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Clinical and molecular studies of the effect of imatinib on advanced aggressive fibromatosis (desmoid tumors)

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Aggressive fibromatosis (AF, also known as desmoid tumor) is a fibroproliferative neoplasm that typically arises in the abdomen but can present as a primary tumor of extrabdominal site, most notably in an extremity location. These tumors have a relatively high local failure rate after primary treatment using surgery and/or radiotherapy but rarely give rise to distant metastases. Most AF have abnormalities in the regulation of WNT pathway signaling, due either to germline/somatic inactivation of APC **or** somatic gain-of-function mutations of beta-catenin. Enforced expression of mutant beta-catenin in murine mesenchymal cells results in formation of AF lesions. The optimal medical therapy of recurrent and/or unresectable AF is uncertain, although some activity of has been reported for small series of patients treated with tamoxifen, NSAIDSs, or chemotherapy. Mace el al. reported the response of two patients with *extra-abdominal* AF to imatinib mesylate (IM) (Cancer 95:2373, 2002). In the current study, we treated 19 patients with with unresectable AF enrolled in a phase II trial investigating the effects of IM on multiple types of cancers, including a variety of sarcomas. The mean patient age was 28 years (range 17–63) with 18 of 19 patients having undergone one or more prior surgeries and14 of 19 patients having undergone prior medical therapy, including tamoxifen, NSAIDS, and/or chemotherapy. Patients were treated with 400 mg bid of IM and clinical activity was assessed using CT/MRI imaging and conventional SWOG (pre-RECIST) response criteria. All patients had progressive disease at the time of study entry. 3/19 patients (16%) had a partial response (all with abdominal primary sites) and an additional 3 pts had SD > 18 months (2 abdominal, 1 extremity primary site), giving an overall clinical benefit rate of 32% (6/19). Tumor specimens were evaluated for genomic or proteomic evidence of activation of IM target kinases and genomic evidence of beta-catenin mutations. There was no association of response/nonreponse with underlying APC or beta-catenin mutations. IHC and immunoblotting revealed no evidence of significant KIT or PDGFRA expression or kinase activation. No intragenic mutations of *KIT, PDGFRA*, or *PDGFRB* were found. Low amounts of PDGFRB activation were seen in immunoblotting experiments, consistent with a possible autocrine/paracrine mechanism of activation. We conclude that IM appears to have significant activity in treating refractory AF arising either in abdominal or extra-abdominal sites, possibly through inhibition of PDGFRB kinase activation. Further studies are needed to 1) better define the clinical activity of IM for the treatment of AF, especially in comparison to other medical therapies; 2) identify the mechanism of action underlying IM response; and 3) identify biomarkers to aid in patient selection for treatment with IM.

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Antitumor activity in preclinical xenograft models of OSI-930, a novel selective tyrosine kinase inhibitor

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Tyrosine kinases have been implicated in many cellular pathways, including growth, survival and apoptosis, and are consequently considered to be biologically relevant cancer targets. We have identified a series of 2,3-substituted thiophene compounds with potent inhibitory activity against the closely-related Kit, KDR, PDGFRα and PDGFRβ enzymes. These targets are implicated in a broad range of tumor types including GIST, small cell lung carcinoma (SCLC), renal cell carcinoma, colorectal carcinoma and glioblastoma. OSI-930 is the lead potential clinical candidate from this series, which potently inhibits (IC50<1 μM) the *in vitro* tyrosine kinase activity of Kit, KDR, PDGFRα/β and other potentially important kinase targets. OSI-930 has good oral bioavailability in mice and prolonged plasma exposure, which allows for single daily dosing in xenograft efficacy studies. Dose-dependent tumor growth inhibition was observed in a number of models, including SW48 colon carcinoma and NCI-H526 and NCI-H209 SCLC. In these studies, maximal effects on tumor growth were observed when OSI-930 was delivered daily at 200 mg/kg. This dose and schedule were well tolerated and minimal body weight loss was observed when OSI-930 was delivered up to 38 consecutive days. Antitumor activity of OSI-930 as a single agent was explored further in a variety of growth-staged xenograft models. Response was evaluated by tumor growth delay, defined as the delay in time for treated tumors to reach a predetermined size (500% of original size) compared to vehicle matched controls. Growth delay was considered biologically relevant when it was at least equivalent to the number of days that the drug was administered. With this criterion, OSI-930 delivered at 200 mg/kg was effective in delaying tumor growth in SCLC (NCI-H209, WBA), colorectal carcinoma (HT29, HCT-116, LS180, DLD-1, COLO 205, SW48), head and neck carcinoma (KB), gastric carcinoma (NCI-SNU-5), glioblastoma (U251) and renal cell carcinoma (SN12C). In the most sensitive of these models (WBA, U251, NCI-SNU-5 and KB), OSI-930 induced tumor regression and durable cures. These results highlight the utility of an agent, which can directly inhibit key targets and suggest that OSI-930 may have broad clinical utility.

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Magnetic resonance spectroscopy confirms the mechanism of action of the choline kinase inhibitor MN58b in human breast cancer cells

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Choline kinase (ChoK) is the enzyme responsible for the generation of phosphocholine (PC) from its precursor choline to form phosphatidylcholine, the most abundant component of the plasma membrane. Increased levels of ChoK activity and PC production in human cancers have been reported (1). Recently, ChoK has also been implicated in cell proliferation playing an important role in mitogenic signal transduction pathways. These observations have resulted in the development of an anti-tumoural strategy focused on ChoK inhibition. MN58b is one of the most potent ChoK inhibitors showing anti-proliferation activity both in vitro and in vivo (1). This work set out to test the hypothesis that phosphorus magnetic resonance spectroscopy (31P MRS) could measure changes in PC levels in MN58b treated cells as an indication that the in vivo 31P MRS might be able to monitor the pharmacodynamics of this drug in patients during clinical trials. The human mammary carcinoma cell line MDA-MB-231 was treated with the specific ChoK inhibitor MN58b (6 uM) for 4, 13, 19, 30 and 48h. MDA-MB-231 cells were also treated with the inactive MN58b analogue ACG20B (6 uM) for 48h. Adherent cells were extracted using a dual phase extraction method. 31P MR spectra were acquired at room temperature on a 500 MHz Bruker spectrometer. Metabolite content was determined by integration and normalised relative to internal standards and cell number. The number of MN58b treated MDA-MB-231 cells was reduced to 78% of control cells at 48h, consistent with decreased proliferation. 31P MRS showed that MN58b treatment led to a significant time-dependent drop in PC levels which started as early as 4h (80.9±5.7%, P=0.04) and was down to (39.5±1.8, P=0.00001) at 48h relative to controls (Fig. 1). In contrast, no statistically significant change in PC level was observed in MDA-MB-231 cells following treatment with ACG20B. This indicates that the 31P MRS detected drop in PC is due to the inhibitory effect of MN58b on ChoK. These results provide further support for the necessary proof-of-principle for the hypothesis that the inhibitory effect on proliferation of MN58b is correlated with its ability to inhibit the production of PC in cells. It also provides an evidence for the potential of MRS as a non-invasive tool for the assessment of anti-tumour activity of ChoK inhibitors in early stage of clinical trials. 1. Lacal, J. C. (2001) IDrugs 4:419–426 This work is supported by Cancer Research UK (C1060/A808/G7643)

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Key roles for HSP90 in tumour neoangiogenesis

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Heat shock protein 90 (Hsp90) chaperones several key signalling molecules involved in angiogenesis, including c-*erb*B-2, Akt, c-met, eNOS and HIF-1α. We have used Hsp90 inhibitors including 17-allylamino,17-demethoxygeldanamycin (17AAG) and geldanamycin (GA) to probe the effects of HSP90 inhibition on key endothelial cell functions required for neoangiogenesis *in vitro*. We also explored the role of Hsp90 in the transcriptional upregulation of angiogenic cytokines via c-erbB oncogene activation and hypoxia in tumour cells, and on angiogenesis in xenograft models *in vivo*.

The expression of client proteins in human endothelial cells (EC) was inhibited in response to 17AAG and geldanamycin in a concentration-