	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.