4044: Development of UCT-01-097, a novel orally available ERK1/2 inhibitor for treating dependent cancers

Neil A. O'Brien[1], Martina S. J. McDermott[1], Brendan M. O'Boyle[2,3], Corey M. Reeves[3], Michael D. Bartberger[2], Oliver C. Losón[2], Kevin Chau[1], Jenny J. Hong[1], Weiping Jia[1], Naeimeh Kamranpour[1], Tong Luo[1], Raul Ayala[1], Athena M. Madrid[1], Minal Barve[4], Leah Plato[4], John Glaspy[1], Brian M. Stoltz[3] and Dennis J. Slamon[1]

UCLA, Los Angeles, CA[1]; 1200 Pharma LLC, Culver City, CA[2]; California Institute of Technology, Pasadena, CA[3]; Mary Crowley Cancer Research, Dallas, TX[4]

BACKGROUND

- The MAPK pathway is the most commonly mutated and dysregulated pathway in cancer
- The success of inhibitors targeting the MAPK pathway is often limited by toxicity, as well as by rapid and diverse mechanisms of resistance
- A prominent adaptive resistance mechanism is compensatory activation of the downstream mediator ERK1/2 that enables tumors to subvert targeted therapies
- Targeting ERK1/2 provides promising potential in overcoming and/or preventing resistance to MAPK targeting agents
- **We evaluated multiple preclinical and clinically staged inhibitors in a 500+ cell line screening platform and identified cancers with subpopulations that are sensitive to this class of inhibitor**
- Pharmacological analyses explain the differences in sensitivity and selectivity across distinct tumor models that we observed between inhibitors of this class
- **Using our comprehensive assessment of the class to establish design criteria, we developed a novel, potent ERK1/2 small molecule inhibitor UCT-01-097 that spares CDKs and shows excellent specificity *in situ***
- Here we present preclinical studies conducted to investigate the therapeutic potential of UCT-01-097

VARIOUS *IN VITRO* PROPERTIES OF UCT-01-097

ERK1 K_d	ERK2 K_d	Hepatocyte $T_{1/2}$ (mins)	P_{app} (10^{-6} cm/s) A to B
3.8 nM	5 nM	57 (Ms); 53 (Rt); 80 (Dog); 83 (Mk); 61 (Hu)	0.171

Table 1. Biochemical potencies, cellular potencies, half-life and cell permeability of UCT-01-097 were evaluated *in vitro*. ERK1 and ERK2 potencies were determined using a competitive binding assay (Eurofins DiscoverX KdELECT, San Diego, USA), and P_{app} was determined using a Caco-2 cell permeability assay (WuXi AppTec, Wuhan, China).

RODENT PHARMACOKINETICS OF UCT-01-097

	AUC_{0-24} (ng*h/mL)	C_{max} (ng/mL)	$t_{1/2}$ (hours)
Rat (100 MPK PO)	24,794	5,417	11
Mouse (200 MPK PO)	34,186	23,49	2

Table 2. Pharmacokinetic properties were characterized in two species and the presented values are the average from multiple animals (WuXi AppTec, Suzhou, China).

IN VITRO PHARMACOLOGY OF UCT-01-097

	% of Control @ 1 µM	
	ERAS-007[1]	UCT-01-097
ERK1	0	0
ERK2	0	0
CDK2	3	60
CDK4	6	82
CDK6	31	85
CDK7	16	25
CDK9	46	100

Table 3. The *in vitro* pharmacology of UCT-01-097 was profiled using a kinase screening assay (Eurofins DiscoverX KinomeScan, San Diego, USA). CDKs are major off-targets for clinically staged ERAS-007[1].

	LY3214996	BVD-523	UCT-01-097	AZD0364	SCH772984
ERAS-007	0.3	0.4	0.4	0.4	0.5
LY3214996	0.8	0.7	0.7	0.7	
BVD-523	0.7	0.7	0.7		
UCT-01-097	0.7	0.7			
AZD0364	0.8				

Table 4. Correlations between the responses of 400+ human cancer cell lines for each of the indicated ERK1/2 inhibitors were determined. ERAS-007 shows the poorest correlation with the rest of the class.

IN SITU PHARMACOLOGY OF UCT-01-097

M275 (Melanoma)

Kinase	IC_{50} (33 nM)	4x IC_{50} (132 nM)
Erk1	67.2	83.0
Erk2	66.0	82.6
DLK	17.5	34.4
BLK	34.5	33.5
CDK9	32.1	32.3
TEC	-25.1	31.5
MAST1/2	-20.1	30.9
ATR	29.1	29.2
CK1d/e	15.7	29.1
MAP2K6	-16.4	28.6

PSN1 (Pancreas)

Kinase	IC_{50} (192 nM)	4x IC_{50} (768 nM)
Erk2	54.2	81.5
Erk1	53.1	80.8
MER, TYRO3	3.8	30.0
MST1/2	-11.0	29.5
PKD2	27.9	27.9
HER3/ErbB3	13.4	25.3
MAP2K2	-4.2	23.6
MAP3K5	6.7	23.5
MAP2K1/2	25.8	23.3
RSK2 domain 1	25.5	23.1

Table 5. *In situ* inhibition of 200+ kinases was determined for UCT-01-097 at its IC_{50} and 4x its IC_{50} in two cell lines (ActivX Biosciences KiNativ, La Jolla, USA). Top 10 hits are presented. Values are precent change in MS signal (i.e., % inhibition).

UCT-01-097 SHOWS BROAD ACTIVITY IN CELL LINE PANEL, WITH ENHANCED SPECIFICITY AND POTENCY COMPARED TO CLINICALLY STAGED BENCHMARKS

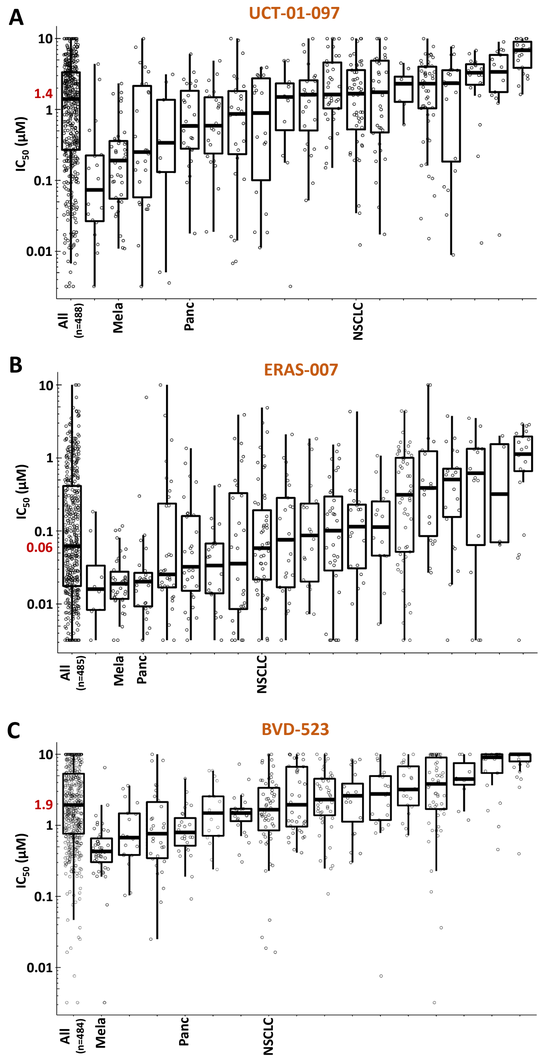


Figure 1. UCT-01-097 **(A)**, ERAS-007 **(B)** and BVD-523 **(C)** were profiled in a panel of 400+ human cancer cell lines from various histological origins. Cell lines were grown in the presence of the inhibitor for 7 days. Each dot plots the IC_{50} of a single cell line, and dots are binned according to each cell line's histological origin. Median IC_{50} is written in red on Y axis.

- ERAS-007 elicits the most potent response from the panel (median IC_{50} = 62 nM as compared to 1,407 nM (UCT-01-097) and 1,930 nM (BVD-523))
- ERAS-007's more potent effect is likely driven by its panCDK pharmacology
- ERAS-007's pharmacology may narrow its therapeutic index
- **UCT-01-097 elicits a wider response from the panel thanks to a pharmacology that largely spares CDKs**

ANTI-TUMOR ACTIVITY IN PANCREAS TUMOR MODEL

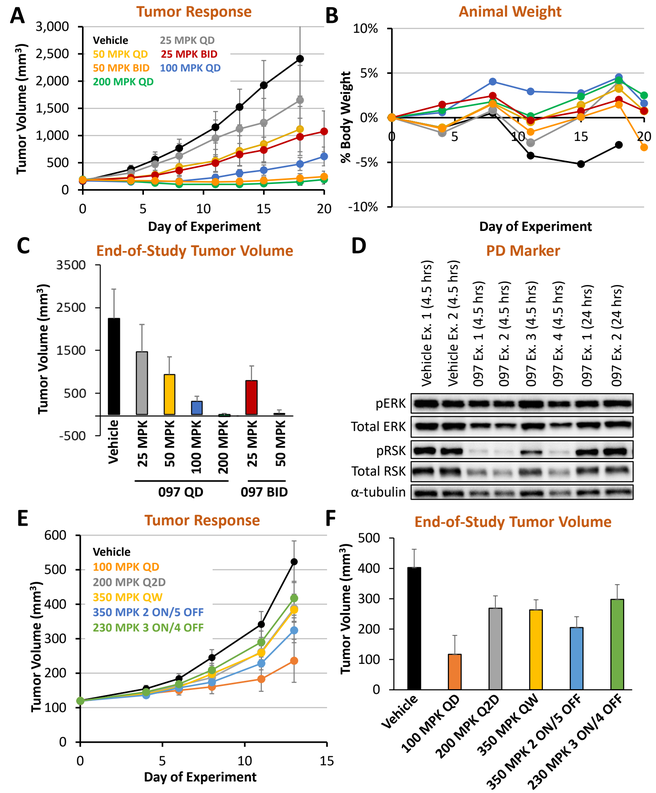


Figure 2. Female CD-1 athymic nude mice were subcutaneously implanted with PSN1. **(A)** Tumor volumes plotted over time. **(B)** Percentage of initial animal weights plotted over time. **(C)** Tumor volumes at Day 21 demonstrate dose dependent tumor response for both the once daily (QD) and twice daily (BID) dosing. **(D)** Western blots of PSN1 tumor lysate samples collected from two animals treated with the vehicle or with 200 MPK QD UCT-01-097. pRSK is a pharmacodynamic marker for ERK1/2 inhibitor activity, and α-tubulin is a loading control. **(E)** Intermittent dosing regimens were tested. **(F)** Day 13 measurements from **(E)**. 097 was dosed PO in all studies.

ANTI-TUMOR ACTIVITY IN MELANOMA TUMOR MODEL

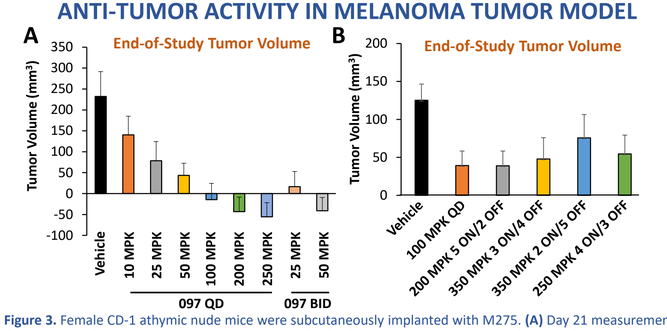
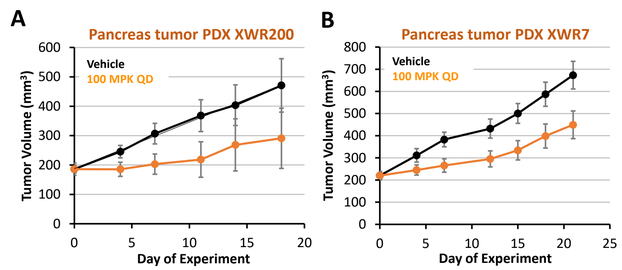


Figure 3. Female CD-1 athymic nude mice were subcutaneously implanted with M275. **(A)** Day 21 measurements demonstrate dose dependent tumor response for both the once daily (QD) and twice daily (BID) dosing regimens. **(B)** Day 21 measurements from an intermittent dosing study. 097 was dosed PO in all studies.

- UCT-01-097 has a potent anti-tumor effect in melanoma models
- **Intermittent dosing regimens offer equivalent anti-tumor effect in melanoma models**

ANTI-TUMOR ACTIVITY IN PANCREAS PDX PANEL

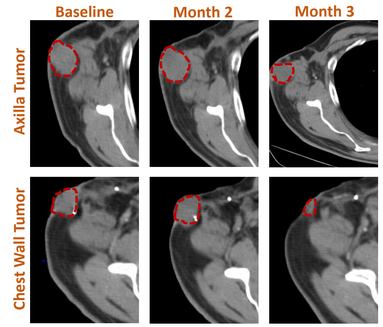


C

Model	% TGI	P Value
XWR19	56.5	0.039
XWR7	51.3	0.045
XWR200	50.5	0.041
XWR6	23.8	0.276
XWR8	22.1	0.196
XWR23	17.7	0.286
XWR187	9.6	0.432
XWR195	-2.9	0.482
XWR60	-18.0	0.117
XWR28	-42.0	0.218

Figure 4. Female CD-1 athymic nude mice were subcutaneously implanted with PDXs from 10 different patients with pancreatic cancers and treated with vehicle or 100 mg/kg UCT-01-097 PO QD. All studies were performed with 8 animals per arm; tumor volumes were determined using caliper measurements and recorded in mm^3. Error bars are SEMs. Representative anti-tumor effects in **(A)** XWR200 and **(B)** XWR7. **(C)** % TGI and P values against respective controls for each model.

FIRST-IN-HUMAN STUDY



Patient History

Patient is a 74-year-old male with a *BRAF*-mutant malignant melanoma who received 4 prior lines of therapy. The patient received 60 mg BID of UCT-01-097 orally and completed 1.5 cycles at the time the Month 3 images were captured.

Figure 5. Representative CT scans from patient. Two tumors showing volume decreases after treatment with UCT-01-097.

SUMMARY & CONCLUSIONS

- Our *in vitro* cell screening studies show that the panCDK pharmacology of ERAS-007 make this inhibitor elicit a more potent response from a large panel of human cancer cell lines
- Such a response likely suggests that tolerability may be a challenge for ERAS-007
- We developed a novel, potent ERK1/2 inhibitor (UCT-01-097), and the preclinical studies presented here demonstrate its applicability for melanoma and pancreatic cancer
- UCT-01-097 demonstrates a potent anti-tumor effect in melanoma models, and intermittent dosing schedules have equivalent anti-tumor effect
- These studies support the investigation of UCT-01-097 in humans and a Phase 1 clinical trial is open and enrolling patients (NCT04761601)
- Preliminary results suggest UCT-01-097 may offer therapeutic benefit to patients with melanoma cancer
- Dose escalation is ongoing and the results of the Phase 1 study will be presented at a future conference

REFERENCES

1. Portelinha et al., *Cell Reports Medicine* (2021) Vol 2 (7): 100350

FUNDING

These studies were funded 1200 Pharma LLC

Request for reprint or additional information: oliver.loson@1200pharma.com