($p < 0.05$). When given therapeutically, both doses of OPG-Fc caused ~80% reduction of tumor burden by day 25 ($p < 0.03$). OPG-Fc dose-dependently reduced osteolysis in both settings, with the 3.0 mg/kg groups showing a complete absence of tumor-induced lesions. TRAP staining confirmed the reduction (with 0.3 mg/kg OPG-Fc) or absence (with 3.0 mg/kg OPG-Fc) of osteoclasts. Finally, therapeutic treatment of OPG-Fc (3.0 mg/kg) significantly ($p = 0.004$) increased the median survival time by 17% vs. vehicle.
Conclusions: RANKL inhibition reduces MDA-231 breast cancer-induced bone lesions and skeletal tumor burden. These data for the first time show that RANKL blockade in a bone metastasis model leads to an overall improvement in survival.

550 POSTER

Dual inhibition of the MAPK pathway by combination targeted therapy: a phase I trial of sorafenib (SOR) and erlotinib (ERL) in advanced solid tumors

I. Duran[1], S. Hotte[1], E. Chen[1], H. Hirte[1], M. MacLean[1], S. Turner[1], G. Pond[1], J. Wright[2], J. Dancey[2], L. Siu[1]. *[1]Princess Margaret Hospital Phase II Consortium, Toronto, Canada; [2]National Cancer Institute, Bethesda, USA*

Background: SOR and ERL are potent, orally available receptor tyrosine kinase (RTK) inhibitors; SOR targets multiple RTKs (VEGFR-2 and PDGFR-β) and serine-threonine kinase including Raf isoforms, while ERL reversibly blocks EGFR. Dual targeting of the MAPK pathway enhanced inhibition of signal transduction and downstream effector processes in preclinical models (Huang, et al. Cancer Res, 2004; Matar et al. Clin Cancer Res, 2004). Given their inhibitory targets profile and efficacy as single agents, the combination of SOR and ERL is of considerable interest in solid malignancies. This study aimed to determine the recommended phase II dose (RPTD) of this targeted combination, their toxicity profile, pharmacokinetic interaction, pharmacodynamic and preliminary clinical activities.
Methods: SOR was administered for a one week run-in period, and then SOR and ERL were given together continuously, with every 4 weeks considered as a cycle. Three dose levels were assessed.
Results: Seventeen patients (pts) were enrolled with median age = 56 (range 30−77), M:F = 9:8 and ECOG 0:1:2 = 6:10:1. To date, 30 cycles (median = 2) have been administered to 16 pts; 1 pt was inevaluable for dose-limiting toxicity (DLT) due to removal from study for an adverse event (AE) during the run-in period. The most common AEs of all grades (as % of cycles) were: fatigue (93%), diarrhea (77%), lymphopenia (73%), hypophosphatemia (70%) and acneiform rash (60%). The most common grade 3 AEs of all causalities (as % of cycles) were: hypophosphatemia (30%), lymphopenia (17%), dyspnea (13%), GGT (13%), fatigue (10%) and hypokalemia (10%). There were no grade 4 or 5 AEs. DLTs at each dose level are listed in table below. The RPTD of this combination was SOR 400 mg bid and ERL 150 mg qd. Among 13 pts evaluable for response thus far, there were 3 PR (1 cholangiocarcinoma, 1 neuroendocrine tumor and 1 small bowel adenocarcinoma), 8 SD and 2 PD.
Conclusions: Vertical signaling inhibition by this combination of SOR and ERL is feasible at the full recommended doses of both agents with acceptable toxicity. Electrolyte abnormalities such as hypophosphatemia may occur and require replacement. Promising clinical activity was observed in several tumor types. Pharmacokinetic evaluations are ongoing and will be presented.

Dose level	SOR dose (mg bid)	ERL dose (mg qd)	Pts with DLT/ Evaluable pts at dose level (n/n)	DLT
1	200	100	0/3	–
2	200	150	1/7	Gr 3 hypophosphatemia
2	400	150	1/6	Gr 2 intolerable diarrhea and anorexia

551 POSTER

Hemangioma is induced by sustained Akt signaling and inhibited by rapamycin

T. Phung[1], M. Hochman[2], C. Perruzzi[1], G. Eyiah-Mensah[1], K. Walsh[3], M. Mihm[4], L. Benjamin[1]. *[1]Beth Israel Deaconess Medical Center, Pathology, Boston, USA; [2]The Facial Surgery Center, Charleston, USA; [3]Boston University School of Medicine, Whitaker Cardiovascular Institute, Boston, USA; [4]Massachusetts General Hospital, Pathology, Boston, USA*

Background: Infantile hemangiomas are the most common soft-tissue tumor of infancy. However, little is known about their pathogenesis. Our goal is to understand the signaling mechanisms that regulate infantile hemangioma development. We hypothesize that sustained Akt activation in endothelial cells is necessary for the development of hemangiomas, and inhibition of mammalian target of rapamycin (mTOR) activity, which is a major downstream effector of Akt, blocks the growth of hemangiomas.
Material and Methods: We generated double transgenic mice with tetracycline-inducible and endothelial cell-specific expression of constitutively active myristylated Akt (myrAkt) and grafted the skin from these mice onto immunocompromised nu/nu mice. Nu/nu mice were then taken off tetracycline to induce myrAkt expression. Some were treated +/− rapamycin (4 mg/kg/day) for 4 weeks. To set up explant cultures, infantile hemangioma tissue was cut into 2 mm^3 pieces, then placed between two layers of fibrin matrix, covered with media, and incubated for 7–10 days.
Results: There was increased Akt and mTOR activation in infantile hemangioma tissue and purified endothelial cells. Induction of endothelial myrAkt expression led to the development of hemangiomas in the skin grafts in nu/nu mice, whereas repression of myrAkt expression resulted in gradual regression/involution of these tumors. Treatment of skin graft recipients with rapamycin, an inhibitor of mTOR, resulted in a significant reduction in hemangioma growth. Furthermore, rapamycin also inhibited the outgrowth of cells in explant cultures of infantile hemangiomas. Investigation into the mechanism of rapamycin action in hemangiomas revealed that in addition to inhibiting S6 kinase, rapamycin also blocked Akt phosphorylation in both cultured human and mouse hemangioma endothelial cells, suggesting that rapamycin inhibition of Akt may in part account for its anti-angiogenic properties.
Conclusions: These findings indicate that Akt is necessary for hemangioma formation. Furthermore, they show the possible clinical utility of rapamycin as an angiogenesis inhibitor in the treatment of hemangiomas and other vascular tumors with hyperactivated Akt/mTOR, and support a novel pathway for rapamycin action via Akt inhibition.

552 POSTER

Integrated population pharmacokinetic analysis of temsirolimus in cancer patients following weekly IV treatments

J.P. Boni[1], S. Zhou[1], J. Burns[1], K. Smith[1], S. Liao[2]. *[1]Wyeth Research, Collegeville, PA, USA; [2]Pharmax Research, Somerset, NJ, USA*

Background: Temsirolimus (TEMSR), a novel anticancer agent, blocks activity of mammalian target of rapamycin (mTOR), a key mediator of cell signaling in the PI3K pathway. This inhibition blocks G1 to S phase transition of the cell cycle. Since pharmacokinetic (PK) variability may influence target signaling and patient (pt) response to treatment, an integrated population pharmacokinetic (PPK) analysis was performed to characterize the variability and to assess covariate effects of weekly IV TEMSR treatment for pts with advanced renal cell carcinoma (RCC).
Materials and Methods: PPK models for TEMSR and its major active metabolite sirolimus (SIR) were individually developed using NONMEM. Mechanistic description for TEMSR in blood and plasma used a 4-compartment model with saturable distribution to blood cells and peripheral tissue. For SIR, a separate, linear 2-compartment model with first-order input was used with factors for TEMSR dose (in mcg) based on structural parameters. PK data in healthy volunteers (following IV TEMSR 1–25 mg/wk), in pts with RCC receiving TEMSR alone or with interferon-alfa, and in pts with breast cancer (BrCA) (IV $\leqslant$ 250 mg/wk) yielded final data for TEMSR of 1153 observations from 90 subjects and for SIR of 1312 from 211 SIR subjects. Covariate factors included age, race, sex, weight, hematocrit, albumin, AST, ALT, bilirubin, creatinine clearance, concomitant interferon-alfa, and study protocol. Typical pt was a 49-year-old white man weighing 81.1 kg.
Results: TEMSR typical value expressions were TVCL (L/hr) = $116 \cdot (1 - 0.377\text{RAFL}) \cdot (1 - 0.619\text{BrCA})$ and volume of distribution plasma TVPL (L) = $9.92 \cdot (1 - 0.377\text{RAFL}) \cdot (1 - 0.619\text{BrCA})$ in which RAFL = 1 for nonwhites, 0 for whites; BrCA = 1 for BrCA and 0 for other studies. SIR apparent TVCL = $6.23 \cdot (\text{dose}/25000)^{0.527}(1 + 0.248\text{RCC})$ and TVV2(L) = $228 \cdot (\text{dose}/25000)^{-0.0265}(1 + 0.191\text{BrCA})$ in which RCC = 1 for RCC pts receiving TEMSR alone, 0 for other. Monte Carlo simulation was used