bounded by endothelial cells while others were bounded by tumour cells. Administration of DMXAA in a previously determined optimal schedule (20 mg/kg followed by two 5 mg/kg doses at 4 and 8 hours; repeated after 11 days) to mice with NZM7 xenografts induced extensive tumour necrosis with a tumour growth delay of 19 days (2/6 cures).
Conclusions: DMXAA has a significant effect on the function of tumour cells exhibiting features of vasculogenic mimicry. This may be of importance to its action in clinical trials.
Support: This work was supported by an Antisoma Post-doctoral Fellowship.

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Molecular tumor characteristics and response to bevacizumab plus irinotecan/5-fluorouracil/leucovorin in metastatic colorectal cancer

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Background: Bevacizumab (BV) is a recombinant, humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF) that has demonstrated survival benefit in first-line treatment of patients with metastatic carcinoma of the colon or rectum. In a phase III study, the addition of BV to irinotecan/5-fluorouracil/leucovorin (IFL) first-line therapy resulted in a 34% reduction in the daily hazard of death compared to IFL alone (HR = 0.66; p=0.00004) (ASCO 2003). Submission of tumor specimens was optional in this study. We sought to explore the effects of baseline molecular tumor characteristics on survival, PFS, and objective response rate.
Methods: Tumor material was analyzed from 232 of the 923 patients in the study; consisting of either tumor cores isolated from paraffin blocks and placed into tissue microarrays or unstained tissue sections. The analysis included *in situ* hybridization (ISH) for VEGF RNA and immunohistochemistry (IHC) for p53 protein (DO-7 antibody, DAKO). Mutational analysis for *KRAS* (exon 1), *BRAF* (exon 15) and *TP53* (exons 5–8) was performed by DNA sequencing of tumor cells isolated by laser capture microdissection (PixCell II, Arcturus). Descriptive summaries of duration of survival, PFS and objective response were produced for each of the categorical variables listed above for each treatment arm. These descriptive summaries consisted of the hazard ratio from unstratified Cox regression and Kaplan-Meier estimates of median time to the event.
Results: 232 patients randomized to receive IFL alone (100) or IFL with BV (132) contributed to the calculation of the hazard ratios. The demographic and background characteristics were generally similar between the study as a whole and the subset in this analysis; this subset did have a higher percentage of subjects with ECOG PFS 0 (study: 57% versus subset: 64%). Mutations in the *KRAS*, *BRAF* and *p53* genes were observed in 35, 6 and 67% of patients, respectively. The type and frequency of p53 mutations were consistent with previously published data for colorectal adenocarcinomas. The IHC assay for p53 protein was positive in 72% of patients; the concordance rate between the two p53 assays was 66%. VEGF ISH on standard paraffin sections is in progress and results will be presented.
Conclusions: Patients benefited from the addition of BV to the chemotherapy regimen, as measured by duration of survival, independent of KRAS, BRAF or TP53 status.

		N	Median survival (mo)		Hazard Ratio
			IFL	IFL/BV	
All		232	17.5	26.5	0.54 (0.35–0.82)
KRAS	Mutant	76	14.9	19.9	0.75 (0.39–1.44)
	Wildtype	140	21.7	27.7	0.57 (0.32–1.01)
BRAF	Mutant	13	8.0	15.9	0.13 (0.02–0.70)
	Wildtype	196	18.7	26.4	0.52 (0.32–0.84)
TP53	Mutant	118	21.7	27.7	0.42 (0.23–0.78)
	Wildtype	58	17.5	not estimable	0.71 (0.31–1.61)
p53	Positive	163	17.6	26.4	0.70 (0.43–1.14)
	Negative	64	13.6	25.1	0.26 (0.11–0.64)

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AMG 706 first in human, open-label, dose-finding study evaluating the safety and pharmacokinetics (PK) in subjects with advanced solid tumors

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Introduction: AMG 706 is a potent and selective small molecule inhibitor of multiple kinases, including vascular endothelial growth factor receptor, platelet derived growth factor receptor, and c-kit. To assess the safety, establish the maximum tolerated dose, and generate PK profiles of oral AMG 706, a clinical study in adult subjects was initiated.
Methods: individuals with advanced solid tumors, refractory to standard therapy or with no standard therapy available, were enrolled in this ongoing, open-label, dose-escalation study. Cohorts of 3 to 9 subjects were orally administered 50, 100, 125, or 175 mg once daily (QD) in an intermittent dose pattern of 21 days of dosing in a 28-day cycle. Subjects remained on study until tumor progression or unacceptable toxicities occurred.
Results: AMG 706 was generally well-tolerated up to 125 mg QD using the intermittent dose schedule. Most adverse events were mild to moderate in severity and reversible. Eight of the 9 subjects in the 125 mg QD cohort remained on study until day 50 including 1 subject with a grade (gr.) 3 hypertension and another with a gr. 3 creatinine and gr. 4 hyponatremia. Twenty-six of the 31 treated subjects reached the day 50 tumor assessment, revealing 1 (leiomyosarcoma) partial response, 3 (gastrointestinal stromal, thyroid, and carcinoid tumors) minor responses (−8% to −23% in the sum of the longest diameter of target lesions), and an additional 9 stable diseases (SD). Six subjects maintained SD for at least 134 days and 3 of these 6 subjects had SD for more than 218 days on study. AMG 706 demonstrated favorable bioavailability and half-life (about 7 hrs) at all dose levels. A single- and multiple-dose PK result comparison suggests that no significant accumulation of drug occurred during the first 3 weeks of AMG 706 administration.
Conclusions: AMG 706 appears to be safe and tolerable at daily doses up to 125 mg. Once daily dosing generated sustained exposure sufficient to elicit partial, minor and SD responses across multiple cancer types, suggesting that AMG 706 has broad anti-tumor activity.

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A synthetic Resveratrol analog inhibits the proangiogenic response of liver sinusoidal cells to tumor-derived factors during hepatic melanoma metastasis formation

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Background: Resveratrol (3,5,4′-trihydroxystilbene) is a naturally occurring phytoalexin with cancer chemopreventive properties. Widespread interest in this molecule and synthetic stilbene analogues have arisen in recent years due to the discovery of its antioxidant, antiinflammatory, antiangiogenic and anti-carcinogenic activities.
Materials and Methods: Using resveratrol as prototype, we synthesized compound 5-((E)-(4-hydroxyphenylimino)methyl)benzene-1,3-diol, an unnatural resveratrol analog (FAS21) obtained in high yield by condensation between readily available reagents 4-aminophenol and 3,5-dihydroxybenzaldehyde. Then, the effects of trans-resveratrol were compared with those of FAS21 through an *in vivo* model of hepatic metastasis by intrasplenically injected B16 melanoma cells. Because tumor-activated hepatic sinusoidal cells contribute to tumor growth via NfkappaB and COX-2-dependent angiogenesis stimulation (Olaso et al, Hepatology 2003;37:674–85), we also investigated the antiangiogenic effect of resveratrol and FAS21 through tumor-hepatic sinusoidal cell interaction assays *in vitro*.
Results: Trans-resveratrol and FAS21, given orally as one single daily dose (1 mg/kg) since day 5 after B16M cell injection, reduced metastasis volume by 62% and metastasis number by 50%. Antitumor effect was selective on hepatic metastases having a sinusoidal-type angiogenesis, where microvessel density decreased while necrotic area increased. Consistent with *in vivo* data, both trans-resveratrol and FAS21 dose-dependently (5–25 μM) inhibited proliferative and migratory responses of human and murine hepatic myofibroblasts to human A375 melanoma and murine B16M-derived soluble factors. Trans-resveratrol also decreased by 70% human and murine hepatic sinusoidal endothelial cell migration towards tumor-conditioned media. The migration of human hepatic myofibroblasts in response to cytokines present in cultured melanoma cell supernatants