AN OPEN-LABEL, RANDOMIZED CROSS-OVER BIOAVAILABILITY STUDY OF ORAL PACLITAXEL AND HM30181A COMPARED WITH WEEKLY INTRAVENOUS (IV) PACLITAXEL IN PATIENTS WITH ADVANCED SOLID TUMOURS.

Christopher GCA Jackson[1,3], Sanjeev Deva[2], Katherine Bayston[3], Karen Eden[3], Paula Barlow[2], Noelyn Anne Hung[4,6], David Cutler[5], Gerald Fetterly[5], Rudolf Kwan[5], Douglas Kramer[5], Wing-Kai Chan[5], and Tak Hung[6]

1. Department of Medicine, University of Otago, Dunedin, New Zealand; 2. Auckland District Health Board, Auckland, New Zealand;
3. Southern Blood and Cancer, Southern District Health Board, New Zealand; 4. University of Otago, Dunedin, New Zealand; 5. Athenex, Buffalo, NY, USA; 6. Zenith Technology Corporation Limited, Dunedin, New Zealand.

ACTRN 12615000894594

DISCLOSURES

This study was sponsored by Athenex, Buffalo, NJ, USA.

I have received travel support to present this work from Athenex.

No other disclosures.

BACKGROUND

Paclitaxel 175mg/m^2 q3w FDA-approved indication in breast cancer; 80mg/m^2 q1w improves PFS and OS in adjuvant breast Ca with less neutropenia, myalgia; more neuropathy[1]

Oral agents may improve convenience, reduce health care utilisation, obviate need for CVADs, and remove cremophor-required premedication

Paclitaxel highly insoluble; actively extruded by gut localised permeability glycoprotein (p-gp). Undergoes extensive first pass metabolism

Prior research with Pgp inhibitors cyclosporin, ritonavir, elacridar could not achieve bioequivalence[2]

HM30181A Methane Sulfonate Monohydrate is a novel, minimaly-absorbed pgp inhibitor with no DLT seen in prior study, n=105.

Prior phase I study dosed at 270mg d1-2, 274mg/m^2 d1-2, 313mg/m^2 d1-2; saturation seen[3]; AUC approached that of paclitaxel 80mg/m^2. Selected 205mg/m^2 over 3 days for current dosing

1. Sparano NEJM 2008; 358:1663-1671; 2. Britten Clin Can Res 2000; 6: 3459-3468; 3. Jackson JCO *2016;* 34: no. 15_suppl Abstr 2569

KX-ORAX-002: study design

Main inclusion and exclusion criteria

Advanced solid tumours

Scheduled to receive Paclitaxel 80mg/m^2 i.v. weekly

Age >18, ECOG 0-1, life expectancy > 3 months

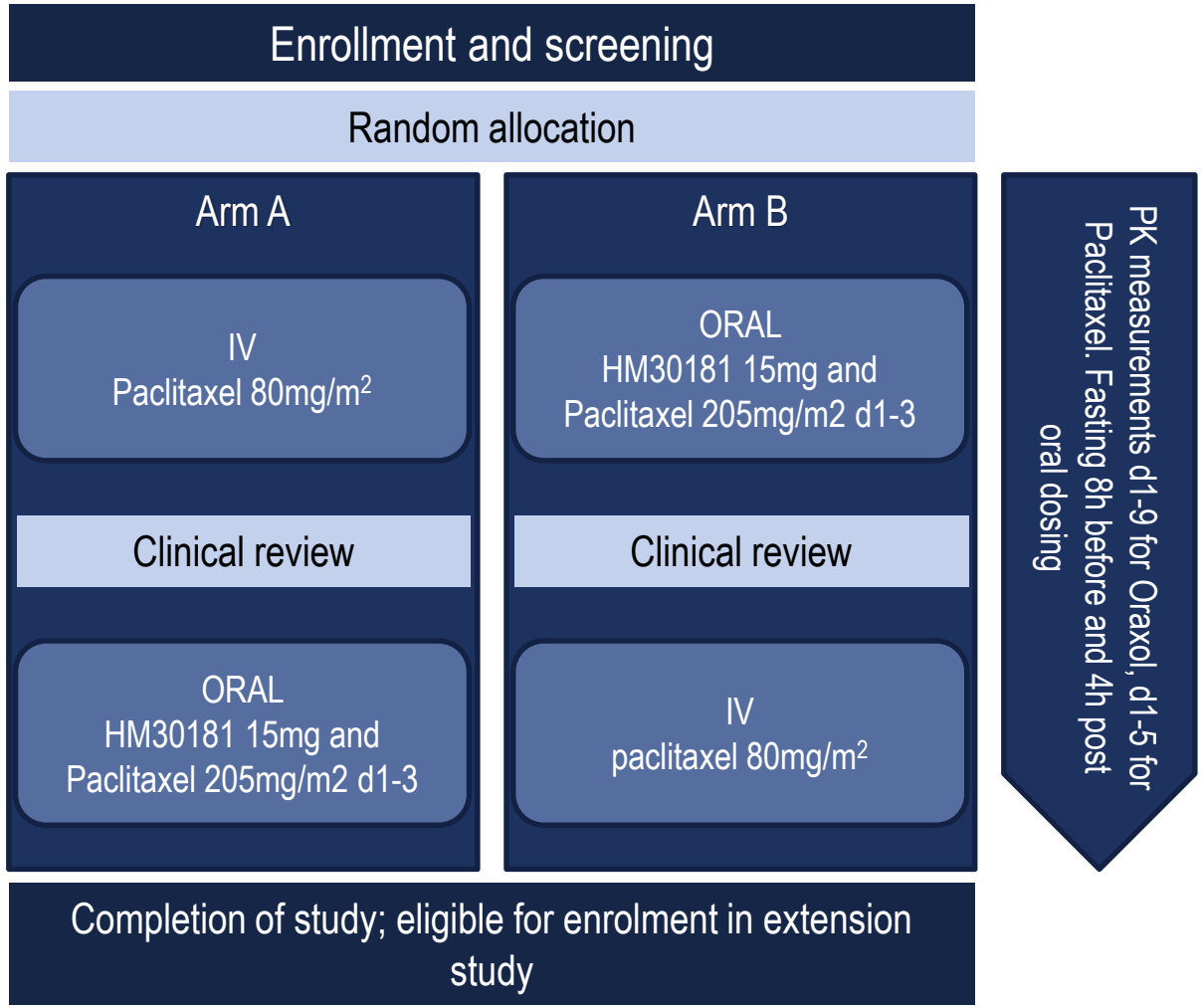
HB>100, Bili <20; ALT<3x ULN, CrCl > 50ml/min

Willing to fast, and undergo confinement for PK's; no UGI surgery or conditions preventing absorption

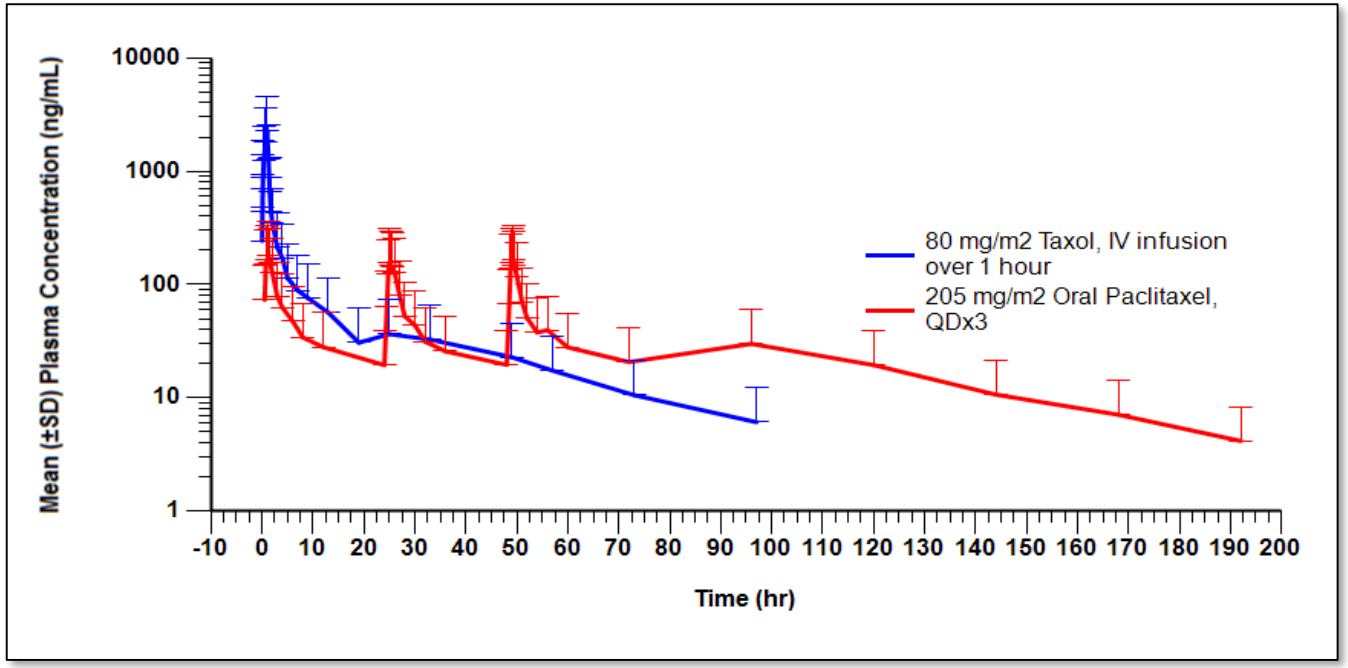
Prohibited meds: CYP 3A4, 2C8 inducers or inhibitors

PGP inhibitors or inducers; critical PGP substrates e.g. digoxin

Characteristics	
Number of Patients	6
Age: mean (SD)	61 (12.76)
Gender	3 Males, 3 Females
BSA (m^2): mean (SD)	1.9 (0.2)
Primary Cancer Diagnosis (n)	Breast Cancer (2), Esophageal (1), Ovarian (1), Prostate (1), Colon (1)



RESULTS: per-protocol interim analysis of first 6 patients



PK Results

Treatment	Mean $AUC_{0-\infty}$ ng*hr/mL (SD)	Mean C_{max} ng/mL Day 1 (SD)	Median T_{max} hr Day 1 (Range)	Mean T1/2 hr (SD)
Oral Paclitaxel 205 mg/m²/day, d1-3	5078 (1723)	231 (134)	1.4 (0.8-3)	38 (16.2)
IV Paciltaxel 80 mg/m², iv, 1 hr	5652 (1013)	2269 (227)	1.0 (1.0-1.0)	23.3 (4.5)

Safety and tolerability

No Grade 3/4 toxicities were observed in either arm

Treatment related toxicities were mild and easily managed in this short exposure period. G1/2 toxicities with ORAL dosing included nausea (2), vomiting (1), diarrhoea (1), neutropenia (1), fatigue (1).

Interim PK results indicate that Oral Paclitaxel and HM30181A (Oraxol) can be dosed to achieve similar blood paclitaxel concentrations to IV paclitaxel in terms of AUC

INTERPRETATION

Oral dosing with paclitaxel is more convenient for patients and has many advantages

HM30181A 15mg and Oral Paclitaxel 205mg/m^2 on days 1-3 achieves similar AUC to IV paclitaxel 80mg/m^2

No G3/4 toxicities were seen, and G1/2 toxicities were easily managed

A total sample size of 30 subjects is required to demonstrate bioequivalence between Oraxol and IV paclitaxel (90% CI of the GMR is within the limits of 80% – 125%), with 80% power.[1]

KX-ORAX-003 is ongoing to establish safety and tolerability with multiple day dosing

This study demonstrates that Oral dosing is feasible and provides an ideal candidate to be tested to replace i.v. paclitaxel

A randomised phase 3 study in metastatic breast cancer is underway comparing IV paclitaxel 175mg/m^2 q3w to weekly ORAL HM30181 and paclitaxel 205mg/m^2 (Oraxol) d1-3

1. Hauschke D *J Pharmacokin Biopharm* 1992; 20:557-561

ACKNOWLEDGEMENTS

We thank:

- the patients and families for the generosity of their time commitment to complete an intensive PK study
- Investigators
- Zentech staff: Louise Broome, Linda Folland
- Site personnel: Suzanne Cox
- Athenex staff

www.otago.ac.nz