5991: Development & characterization of a novel CDK4/6 inhibitor for the treatment of dependent cancers

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BACKGROUND

- CDK4/6 inhibitors give clinical benefit to patients with metastatic ER+/HER2- breast cancer (mBC), particularly when given in combination with endocrine therapies
- Abemaciclib has distinguished itself from palbociclib and ribociclib with its therapeutic benefit, and ribociclib is distinguished from the others for its superior exposure
- Although this class of inhibitor has been extensively studied in several other cancer types, CDK4/6 inhibitors have not been approved as a treatment outside of ER+/HER2- mBC
- **We evaluated palbociclib, ribociclib and abemaciclib in a 500+ cell line screening platform and identified several cancers outside of breast that may have subpopulations that are sensitive to CDK4/6 inhibition**
- Comprehensive molecular profiling of the cell lines at baseline allowed us to investigate potential associations with sensitivity to these compounds
- These analyses identified potential biomarkers of sensitivity in non-small cell lung carcinoma (NSCLC) and colorectal cancer (CRC) that will be evaluated in human clinical studies
- **Using 1200 Pharma's proprietary chemistry, we developed UCT-03-008, a potent CDK4/6 small molecular inhibitor with a pharmacology like that of abemaciclib and pharmacokinetic properties similar to those of ribociclib**
- Here we present preclinical studies conducted to investigate the therapeutic potential of UCT-03-008

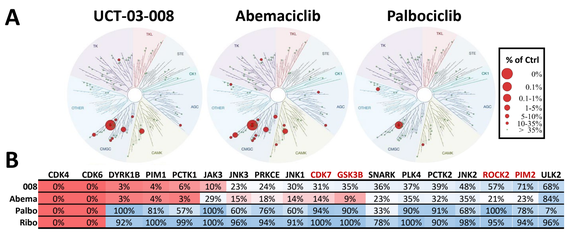
UCT-03-008 HAS AN ABEMA-LIKE PHARMACOLOGY WITH RIBO-LIKE EXPOSURE

	Abemaciclib	Palbociclib	Ribociclib	UCT-3-008
***In vitro* Characteristics**				
Pharmacology	CDK4/6 PIM1/2 PCTK1 GSK3β DYRK1	CDK4/6	CDK4/6	CDK4/6 PIM1 PCTK1 GSK3β DYRK1
CDK4/6 IC_{50} (nM)	2/10	11/15	10/39	3/14
CDK4/6 Ratio	5	1.4	3.9	4.7
Cell IC_{50} (nM)	34	58	294	71
Human Pharmacokinetic Properties				
Half-life Elimination (hrs)	18.3	29±5	30 – 55	Approx. 70 (study ongoing)
Dosing	BID	QD	QD	QD
Dosing Holiday	As needed	3 wks on, 1 wk off	3 wks on, 1 wk off	TBD

Table 1. The pharmacology, biochemical potencies and cellular potencies for CDK4/6 inhibitors were evaluated. IC_{50}s against CDK4:Cyclin D and CDK6:Cyclin D were determined with an enzymatic assay, and the average cellular IC_{50} was determined with a panel of 14 human breast cancer cell lines and using a 7-day growth assay. Half-life elimination data for abemaciclib, palbociclib and ribociclib are taken from the indicated references; and half-life elimination data for UCT-03-008 is from 4 patients dosed at 145 mg/day in our ongoing Phase 1 clinical trial.

- Others have proposed that the complex pharmacology of abemaciclib contributes to its distinguished clinical benefit[1,2]
- Additionally, the higher CDK4 to CDK6 inhibitory ratio may contribute to the greater tolerability of abemaciclib as compared to other CDK4/6 inhibitors[1,2]
- Ribociclib's exposure and long half-life likely contribute to its therapeutic action[3]
- **UCT-03-008's possesses a very similar pharmacology to that of abemaciclib (Fig. 1)**
- **The steady-state pharmacokinetics of UCT-03-008 in preclinical models and the preliminary data from humans (Fig. 2) suggest that 008 possesses an exposure profile similar to that of ribociclib**

KINOME PROFILING OF UCT-03-008 & COMPARATORS

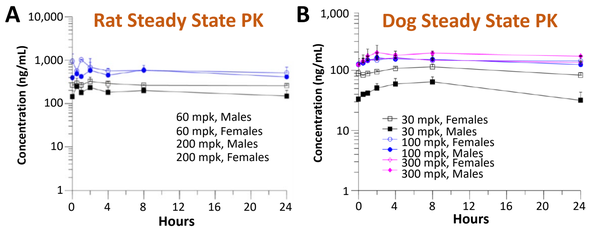


B

	CDK4	CDK6	DYRK1B	PIM1	PCTK1	JAK3	JNK3	PRKCE	JNK1	CDK7	GSK3B	SNARK	PLK4	PCTK2	JNK2	ROCK2	PIM2	ULK2
008	0%	0%	3%	4%	6%	10%	23%	24%	30%	31%	35%	36%	37%	39%	48%	57%	71%	68%
Abema	0%	0%	3%	4%	3%	29%	15%	18%	14%	14%	9%	23%	35%	32%	35%	21%	23%	84%
Palbo	0%	0%	100%	81%	57%	100%	60%	76%	60%	94%	90%	33%	90%	91%	68%	100%	78%	7%
Ribo	0%	0%	92%	100%	99%	100%	96%	94%	91%	100%	100%	78%	100%	90%	98%	95%	94%	96%

Figure 1. Active site binding to more than 400+ human kinases (Eurofins DiscoverX KinomeScan, San Diego). Inhibitors were evaluated at 200 nM; measurements are presented as % of Control. **(A)** Human kinase dendograms for UCT-03-008 (Left, "008"), Abemaciclib (Middle, "Abema") and Palbociclib (Right, "Palbo"). **(B)** Table of kinases where >34% of control was seen for any inhibitor. The pharmacology of UCT-03-008 is very similar to that of abemaciclib, however, notably, UCT-03-008 does not inhibit several off-targets as potently as seen with abemaciclib (kinase names in **red**).

PHARMACOKINETIC PROPERTIES OF UCT-03-008



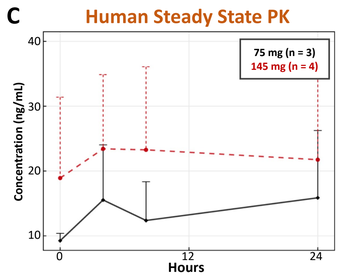


Figure 2. UCT-03-008 pharmacokinetics across species. Mean steady state plasma concentrations following repeat daily PO administration in **(A)** Sprague-Dawley rats and **(B)** Beagle dogs dosed orally once a day for 7 days. **(C)** Cycle 2 (approximately 56 days of dosing) steady state plasma concentrations in humans dosed orally once daily with 75 mg or 145 mg.

UCT-03-008 SHOWS BROAD ACTIVITY IN CELL LINE PANEL

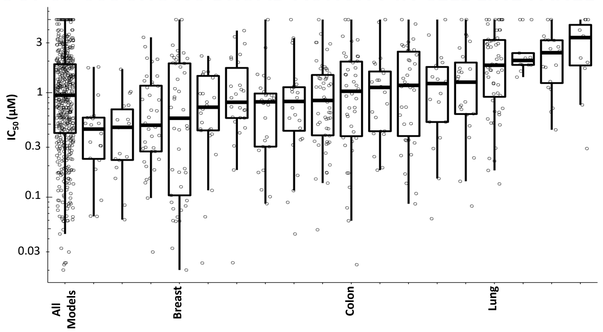


Figure 3. UCT-03-008 was profiled in a panel of 500+ human cancer cell lines from various histological origins. Cell lines were grown in the presence of the inhibitor for 7 days. Each dot plots the IC_{50} of a single cell line, and dots are binned according to each cell line's histology type.

ANTI-TUMOR ACTIVITY IN ER+/HER2- BC MODELS

Figure 4. Female CD-1 athymic nude mice were subcutaneously implanted and treated with vehicle or the indicated agent(s) with the indicated doses and schedule. 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. **(A)** Single agent, dose-dependent anti-tumor effect in a ZR75-1 model and **(B)** animal weight changes. **(C)** Single agent and combination anti-tumor effect in a MCF7 model.

ANTI-TUMOR ACTIVITY IN NSCLC MODELS

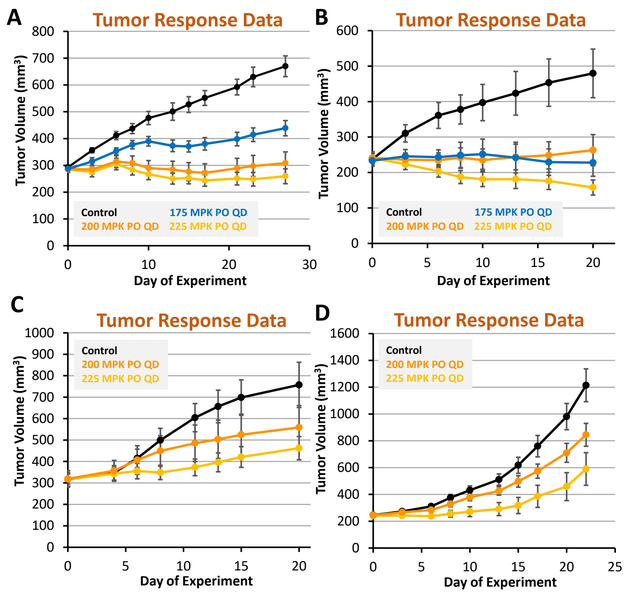


Figure 5. Female CD-1 athymic nude mice were subcutaneously implanted and treated with vehicle or the indicated dose of UCT-03-008. All studies were performed with 8 animals per arm and all animals were dose PO QD. Dose-dependent anti-tumor effect in **(A)** a HCC827 (*KRAS*-normal) model; **(B)** a NCI-H1435 (*KRAS*-normal) model; **(C)** a NCI-H2172 (*KRAS*-normal) model; and **(D)** a CaLu-6 (*KRAS*-mutant) model.

ANTI-TUMOR ACTIVITY IN VARIOUS OTHER MODELS

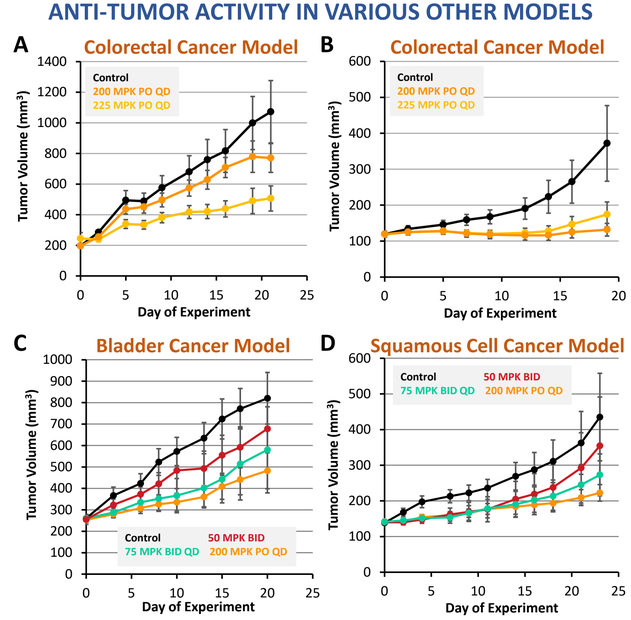


Figure 6. Female CD-1 athymic nude mice were subcutaneously implanted and treated with vehicle or the indicated dose of UCT-03-008. All studies were performed with 8 animals per arm and all animals were dose PO QD. Dose-dependent anti-tumor effect in **(A)** a SNU-C1 (colorectal) model; **(B)** a NCI-H716 (colorectal) model; **(C)** a SW780 (bladder) model; and **(D)** a CAL27 (squamous cell carcinoma) model.

SUMMARY & CONCLUSIONS

- Our preclinical studies suggest that CDK4/6 inhibitors may have applications outside ER+/HER2- mBC
- The more complex pharmacology of abemaciclib has been proposed to contribute to its distinguished clinical benefit[1]
- The long half-life and continuous exposure of ribociclib are thought to be important qualities[3] because they engender greater time-on-target, which is critical to successfully abrogating cell cycle progression in cancer
- Using 1200 Pharma's proprietary chemistry, we developed a potent CDK4/6 inhibitor that combines the unique pharmacology of abemaciclib with the pharmacokinetic qualities of ribociclib
- The preclinical studies presented here suggest that combination of the key qualities of each of abemaciclib and ribociclib engenders efficacy in many human solid tumor models
- These studies support the investigation of UCT-03-008 in humans and a Phase 1 clinical trial is open and enrolling (NCT05103046)
- Preliminary human pharmacokinetic analyses show a remarkable half-life for UCT-03-008 and the desired exposure profile
- Dose escalation is ongoing and the results of the Phase 1 study will be presented at a future conference

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