	Tumour size	Compound used	Dosage	Time points
Autoradiography	Small	^{123}I-HYP	100 μCi/mouse (n = 5)	4h, 24h p.i.
Fluorescence microscopy	Small	HYP	10 mg/kg (n ⩾ 3)	6h, 24h, 48h, 72h p.i.
Planar gamma scintigraphy	Bulky	^{123}I-HYP	170 μCi/mouse (n = 5)	30h, 55h p.i.
Therapy study			control: saline at day 0, 6, 13 (n = 6)	*day 0, 6, 13, 18 **day 24
(*FDG micro-PET)	Small	^{131}I-HYP	group 1: 300 μCi at day 0, 6, aline at day 13 (n = 6)	*n/a **day 24
(**Autoradiography)			group 2: 300 μCi at day 0, 6, 13 (n = 6)	*day 13, 18 **day 24

Results: The intratumoral distribution in RIF-1 tumours was investigated by means of fluorescence microscopy (HYP) and autoradiography (^{123}I-HYP). Results show high uptake of the tracers in necrosis at 24 h, lasting for up to 72 h p.i. Ratios of activity of ^{123}I-HYP in necrotic tissue over viable tumour reached up to 19.63±4.66, correlating with 9.20% ID/gram in necrosis. Nude mice bearing RIF-1 tumours that received 3 injections of 300 μCi over a 3-week treatment period showed stabilization in tumour growth for 5 days, as measured by caliper and micro-positron emission tomography using [^{18}F]fluorodeoxyglucose.
Conclusion: Based on these results, we suggest the potentials of radiolabeled hypericin 1) in diagnostic aspects including prognosis or staging assessment of bulky necrotic cancers, monitoring of treatments and therapeutic follow-up; and 2) in cancer treatment based on tumour necrosis. In conclusion, we showed that hypericin radiolabelled with iodine is a necrosis avid tracer that can be used both as a tumour diagnostic and therapeutic.

1232 POSTER

Creatinine Clearance (CrCl) as a Predictive Marker for the Risk of Toxicity From Molecularly Targeted Agents (MTA) in Phase I Trials

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Background: Phase I trials are designed to define toxicity and maximum tolerated dose of a new drug. Molecularly targeted agents (MTAs) are primarily administered orally at a flat dose independent of patient height, weight and creatinine clearance (CrCl). The aim of this study was to evaluate for a correlation between both baseline CrCl and body surface area (BSA) and the development of grade (gr) 3 and 4 toxicities during the first course of therapy within a phase I trial.
Materials and Methods: A retrospective analysis was performed on all patients (pts) treated within phase I trials at the Royal Marsden Hospital, between January 2005 and December 2009. Data collected included all gr 3/4 toxicities possibly related to the drug, dose and laboratory assessments including serum creatinine, height and weight. CrCl was calculated using Cockroft-Gault (CG) formula and Modification of Diet in Renal Disease (MDRD) formula.
Results: 960 pts were included for the analysis. Median age: 59 years; 54% were male. 80% received single agent MTA, 17% received MTA in combination with classic cytotoxic (CTX) therapy and 3% received single agent novel CTX. 226 patients (23%) developed at least one episode of gr 3/4 toxicity and four patients (0.4%) experienced gr 5 toxic deaths. In pts developing toxicity, mean CG and MDRD were 90 and 74 ml/min compared with 100 and 78 ml/min for pts without toxicity (p = 0.002 and p = 0.016) respectively. A CG >120 ml/min was associated with a significantly lower risk of toxicity (14% vs. 25%) compared to a CG <120 ml/min (p = 0.001). Multivariate logistic regression analysis showed that CrCl was an independent variable that influenced gr 3/4 toxicity (OR = 0.99 [95% CI 0.98–0.99]). BSA did not correlate with risk of toxicity.

Table 1. Toxicity according to agent received and creatinine clearance by Cockroft-Gault (CG)

CG	MTA		CTX	
	G3/4 Toxicity	No Toxicicty	G3/4 Toxicity	No Toxicity
>120	14 (9.6%)	132 (90.4%)	11 (34.4)	21 (65.6%)
120–100	14 (13.2%)	92 (86.8%)	20 (55.6%)	16 (44.4%)
100−60	65 (18.9%)	279 (81.1%)	46 (49.5%)	47 (50.5%)
<60	18 (24%)	57 (76%)	6 (42.9%)	8 (57.1)
Total	111 (16.5%)	560 (83.5)	83 (47.4%)	92 (52.6)
	P = 0.016		*P* = 0.33	

Conclusions: Within the constraints of phase I trials where pts with a creatinine of >X1.5 the upper limits of normal are excluded, the risk of gr 3/4 toxicities is associated with a lower CrCl. CrCl calculated by CG is a valuable tool that can be utilized to predict the risk of significant toxicity with MTAs in phase I trials.

1233 POSTER

Phase I/II Study With Trabedersen (AP 12009) Monotherapy for the Treatment of Patients With Advanced Pancreatic Cancer, Malignant Melanoma or Colorectal Carcinoma

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Background: TGF-β2 overexpression in solid tumours triggers key cancer pathomechanisms, particularly immunosuppression and metastasis. The antisense oligonucleotide trabedersen specifically inhibits TGF-β2 expression. This study evaluates the MTD, safety, pharmakokinetics, and efficacy of i.v. trabedersen treatment in patients with advanced solid tumours.
Methods: This open label, multicenter, Phase I/II study enrolled a total of 61 patients. Of these, 33 patients with pancreatic carcinoma (PanCa, stage III/IV, N = 23), malignant melanoma (MM, stage III/IV, N = 5), or colorectal carcinoma (CRC, stage III/IV, N = 5) were enrolled during dose-escalation. Patients were treated in cohorts with i.v. trabedersen monotherapy as 2nd to 4th-line therapy with escalating doses in 2 treatment schedules (1st schedule: 7d on, 7d off; 2nd schedule: 4d on, 10d off; up to 10 cycles). Within the 1st schedule, the MTD was established at 160 mg/m^2/d. In the 2nd schedule dose-escalation was stopped before reaching an MTD. A well tolerated dose (140 mg/m^2/d) with encouraging efficacy was identified. An additional cohort of 14 patients with MM or PancCa each was treated with this dose and schedule (140 mg/m^2/d; 4d on, 10d off).
Results: Trabedersen was safe and well-tolerated. The only expected adverse reaction identified was transient thrombocytopenia (max. NCI-CTC grade 3).
The mOS of all PanCa patients treated 2nd-line (independent of dose and schedule, N = 15) was 6.9 months [95% CI: 2.9, 13.4], while the mOS of PanCa patients treated with the 2nd schedule-140 mg/m^2/d regimen (N = 9) was 13.4 months [95% CI: 2.2, 39.7]. One PanCa patient (treated 3rd line) had a complete response of liver metastases and is still alive after 61 months (as of Oct2010).
Promising efficacy data were also seen in 4 of the 5 MM patients during dose-escalation: one patient with metastatic and DTIC-resistant melanoma is still alive 25.5 months after start of treatment; 3 other patients with stage IV melanoma, treated 3rd or 4th-line with trabedersen survived for 11.4, 13.8, and 18.6 months (as of Feb2011).
Conclusions: Trabedersen showed good safety and encouraging survival. The follow-up of 14 MM patients treated with the 4d on, 10d off-140 mg/m^2/d regimen is ongoing. A randomized, active-controlled Phase II/III study in PanCa patients is in preparation.

1234 POSTER

A First in Man Phase 1 Study of JNJ-26481585, a Novel Oral Histone Deacetylase Inhibitor (HDACi) in Advanced Cancer Patients − Evidence of Target Modulation, Antitumour Activity and Additional Safety Data in an Expanded Patient Cohort

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Background: JNJ-26481585 is a potent, hydroxamate, pan-HDACi with extensive tissue distribution, improved PD parameters and broad activity in solid and hematologic tumour models.

Methods: JNJ-26481585 was administered orally, once daily (QD) in 3-weekly cycles to advanced cancer patients (pts) using a 2-stage accelerated titration design. Due to poor tolerance of the QD dosing, three intermittent schedules were explored: 1) 4 days on, 3 days off; 2) every Mon, Wed, Fri (MWF); and 3) every Mon, Thurs (M-Th). Primary objectives were safety, maximum tolerated dose (MTD) and pharmacokinetics (PK). Secondary objectives were pharmacodynamic (PD) effects in normal and tumour tissues (acetylated Histone 3, Ki67), PK food effect and anti-tumour activity.
Results: 78 patients (40 M, median age 56 yr, ECOG PS 0/1/2: 29/44/2, 3 pts NA) received JNJ-26481585. The number of pts, dose-limiting toxicities (DLTs) and MTD for each cohort and schedule are summarised in Table 1. Common grade 1−2 toxicities were: fatigue, anorexia and nausea. PK showed rapid absorption, high volume of distribution, dose-proportionality (range 2−19 mg) and no clinically meaningful food effect. From the 8 mg dose level onward increased acetylated Histone 3 and reduced Ki67 in tumour and skin biopsies were observed independent of the schedule. A partial response lasting 5 months (mo.) was seen in one patient with melanoma. Stable disease was seen in 8 pts (range 4–10.5 mo. tumour types included melanoma, NSCLC, CRPC, nasopharyngeal cancer, cholangiocarcinom and Bartholin's gland carcinoma).
Conclusions: The adverse event profile of JNJ-26481585 is comparable to other HDACi. Intermittent administration is better tolerated than QD. The recommended dose for phase 2 trials is 12 mg on the MWF schedule based on tolerability; further safety, anti-tumour activity, PK predictions and PD activity are being explored in an expanded patient cohort.

Table 1

Schedule	2 mg	4 mg	6 mg	8 mg	10 mg	12 mg	15 mg	16 mg	19 mg
QD	N = 2	N = 2	N = 6 1 DLT (*bilirubin rise*)	N = 8 1 DLT (*NSVT**) **MTD**	–	N = 2 2 DLTs (*NSVT*, fatigue*)	–	–	–
4 days on, 3days off	–	–	N = 3	N = 3	N = 6 0 DLTs **MTD**	N = 7 2 DLTs (*NSVT*, infection*)	–	–	–
MWF	–	–	N = 3	N = 3	–	N = 7+5 1 DLT (*hypertension + troponin rise*) **MTD**	–	N = 6 0 DLTs***	–
M-Th	–	–	–	N = 3	–	N = 3	N = 6 0 DLTs **MTD**	–	N = 3 2 DLTs (*T-wave inversion, SVT***)

*non-sustained ventricular tachycardia; **supraventricular tachycardia; ***palpitations + increased ventricular ectopics in 2 pts in Cycle 2.

1235 POSTER

Moguntinones − New Selective Inhibitors for Treating Human Gastrointestinal Tumours

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Background: Moguntinones are new innovative synthetic designed small molecules which are molecules with structural features of 3 natural products. They have been invented and patent-protected as tyrosine kinase inhibitors by the Institute of Pharmacy in cooperation with the I. and III. Dept. of Medicine, Mainz. Moguntinones display a new generation of inhibitors for tumur progression, angiogenesis and tumour cell resistance. Our aim was to analyse their antineoplastic effects in vitro and in vivo in human gastrointestinal cancers.
Methods: To establish their mode of action, firstly Moguntinones were analysed in the HET-CAM assay and characterized using IC50 values of kinase assays. Secondly. the human colon cancer HT-29, DLD-1, SW480 and gastric cancer MKN-45, AGS cells were analysed in vitro and in vivo after incubation with Moguntinones, for their interference with signalling pathways by RNA and protein levels (RT-PCR, Western, ELISA, FACS). Additionally, different viability and apoptosis assays were analysed after Moguntinones were combined with or without cytostatic drugs. The *in vitro* data were then verified in a human xenograft NOD/SCID mouse models.
Results: The first generation of Moguntinones showed clear antiangiogenic effects in HET-CAM assays and different spectra of activity in the kinase kinome, most commonly acting on VEGFR 1−3, PDGFR and FLT-3 receptor. Retaining the essential pharmacophore little structural changes lead to better biological antineoplastic and antiangiogenic effects. Moguntinones alone induced apoptosis only in higher micromolar concentrations. Furthermore, we observed strong synergistic effects for induction of apoptosis in lower concentrations of Moguntinones and combinations with cytostatic drugs, especially topoisomerase inhibitors such as irinotecan. In *in vivo* mouse models, similar reductions of tumour growth and tumour weight were seen with no limitation of treatment effects, even in KRAS-, BRAF-or PI3K-mutated colon and gastric cancer cells. Here, signalling pathways of Stat, GSK3b and FAK where inhibited. The antineoplastic effects could not be shown on normal epithelial HUVEC cells.
Conclusions: Our *in vitro* and *in vivo* data clearly support significant pro-apoptotic, anti-angiogenic and antiproliferative effects of Moguntinones in the combination with cytotoxic agents. The data argue for a high effectiveness of Moguntinones to complement standard therapies and to overcome tumour resistance. Our groups aim to bring these substances into a clinical phase I study.

1236 POSTER

Phase I Study to Assess the Safety, Tolerability and Pharmacokinetics of the Multikinase Inhibitor Regorafenib (BAY 73–4506) in Japanese Patients With Advanced Solid Tumours

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Background: Regorafenib (BAY 73–4506) is a novel, broad-acting tumour deactivating agent that inhibits angiogenic (VEGFR1−3, TIE2), stromal (PDGFR, FGFR), and oncogenic kinases (KIT, RET, RAF). In preclinical models, regorafenib has shown a broad spectrum of antitumour activity. Regorafenib 160 mg once daily (o.d.) in repeating cycles of 21 days on/ 7 days off was determined as recommended dose for phase II/ III in the US and EU countries. The aim of this study was to assess the safety, tolerability, pharmacokinetics (PK) and antitumour activity of regorafenib in Japanese patients (pts) with advanced solid tumours (ClinicalTrials.gov ID: NCT00960258). This trial is sponsored by Bayer and has completed enrollment.
Methods: Regorafenib 160 mg o.d. was administered orally in repeating cycles of 21 days on/7 days off until discontinuation due to toxicity or tumour progression. PK was evaluated after a single dose of 160 mg prior to the start of multiple dosing and after 21 days of multiple dosing in Cycle 1. Adverse events (AEs) were graded by NCI CTCAE v 3.0. Efficacy was evaluated using RECIST v 1.0.
Results: Fifteen pts were treated (pancreatic cancer 6 pts, neuroendocrine tumour 3 pts, other tumour types 6 pts). Commonly reported drug-related AEs of all grades included diarrhea (67%), hand-foot skin reaction (HFSR) (67%), hypophosphatemia (53%) and AST elevation (53%). Grade 3 or 4 drug-related AEs included hypophosphatemia (27%), lymphopenia (27%), HFSR (13%), AST/ ALT elevations (13%) and hepatobiliary related event (13%). Dose reduction in Cycle 1 occurred in 2 pts (hypertension, neutropenia); another pt had a dose reduction in Cycle 2 (AST/ ALT elevations). PK results of regorafenib on Day 21 of Cycle 1 showed that mean C_{max} and AUC(0−24) were 2512 mg/L and 32980 mg*h/L respectively. Terminal half life and t_{max} on Day 21 of Cycle 1 were not changed from the day of first dosing. A substantial accumulation was observed between a single dose and Day 21. Fifteen pts were evaluable for efficacy. Partial response was observed in 1 pt, who is ongoing in Cycle 14. Six pts had stable disease, two of whom are still ongoing in Cycles 12 and 20.
Conclusions: Regorafenib 160 mg o.d. given in 21 days on/7 days off repeating cycles was well-tolerated and demonstrated antitumour activity in Japanese pts with advanced solid tumours. The safety profile and PK parameters observed in the Japanese pts were comparable to those observed in Phase I studies in Caucasian pts.

1237 POSTER

WIN55,212−2 as a Potential Treatment for Estrogen-receptor Negative Breast Cancer

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Approximately 30% of all breast cancers are estrogen-receptor (ER) negative, which are often of poorer prognosis and more aggressive behavior compared to ER positive breast cancer cases. While estrogen receptor antagonists have been successfully used for the treatment of ER positive tumours, there have been no specific treatment options for triple negative breast cancers. Our study focused on anticancer potential of a synthetic cannabinoid, WIN55,212−2, in human ER negative breast cancer cells both *in vitro* and *in vivo*. Results demonstrated that WIN55,212−2 produced cytotoxicity toward MDA-MB-231 and MDA-MB-468 cells with