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.
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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