24 h of incubation with CKIE. Downregulation of E2F-1 and PCNA mRNA expression could be demonstrated after treatment with CKIE. [^{18}F]CKIE indicated high stability in physiological buffer and cell culture medium. Cellular radiotracer uptake using [^{18}F]CKIE increased with time amounting to 46.3±11.2%ID/mg protein in HT-29 and 46.2±13.8%ID/mg protein in FaDu cells, respectively, after 60 min at 37ºC. Uptake of [^{18}F]CKIE could be blocked with nonradioactive CKIE dependent on concentration (e.g., 23.5±3.7%ID/mg protein with 5 μM CKIE after 60 min at 37ºC).
Conclusion: CKIE was identified as the most potent fluorine containing pyrido[2,3-*d*]pyrimidin-7-one derivative analyzed in our study causing arrest of tumour cells in G1 phase due to inhibition of the Cdk4/6/pRb/E2F pathway. *In vitro* radiotracer uptake studies using [^{18}F]CKIE demonstrated tumor cell uptake, which is an important prerequisite for further PET studies in tumor-bearing mice.

1202 ORAL

In silico modelling of Doxorubicin penetration through multicell layers

R. Phillips[1], P.M. Loadman[1], C.J. Evans[2], P.F. Jones[3], S.W. Smye[4], B.D. Sleeman[5], C.J. Twelves[3]. *[1]Institute of Cancer Therapeutics, Tom Connors Cancer Research Centre, Bradford, United Kingdom; [2]University of Leeds, Leeds Institute of Genetics, Leeds, United Kingdom; [3]University of Leeds, Leeds Institute of Molecular Medicine, Leeds, United Kingdom; [4]St James University Hospital, Department of Medical Physics, Leeds, United Kingdom; [5]University of Leeds, Department of Applied Mathematics, Leeds, United Kingdom*

Background: Inadequate delivery of anti-cancer drugs to solid tumours is a significant factor limiting efficacy. Factors determining drug delivery to tumours are complex but the pharmacokinetic (PK) properties of the drug and its ability to leave the blood vessel then penetrate avascular tissue are critically important. The aim of this study was to develop an *in silico* model based on *in vitro* measurements that can predict how far a drug will penetrate from a blood vessel within its PK lifespan using the transport of doxorubicin through multicellular layers as a model and assessing the potential impact of efflux via P-Glycoprotein (PgP) on drug penetration.
Materials and Methods: Three cell lines were employed; DLD-1 (human colon carcinoma), MCF7 (human breast carcinoma) and NCI/ADR-Res (doxorubicin resistant and PgP over expressing OVCAR8 cells). Cells were cultured on Transwell culture inserts to thicknesses between 20 and145 μm as determined by microscope analysis of histological sections. Doxorubicin at concentrations of 100, 50 or 25 μM was added to the top chamber of the Transwell apparatus, and the concentration of drug appearing in the bottom chamber determined as function of time by HPLC-MS/MS.
Results: In all cell lines, the rate of drug penetration was inversely proportional to the thickness of the multicell layer; the presence of PgP (NCI/ADR-Res) did not alter the rate of doxorubicin penetration compared to the wild type MCF7 cells. We established a mathematical model based upon the fact that the transport of doxorubicin across cell membrane bilayers occurs by a passive "flip-flop" mechanism of the drug between two membrane leaflets with the Transwell setup treated as a series of compartments and the multicell layer as a series of cell layers, separated by small intercellular spaces. This initial model demonstrates good agreement between predicted and actual drug penetration rates *in vitro*.
Conclusions: We have developed an effective preliminary model. Further studies incorporating both real and simulated PK parameters are underway. Our ultimate objective is to make predictions of which dose and schedule of drug administration is likely to be the most efficacious; the model could also be used to identify and prioritise the development of those compounds in pre-clinical development most likely to achieve adequate tumour drug concentrations.

1203 ORAL

Pharmacokinetic and pharmacodynamic Phase I trial of ARQ 197 incorporating dynamic contrast-enhanced (DCE) and diffusion weighted (DW) magnetic resonance imaging (MRI) studies investigating the antiangiogenic and antitumor activity of selective c-Met inhibition

T.A. Yap[1], M.P. Lolkema[1], N. Tunariu[2], D.S.W. Tan[1], A.T. Brunetto[1], M. Germuska[2], E. Garmey[3], J. Li[3], N. deSouza[2], J.S. de Bono[1]. *[1]Royal Marsden Hospital, Drug Development Unit, Sutton, United Kingdom; [2]The Institute of Cancer Research, Cancer Research UK Clinical Magnetic Resonance Research Group, Sutton, United Kingdom; [3]ArQule Inc, Clinical Development, Woburn, USA*

Background: ARQ 197 (ARQ) is a selective non-ATP competitive inhibitor of c-Met, a receptor tyrosine kinase implicated in tumor cell proliferation, migration, apoptosis and angiogenesis. Promising preclinical data and declines in circulating endothelial cell (CEC) levels in patients (pts) receiving ARQ support antiangiogenic potential of c-Met inhibition.
Materials and Methods: ARQ was administered orally twice daily (bid) to pts with advanced solid tumors. Pre and post-therapy tumor biopsies were mandated in all patients (n = 16) for c-Met and FAK immunohistochemical pharmacodynamic (PD) studies during dose escalation. CEC enumeration was evaluated at multiple timepoints. 12 pts are being investigated in the maximum tolerated dose (MTD) expansion cohort with DCE and DW MRI studies.
Results: 29 pts (14F/15M; mean age 54.4 yrs; mean of 4.4 prior therapies) received ARQ at doses 100 (n = 3), 200 (n = 6), 300 (n = 16) and 400 (n = 4) mg bid. 3 pts experienced dose limiting toxicities: CTCAEv3 grade (G) 3 fatigue at 200 mg bid (n = 1); G3 hand-foot syndrome and G3 mucositis at 400 mg bid (n = 1); G3 febrile neutropenia at 400 mg bid (n = 2). This established the ARQ MTD/recommended phase 2 dose (RP2D) at 300 mg bid. Other toxicities were G1–2, such as fatigue (n = 5); diarrhea, nausea and vomiting (n = 3). Mean $AUC_{0-12\,h}$ and C_{max} increased linearly through the MTD. Statistically significant post-ARQ inhibition of high baseline phosphorylated c-Met and FAK expression in tumor tissue was seen in all dose cohorts confirming target inhibition. Disease stabilization (SD) was seen in 11 pts for up to 23 weeks with tumor regressions up to 12.4% (metastatic gastric cancer pt). 13 of 20 pts had post-ARQ CEC declines of up to 100%, supporting antiangiogenic effects of ARQ. In the DCE-MRI cohort to date, preliminary analyses of k_{trans} histograms from pelvic and liver lesions showed a reduction in k_{trans} values on day 7 of ARQ, consistent with antiangiogenic effects.
Conclusions: ARQ is well tolerated with MTD/RP2D of 300 mg bid, linear pharmacokinetics and c-Met and FAK PD inhibition. Promising antitumor activity was observed. CEC and preliminary DCE-MRI data support antiangiogenic effects of c-Met inhibition with ARQ. Correlation with DCE parameters and DW changes will be presented. Following preliminary antitumour activity, a cohort expansion of 10 castration resistant prostate cancer patients is ongoing.

1204 ORAL

A Phase I study evaluating the pharmacokinetics (PK) and pharmacodynamics (PD) of the oral pan-phosphoinositide-3 kinase (PI3K) inhibitor GDC-0941

R. Kristeleit[1], D. Sarker[1], M. Forster[1], M. Lolkema[1], D. Olmos[1], K. Mazina[2], M.V. Dolezal[2], J.A. Ware[2], Y. Yan[2], J.S. de Bono[1]. *[1]The Royal Marsden NHS trust – Institute of Cancer Research, Drug Development Unit, Sutton Surrey, United Kingdom; [2]Genentech Inc., 1 DNA Way, San Francisco, USA*

Background: The PI3K-PTEN-AKT signalling pathway is deregulated in a wide variety of cancers. GDC-0941 is a potent and selective oral pan-inhibitor of class I PI3K, with 3nM IC50 for the p110-alpha subunit in vitro and 28nM IC50 in a cell-based phosphorylated AKT (pAKT) assay, and demonstrates activity in several preclinical models (breast, ovarian, lung and prostate).
Materials and Methods: Patients (pts) with histologically confirmed advanced solid tumours and Eastern Cooperative Oncology Group performance status 0–1 were enrolled in a Phase I study of GDC-0941 (sponsored by Genentech), using a 3+3 escalation design at a single institution. Treatment was a single dose of GDC-0941 with a 1-week (wk) washout, followed by GDC-0941QD on a 3-wk on, 1-wk off schedule. Objectives were to determine the maximum tolerated dose and dose-limiting toxicity (DLT), evaluate PD endpoints in surrogate tissue (pAKT in platelet-rich plasma [PRP]) and tumour tissue (pAKT and pS6 in paired tumour biopsies and fluorodeoxyglucose (FDG) uptake via positron emission tomography imaging), and describe any observed antitumour activity.
Results: Eighteen patients have been enrolled in 5 successive cohorts (15–80 mg QD). GDC-0941 was generally well tolerated with no drug-related Grade 3–4 adverse events or DLT to date. Grade 1–2 diarrhoea, nausea, vomiting, fatigue, dysgeusia, peripheral sensory neuropathy, dry mouth, thrombocytopenia and increased alanine and aspartate aminotransferase levels have been observed. Preliminary PK data suggest GDC-0941 is rapidly absorbed (T_{max} range 1–2 hrs) and displays dose-appropriate increases in fasting mean C_{max} and AUC_{inf}. At current GDC-0941 doses we have exceeded exposures associated with efficacy in preclinical models. Preliminary surrogate PD data demonstrate decreased levels of pAKT in PRP associated with GDC-0941 plasma concentrations. Moreover, a good correlation between *ex vivo* and *in vivo* inhibition constants for pAKT exist with greatest inhibition (approximately 80%) occurring following the 80 mg dose. Evaluation of GDC-0941 effects on PI3K pathway modulation in paired tumour biopsies is currently underway.
Conclusions: GDC-0941 is generally well tolerated when administered QD at doses associated with inhibition of pAKT in surrogate tissues and displays linear PK from 15–80 mg. Evidence of surrogate tissue PD activity has been observed. Dose-escalation continues and updated PK/PD data will be presented.