systolic and diastolic pressures, although not meeting clinical criteria for hypertension. Growth perturbation over a one month term of therapy was not detected. Encouraging disease stabilization was observed in subset of patients with bone and soft-tissue sarcomas. Limited pharmacokinetic data support bevacizumab dosing schedules for children similar to those used in adults. Analysis of apoptotic and viable circulating endothelial cells was feasible in children, and results are promising for mechanistic validation and potential surrogate clinical application. Further evaluation of VEGF blockade therapy in the pediatric population is warranted. Combination studies of bevacizumab with epidermal growth factor receptor inhibition or cytotoxic chemotherapy, and assessment of oral multitargeted small molecular receptor kinase inhibitors BAY 43–9006 and SU11248 are planned or ongoing through the COG.

248/249 INVITED

Clinical phase I-II and pharmacokinetic study of plitidepsin in children with malignant tumors

B. Geoerger[1], F. Doz[2], E. Estlin[3], P. Kearns[4], S. Bezares[5], C. Pico[5], G. Vassal[1]
. *On behalf of ITCC. [1]Institut Gustave Roussy, Department of Pediatrics and "Pharmacology and new treatments in cancer", Villejuif, France; [2]Institut Curie, Department of Pediatrics, Paris, France; [3]Royal Children's Hospital, Oncology, Manchester, UK; [4]Royal Hospital for Children, Oncology, Bristol, UK; [5]PharmaMar SAU, Clinical R&D, Madrid, Spain*

Background: Plitidepsin is a cyclic depsipeptide isolated from the tunicate *Aplidium albicans*, nowadays manufactured by synthesis. It is a rapid and potent inducer of apoptosis and preliminary clinical activity has been observed in several adult malignancies. Phase I trials in adults explored 5 different schedules. Muscle and liver toxicities were dose-limiting; haematological toxicity was not observed at the recommended dose (RD). Preclinical data suggest activity in pediatric leukemia.
Methods: This is a multicentre, open-label, non-randomized phase I-II study with a dose finding stage in children with solid tumors, and subsequently two expanded cohorts in leukemia and solid tumors at the RD. Plitidepsin was administered as a 3 h iv infusion every 2 weeks (= 1 cycle). The initial dose level was 4 mg/m^2 (80% of the RD in adults) with a classic escalation to 5 and 6 mg/m^2.
Results: 22 patients have been entered to date with median age 7.5 years (range 2–17). 70 cycles in 21 patients were evaluable for toxicity. Eight patients were treated at 4 mg/m^2, five at 5 mg/m^2, seven at 6 mg/m^2, and two in the extension phase at 5 mg/m^2. One patient presented dose-limiting G2 myalgia lasting more than 2 weeks at 4 mg/m^2. One patient experienced asymptomatic G4 CPK elevation and one other G3 non-transient transaminitis at 6 mg/m^2, suggesting 5 mg/m^2 as the RD in children. Non-hematological toxicities included muscle side effects (G1–2 myalgia, muscle weakness, muscle cramps and G1–4 CPK elevation), G1–3 fatigue, G1–3 transaminitis, G3 vomiting, G3 hypersensitivity reaction. Pharmacokinetic data are similar to those reported in adult (extensive tissue distribution, a long half-life); if any, clearance was slightly higher and half-life shorter. Partial tumor response was observed in a refractory neuroblastoma and some evidence of activity in a medulloblastoma and a pancreatoblastoma.
Conclusions: Plitidepsin was well tolerated in children with muscle side effects being the most relevant toxicity observed. The RD for the pediatric population is equivalent to the RD in adults. The extension phase in solid tumors and leukemia is ongoing.

Thursday 9 November 14:45–16:15

PLENARY SESSION 6

Proffered Papers

250 ORAL

Presurgical treatment of metastatic renal cell carcinoma patients with bevacizumab and erlotinib: preliminary efficacy and biomaker data

E. Jonasch[1], D. Tsavachidou[2], C. Wood[3], P. Tamboli[4], S. Tu[1], C. Thomas[1], K.A. Do[4], S. Matin[2], T. McDonnell[2], N. Tannir[1]. *[1]University of Texas M.D. Anderson Cancer Center, Genitourinary Medical Oncology, Houston, USA; [2]University of Texas M.D. Anderson Cancer Center, Molecular Pathology, Houston, USA; [3]University of Texas M.D. Anderson Cancer Center, Urology, Houston, USA; [4]University of Texas M.D. Anderson Cancer Center, Pathology, Houston, USA; [4]University of Texas M.D. Anderson Cancer Center, Biostatistics & Applied Math, Houston, USA*

Background: A number of new targeted therapies are being developed for metastatic renal cell carcinoma (mRCC) The role and timing of cytoreductive nephrectomy in patients receiving targeted therapies has not been defined. We have initiated a study investigating the role of presurgical treatment of mRCC patients with bevacizumab and erlotinib, and present data on tumor response and biomarker readouts in the first 19 patients in this protocol.
Materials and Methods: Patients were previously untreated, did not have brain metastases, had a performance status of 0 or 1, predominant clear cell histology, and had not undergone cytoreductive nephrectomy. Patients received bevacizumab 10 mg/kg IV every 2 weeks for 4 doses, and erlotinib 150 mg daily for 8 weeks. Two weeks after the last dose of erlotinib, and 4 weeks after the last dose of bevacizumab, patients underwent cytoreductive nephrectomy. Patients who demonstrated disease stability or response were restarted on treatment one month post-surgery and continued until disease progression. Phospho and total EGFR, AKT, S6, FAK and ERK were evaluated by Western blots and by immunohistochemistry on tissue microarrays, and compared to control untreated RCC tissue.
Results: Between 3/23/2005 and 6/04/06, 27 patients were enrolled out of a total planned accrual of 50 patients As of June 4, 2006, 19 patients were evaluable. One patient had a CR in target lesion and stability in his nontarget lesion (bone). There were 3 PRs, 13 patients with stable disease and 3 patients with progressive disease.
Evaluation of protein expression of key signaling molecules controlling proliferation, survival and migration (phospho-AKT, total AKT, PTEN, phospho-FAK and phospho-ERK) did not reveal any statistically significant change between the treated and the untreated groups, with the exception of a modest increase in overall AKT expression in the treated group (p value <0.02). p-ERK and p-AKT (and p-FAK less strongly, p value <0.02) correlate with disease grade, regardless of treatment status (increase in grade IV, p value <0.002).
Conclusions: Early data suggest presurgical treatment with bevacizumab and erlotinib is safe and efficacious in patients with previously unresected, untreated mRCC, with shrinkage of both metastatic disease and primary tumors. There is previous (pre-clinical) evidence for target inhibition of both VEGFR and EGFR, but key downstream signaling molecules were not affected in this study. Further investigation is required to elucidate the pathways involved in mediating the therapeutic effect of these drugs.

251 ORAL

The phosphatidylinositide 3-kinase (PI3-kinase) inhibitor PI103 sensitises some ovarian carcinoma (OC) cell lines to paclitaxel or carboplatin

B. Bhattacharya[1], B. Krishnan[1], S. Kaye[1], M. Ormerod[1], P. Workman[2], A. Jackman[1]. *[1]Institute Of Cancer Research, Medicine, Sutton, Surrey, United Kingdom; [2]Institute Of Cancer Research, Cancer Research Uk Centre For Cancer Therapeutics, Sutton, Surrey, United Kingdom*

PI3-kinase, through phosphorylation of its downstream substrate, AKT, is an important mediator of proliferation and survival signals. Activation of this pathway has been linked to cytotoxic drug resistance and to the ability of PI3-kinase inhibitors, such as LY294002, to sensitise some tumour cell lines to cytotoxic drugs. PI103 is a novel potent inhibitor of the catalytic p110α/β catalytic subunits of PI3-kinase and of mTOR. The PI3-kinase/AKT pathway is frequently activated in OC due to aberrations at different points in the pathway. SKOV-3 cells overexpress ErbB2,