40 to 60 hours

Response of Plasma Soluble KDR to Treatment with ENMD-2076 (Cohorts 1 - 4)



Mean plasma soluble KDR went from 9977 pg/mL (95% CI 8901, 10992) at Baseline to 7109 pg/mL (95% CI 6429, 7789) at C1D28

Waterfall Plot of RECIST Measurements (n=19)



Study 2076-CL-001 Results/Conclusions

- Dose limiting toxicities of hypertension and neutropenia are observed at the 200 mg/m²/d dose level
- Steady state concentrations of ENMD-2076 approach 1 μM with a half life of 40 to 60 hours; an active metabolite, ENMD-2060, is present at concentrations of 0.3 μM with a half life of 100 hours
- Plasma soluble KDR reductions are seen in all patients when compared to their baseline
- Clinical benefit has been demonstrated with reductions in tumor volume, reductions in tumor markers, and improvement in cancer-related symptoms in melanoma, renal cell, ovarian, and colorectal cancer patients
- Expanded Phase 1 cohorts at the MTD and trials in myeloma and leukemia are underway that incorporate additional PD assessments
- ENMD-2076 represents an active and unique oral kinase inhibitor that targets a combination of Aurora A and angiogenesis kinases