design. Further treatment courses were administered in the absence of disease progression and after recovery from toxicity after a 3-week observation. A total of 50 patients were treated at doses from 12 to 450 mg.
Results: Reversible hematotoxicity was the main side effect with thrombocytopenia, neutropenia and febrile neutropenia constituting the dose limiting toxicities. Fatigue was the only drug related non-hematologic event occurring in more than or equal to 10% of patients. The MTD was defined at 400 mg. Safety data obtained from expanded patient cohorts at 300 and 350 mg will be considered for the definition of the recommended Phase 2 dose. The mean number of courses was 4 per patient over all dose groups. Up to 16 courses of treatment were administered in two patients still on treatment without evidence of accumulating toxicity. Preliminary PKs were evaluated in 29 patients and demonstrated linearity in the therapeutic dose range, a large volume of distribution (>3600 L), moderate clearance (900 mL/min, gCV 35%) and a long half-life of around 110 hours. Confirmed partial responses were observed in a patient suffering from advanced urothelial cancer (sustained partial remission after >16 treatment courses) and a patient with relapsed ovarian cancer. Stable disease as best response was reported in another 32% of patients.
Conclusions: In summary BI 6727 is a potentially first in class Plk1 inhibitor with a very favorable PK and safety profile at the tested dose and schedule. Encouraging antitumor activity has been observed supporting Plk1 as a therapeutic target and warranting further clinical investigation.

Wednesday, 22 October 2008 16:30–18:15

PLENARY SESSION 3

Molecular targets – state of the science B

37 INVITED

Drugging the cancer chaperone Hsp90: From chemical biology with natural products to active drugs in the clinic

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Despite initial scepticism, the Hsp90 molecular chaperone has emerged as an exciting new drug target. A big potential advantage is that inhibition of Hsp90 causes simultaneous combinatorial depletion of multiple oncogenic 'client' proteins. This leads to parallel blockade of many cancer-causing pathways and to the antagonism of all the hallmarks of malignancy. Therapeutic selectivity is achieved by exploiting both the dependence of cancer cells on oncogenic clients and also the stressed state of malignant cells (Workman et al Ann NY Acad Sci 1113 202–216 2007). The combinatorial effects of Hsp90 inhibitors should make development of resistance more difficult than for agents having more limited effects, and recent results from our lab support this view (Gaspar, Pacey et al submitted). The Hsp90 field was opened up by chemical biology research on the natural product Hsp90 inhibitors geldanamycin and radicicol. These agents not only provided the basis for several drugs now in clinical development, but were also crucial chemical tools to help explore Hsp90 structure and function. The geldanamycin inhibitors 17-AAG (tanespimicin), 17-DMAG (alvespimicin) and the 17-DMAG hydroquinone (IPI-504) have all entered clinical trials. The first-in-class Hsp90 drug, 17-AAG, provided proof of concept for Hsp90 inhibition in tumor tissue of patients at well tolerated doses (Banerji et al J Clin Oncol 23 4152–4161 2005). Therapeutic activity is reported with 17-AAG, eg in melanoma patients with KRAS and RAF mutations (Banerji et al Mol Cancer Ther 7 737–739) and ERBB2-positive breast cancer patients resistant to trastuzumab. There is also potential in multiple myeloma through effects on specific clients and by exploiting the unfolded protein response (Davenport et al Blood 110 2641–2649 2007). Additional sensitive tumor types are being defined based on dependence of key proteins and pathways on Hsp90 (Workman and Powers Nat Chem Biol 3 455–457 2007). Following the natural product-based agents, second generation, small molecule inhibitors have been developed using a combination of high-throughput screening technologies and structure-based design (Sharp and Workman Adv Cancer Res 95:323–348 2006; Smith and Workman, Drug Discovery Today: Therapeutic Strategies, published on-line 3 April 2008). From the purine scaffold inhibitor class the orally active agent BIIB021 is now in clinical trials. The pyrazole/isoxazole class of synthetic small molecule inhibitors that we discovered contains the essential resorcinol unit also present in radicicol (Cheung et al Bioorg Med Chem Lett 15 3338–3343 2005) and NVP-AUY922, derived from this series, has entered clinical studies (Brough et al J Med Chem 51 196–218 2008; Eccles et al Cancer Res Cancer Res 68 2850–2860 2008). Other inhibitors show promise in preclinical and clinical development. The emerging new drugs illustrate the benefits of high-throughput compound library screening, structure-based design and chemical biology approaches. Opportunities and challenges for Hsp90 inhibitors will be discussed, including use in combination, as in ovarian cancer with deregulated PI3 kinase signalling (Sain et al N Mol Cancer Ther 5 1197–1208 2006; Banerji et al Cancer Chemother Pharmacol Jan 10 2008 Epub ahead of print). All the current Hsp90 drugs in the clinic act by blocking the essential nucleotide binding and ATPase activity required for chaperone function. Potential new approaches will be discussed, for example interference with cochaperone binding and function. Our increasing understanding of the structure-function relationships for the Hsp90 multichaperone complex provides the basis for new therapeutic approaches (Pearl, Prodromou and Workman, Biochem J 439–453 2008; Smith and Workman, Drug Discovery Today: Therapeutic Strategies, published on-line 3 April 2008). As an example, we have shown that silencing of the Hsp90 ATPase-activating protein AHA1 decreases the activation but not the stability of Hsp90 client proteins and increases the sensitivity of cancer cells to 17-AAG (Holmes et al Cancer Res 68 1187–1196 2008). Biomarkers for use with Hsp90 inhibitors will be described, including those identified in our gene expression and proteomic profiling studies (Maloney et al Cancer Res 67 3239–3253 2007). Success with Hsp90 inhibitors has encouraged therapeutic targeting of other elements of the heat shock response that is regulated by HSF1 (Powers and Workman P FEBS Lett 581 3758–3769 2007; Workman and de Billy Nat Med 2007 13 1415–1417 2007). The progression from chemical biology tools to active drugs in the clinic has been impressive. Basic and translational research on Hsp90 have been interwoven and mutually beneficial and this synergy has pointed to future directions to enhance our understanding of the structure and function of molecular chaperones and their exploitation in cancer and other diseases.
Supported by Cancer Research UK

38 INVITED

Bortezomib therapy of multiple myeloma

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As a result of these advances in oncogenomics on the one hand and increased understanding of the role of the BM in the pathogenesis of MM on the other, a new treatment paradigm targeting the tumor cell and its BM microenvironment to overcome drug resistance and improve patient outcome has now been developed in MM. Bortezomib can induce cytotoxicity against MM cells in the BM milieu and can overcome cell adhesion mediated drug resistance to conventional therapies. This data, coupled with phase I clinical trial data showing responses in MM, led to the phase II SUMMIT clinical trial in relapsed refractory MM, which achieved durable responses and associated clinical benefit, leading to its FDA and EMEA approval in this setting. The APEX clinical trial in relapsed MM showed that bortezomib was superior to high dose dexamethasone in terms of extent and frequency of response, time to progression, and overall survival, leading to FDA and EMEA approval extending to these patients as well. Excitingly, when combined with dexamethasone it has increased frequency and extent of response both before and after high dose melphalan and autologous stem cell transplantation. In the older non-transplant patients, initial therapy with bortezomib combined with melphalan and prednisone achieved significant increases in overall and extent of response, associated with prolonged progression free and overall survival. In both upfront trials prognostic factors and cytogenetic abnormalities that confer adverse prognosis to conventional and high dose therapy did not impact outcome. Recent studies have shown additional benefits for bortezomib therapy including preclinical evidence of osteoblast stimulation and osteoclast apoptosis, elevation of bone alkaline phosphatase consistent with new bone formation correlating with response to Bortezomib, efficacy of Bortezomib in patients with renal failure including those on dialysis, and effectiveness of Bortezomib in patients with renal compromise and on dialysis. More recently, several next generation proteasome inhibitors have shown promise at overcoming Bortezomib resistance in preclinical models and are under clinical evaluation. Carlfizomib more potently inhibits the chymotyrptic proteolytic activity and is under evaluation in two phase II clinical trials in MM, having shown early signs of responses in phase I studies. NPI-0052, a second generation proteasome inhibitor targeting chymotryptic, tryptic-like, and caspase-like proteolytic activities, is also in phase I clinical trial in MM. Finally, CEP-18770 is an oral inhibitor of chymotryptic proteolytic activity which is also entering clinical trials. At present, the qualitative or quantitative extent of proteasome inhibition associated with clinical efficacy in MM remains to be defined. Remarkably Bortezomib can be used in combination treatments to either sensitize or overcome drug resistance. For example, Bortezomib inhibits DNA damage repair, and a phase III trial demonstrated significantly increased extent and frequency of

response, as well as duration of response and overall survival, in patients treated with Bortezomib with doxil versus Bortezomib alone, leading to its FDA and EMEA approval. Bortezomib has been combined with Hsp90 inhibitors to block both aggresomal and proteasome degradation of protein; phase I/II clinical trials have shown that it can sensitize or overcome resistance to Bortezomib, and a phase III trial is comparing Bortezomib versus Bortezomib and Hsp90 inhibitor tanespimycin in relapsed MM. Bortzomib induces apoptosis but activates Akt in vitro, and the Akt inhibitor with Bortezomib triggers synergistic cell death. Bortezomib with perifosine achieves responses in the majority of patients with relapsed refractory MM, including to Bortezomib. Bortezomib and lenalidomide trigger primarily caspase 9 and 8 mediated apoptosis, respectively; the combination triggers dual apoptotic signaling and synergistic death in vitro. This combination achieves 58% response in patients with relapsed refractory MM in whom either drug is ineffective when used alone, and 98% responses when use to treat newly diagnosed disease. Finally, blockade of aggresomal and proteasomal degradation of proteins by histone deacetylase inhibitors and Bortezomib, respectively, is synergistic in preclinical studies, and already clinical trials of the histone deacetylase inhibitor SAHA with Bortezomib show benefit in the majority of patients with relapsed refractory MM. Future translational research will focus on the development of scientifically-based combination therapies with Bortezomib to achieve high frequency and durable responses in the majority of patients with MM.

39 INVITED

Targeting steroid hormone receptors for ubiquitination and degradation in breast and prostate cancer

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Background: Protacs (Proteolysis Targeting Chimeric molecules) target proteins for destruction by exploiting the ubiquitin-dependent proteolytic system of eukaryotic cells. We hypothesized that these Protacs would recruit hormone receptors to the VHL E3 ligase complex, resulting in the degradation of receptors, and decreased proliferation of hormone-dependent cell lines.
Materials and Methods: We designed two Protacs that contain the peptide 'degron' from HIF-1a, which binds to the Von-Hippel-Lindau (VHL) E3 ubiquitin ligase complex, linked to either dihydroxytestosterone (DHT) that targets the androgen receptor (AR) (Protac-A), or linked to estradiol (E2) that targets the estrogen receptor a (ERalpha) (Protac-B). Both breast and prostate cancer cells were treated with Protacs. Inhibition of growth and the levels of ER and AR were determined.
Results: Treatment of estrogen-dependent breast cancer cells, MCF-7 and T47D, with Protac-B induced the degradation of ERalpha in a proteasome-dependent manner. Protac-B inhibited the proliferation of ERalpha-dependent breast cancer cells by inducing G1 arrest, inhibition of retinoblastoma phosphorylation and decreasing expression of Cyclin D1, progesterone receptors A and B. Protac-B treatment did not affect the proliferation of estrogen-independent breast cancer cells that lacked ERalpha expression. Similarly, Protac-A treatment of androgen-dependent prostate cancer cells (LNCaP) induced G1 arrest but did not affect cells that do not express AR.
Conclusions: Our results suggest that Protacs specifically inhibit the proliferation of hormone-dependent breast and prostate cancer cells through degradation of the ERalpha and AR respectively.

40 INVITED

Role of autophagy in cancer and therapy

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Autophagy plays a critical protective role maintaining energy homeostasis and protein and organelle quality control. These functions are particularly important in times of metabolic stress and in cells with high energy demand such as cancer cells. In emerging cancer cells, autophagy defect may cause failure of energy homeostasis and protein and organelle quality control, leading to the accumulation of cellular damage in metabolic stress. Some manifestations of this damage, such as activation of the DNA damage response and generation of genome instability may promote tumor initiation and drive cell-autonomous tumor progression. In addition, in solid tumors, autophagy localizes to regions that are metabolically stressed. Defects in autophagy impair the survival of tumor cells in these areas, which is associated with increased cell death and inflammation. The cytokine response from inflammation may promote tumor growth and accelerate cell non-autonomous tumor progression. The overreaching theme is that autophagy protects cells from damage accumulation under conditions of metabolic stress allowing efficient tolerance and recovery from stress, and that this is a critical and novel tumor suppression mechanism. The challenge now is to define the precise aspects of autophagy, including energy homeostasis and protein and organelle turnover, that are required for the proper management of metabolic stress that suppress tumorigenesis. Furthermore, we need to be able to identify human tumors with deficient autophagy, and to develop rational cancer therapies that take advantage of the altered metabolic state and stress responses inherent to this autophagy defect.

Wednesday, 22 October 2008

Poster Sessions

Angiogenesis

41 POSTER

DCE-MRI endpoints reveal decreased tumor vascularity in patients with liver metastases: a Phase I dose escalating study with IMC-1121B

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Background: IMC-1121B is a fully human monoclonal IgG1 antibody (MAb) that binds with high affinity (~50 pM) to the extracellular domain of VEGFR-2. The goal of the present study was to evaluate changes in liver lesions in IMC-1121B treated patients based on quantitative endpoints from dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) studies.
Materials and Methods: Patients with advanced solid malignancy were treated with escalating doses of IMC-1121B (6 to 20 mg/kg) administered intravenously weekly (Study CP12–0401) or every 2 or 3 weeks (Study CP12–0402). Thirteen patients with liver metastases were evaluated for tumor perfusion and permeability by fast series DCE-MRI (0.1 mmol/kg gadolinium-DTPA injection) at baseline and at the end of Cycle 1.
Results: Three quantitative endpoints for tumor vascularity were calculated based on gadolinium uptake curves: IAUC for tumor perfusion; Ve for capillary leakage and Ktrans for overall tumor vascularity. Responders were identified when a decrease in all three DCE-MRI parameters was seen between the baseline and Cycle 1; non-responders were assigned based on increased values of IAUC, Ve and Ktrans at the end of Cycle 1. From total of 13 patients enrolled in DCE-MRI studies, 9 patients have shown significant antiangiogenic response to IMC-1121B treatment as revealed by decreased IAUC, Ve and Ktrans values at the end of Cycle 1 (when compared to their initial baseline). Maximum response (−66% for IAUC; −81% for Ve and −40% for Ktrans) was achieved in the patient treated with the highest IMC-1121B dose in Study CP12–0402, 20 mg/kg administered every three weeks. Two non-responders in Study CP12–0401 (8 and 10 mg/kg every week) and two non-responders in Study CP12–0402 (8 mg/kg every 2 weeks and 15 mg/kg every three weeks) were identified. Serum VEGF levels at 168 hours consistently increased consistently for all dose groups. The drug was well tolerated; two mechanism-based dose-limiting toxicities were observed at 16 mg/kg weekly (CP12–0401): symptomatic hypertension and deep venous thrombosis.
Conclusions: Dose escalation with IMC-1121B led to significant antiangiogenic effects in liver lesions readily assessed by DCE-MRI. There was a good correlation between the dose level and the antivascular effect, with all three patients from the highest dose cohort (16 mg/kg administered weekly for CP12–0401 and 20 mg/kg for administered every three weeks CP12–0402) showing a significant antiangiogenic response.