(SPC) from RHuT or RRT vaccinated mice were mixed with neu+ tumor cell lines and injected subcutaneously into the mammary fat pad of wt mice, a significant difference in tumor incidence was observed, being SPC from RHuT vaccinated mice the most effective. Immunohistochemical analysis revealed a clear differences in the type of the immune infiltrate in the tumor site. Mechanisms responsible for this kind of phenomena are under investigation.

Wednesday, 17 November 2010

Poster Sessions

Late breaking posters

4LB LATE BREAKING POSTER

A first synthesis of [18F]-lapatinib: a new agent for positron emission tomographic studies of kinase receptors

For full abstract, see p. 4.

5LB LATE BREAKING POSTER

Anti-tumor activity of MPC-9528, GMX1778 and APO866: Nampt inhibitors of three different structural classes

For full abstract, see p. 4.

6LB LATE BREAKING POSTER

The Nampt inhibitor MPC-9528 and the PARP inhibitor olaparib synergize in killing a BRCA-deficient cancer cell line

For full abstract, see p. 5.

Molecular-targeted therapies – preclinical

50 POSTER

A phase I study of the safety, tolerability and pharmacokinetics of pazopanib (P) in combination with gemcitabine (G) for advanced solid tumors

H. Richly[1], S.D. Rubin[2], A. Madi[3], M. Jeffels[3], B. Nokay[1], D. Gibson[2], S. Weller[4], M.E. Scheulen[1], R. Plummer[3]. *[1]West German Cancer Center, University of Essen, Essen, Germany; [2]GlaxoSmithKline, Oncology, Collegeville, USA; [3]Northern Centre For Cancer Care, Oncology, Newcastle, United Kingdom; [4]GlaxoSmithKline, Oncology, Research Triangle Park, USA*

Background: P (Votrient®), an oral angiogenesis inhibitor targeting VEGFR-1, -2, and -3, PDGFR-α and -β, and c-Kit, is FDA approved for advanced RCC. The combination of P + G is a novel regimen that may have broad clinical applicability.
Methods: Eligible pts had progressed on standard therapy, had adequate organ function, and received no prior anti-VEGF(R) therapy. A 3 + 3 dose escalation design was followed by an expansion phase. G was administered as a 30-min IV infusion on days 1 and 8 of each 21-day cycle at escalating dose levels (DL) of 1000 or 1250 mg/m^2. P was administered orally once-daily at escalating DLs of 400 or 800 mg. In the dose escalation phase, sparse sampling was performed to estimate peak and trough concentrations of P (C1D1: pre-dose and 3.5 h; C1D8 and C2D1 at pre-dose), and of G and its metabolite dFdU (C1D1 and C1D8 at pre-dose and end of infusion). In the cohort expansion phase, serial PK sampling was performed to characterize full PK profiles of G and dFdU with G given alone (C1D1) and in combination with P (C2D1). 24-hour P PK was determined on C2D1.
Results: 22 pts were enrolled; common tumor types were melanoma n = 8, NSCLC n = 4; CRC n = 4. The most frequent drug-related AEs (as a % of all pts) were fatigue 68%, neutropenia 59%, nausea 55%, anorexia 50%, and thrombocytopenia 41%. Most common Gr 3/4 AEs (as a % of all pts) were neutropenia 45% and thrombocytopenia 18%. Gr 3 (without Gr 4 observed) AEs were ALT increase 18%, and 9 % each for: lymphopenia, fatigue, diarrhea, abdominal pain, hyperbilirubenia. A non-neutropenic pt in DL 0 with sarcoma metastatic to lungs died of pneumonia at Day 105. Mean DIs of P and G for each DL are listed in Table. DL 2 was expanded to 13 pts to further assess tolerability. PK analysis indicates that systemic exposures of P, G, and dFdU in both dose escalation and cohort expansion phases appeared consistent with historical data. Comparison of G and dFdU PK parameter ratios (C2D1/C1D1) in expansion phase indicates P has no effect on the PK of G or dFdU. Best responses were: 1 PR (melanoma), 14 SD, 4 PD, 3 UNK. Durable disease control was observed with various tumor types; cholangiocarcinoma (cycle 17), melanoma (cycle 14), CRC (cycle 12).
Conclusions: P + G appears clinically active and tolerable for extended periods. Although an MTD was not reached, based upon analysis of tolerability as a function of DI, P 800 mg daily + G at 1000 mg/m^2 on days 1 and 8 every 21 days will be tested in phase II studies.
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Dose level (n)	P (mg) daily	G (mg/m^2 d1, 8 q21 d cycle	Mean (%) P/G dose intensity (DI)	No. of subjects/ type of DLT
0 (n = 6)	400	1000	92.4/79.7	1/Gr 4 thrombocytopenia
1 (n = 3)	800	1000	81.7/83.1	0/
2 (n = 13)	800	1250	94.9/86.1	1/Gr 3 fatigue

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Deacetylation and inactivation of peroxiredoxin by SIRT2 increases sensitivity of breast cancer cells to oxidative stress

V. Coothan Kandaswamy[1], J. Chen[1], W. Fiskus[1], R. Rao[1], S. Nalluri[1], K. Buckley[1], R. Balusu[1], K. Bhalla[1]. *[1]Medical College of Georgia, Cancer Center, Augusta, USA*

SIRT2, the mammalian ortholog of yeast *Hst2,* is a predominantly cytosolic and nuclear member of the class III, NAD+ dependent, histone deacetylase family. In the cytosol, SIRT2 co-localizes with microtubules and deacetylates α-tubulin at the lysine-40, indicating a role in proper cytokinesis. Here, we determined the other biologically important SIRT2 targets and their functions. In HEK293 cells, knockdown of SIRT2 followed by differential in-gel electrophoresis of the cytosolic extract and mass spectrometric analysis identified several significantly hyper-acetylated proteins, including peroxiredoxin 1. Peroxiredoxins (PXDs) are ubiquitous family of evolutionarily conserved, thiol-dependent peroxidases, which catalyze the reduction of hydrogen peroxide (H2O2). SIRT2 co-immunoprecipitated with PXD1, and ectopic over-expression of SIRT2 deacetylated PXD1 in HEK 293 cells. While hyperacetylation activates, deacetylation is known to inhibit the antioxidant activity of PXD1. Ectopic over-expression of SIRT2, but not the catalytically dead SIRT2 mutant, markedly increased intracellular reactive oxygen species (ROS) levels and increased ROS-induced DNA damage (determined by comet assay), as well as increased the sensitivity of the human breast cancer MCF7 and MDA MB231 cells to oxidative stress induced by H2O2. SIRT2 over-expression also significantly increased the sensitivity to ROS-inducing agents such as arsenic trioxide and menadione. Ectopic over-expression of SIRT2 induced FOXO3a and BIM levels, which was associated with increased caspase-3 activity and apoptosis of breast cancer cells. Additionally, wild type zebrafish embryos 48 hours post-fertilization were treated with 1.0 mM of splice-blocking morpholino (MO) targeting the exon 6 of the SIRT2 pre-mRNA versus the mismatch-control MO and/or 3.0 mM of H2O2. Exposure of zebrafish embryos to control MO and H2O2 increased ROS and produced cardiac edema and abnormal body curvature. In contrast, knockdown of SIRT2 in the zebrafish embryos decreased H2O2-induced ROS levels and abrogated ROS mediated cardiac edema and abnormal body curvature. These in vitro and in vivo findings demonstrate that SIRT2 regulates PXD1 acetylation and sensitivity to oxidative stress. These results also highlight the possibility that increased SIRT2 levels and activity can be therapeutically exploited for augmenting antitumor effects of agents that induce cancer cell death by increasing intracellular ROS levels.

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Discovery of novel fused thiadiazoles as potent inhibitors of phosphoinositide-3-kinase (PI3K) and/or the mammalian target of rapamycin (mTOR)

J. Pastor[1], G. Kurz[1], M.R. Rico Ferreira[1], D. Soilan[1], M.A. Ortega[1], S. Martinez[1], O. Rabal[1], I. Palacios[1], A. Cebria[1], J.R. Bischoff[1]. *[1]Spanish National Cancer Research Centre, Experimental Therapeutics, Madrid, Spain*

Several inhibitors of phosphoinositide-3-kinase (PI3K) are currently being evaluated in early clinical studies for their ability to block PI3K/Akt pathway signaling that is found to be activated in many tumors. Here, we disclose a novel series of PI3K inhibitors based on fused thiadiazole bicycles and present their synthesis, structure–activity and structure–property relationships. We identified analogs with potent PI3K activity in the low nanomolar range and discuss their cross-reactivity with Flt3 as well as their cellular activity.
The mammalian target of rapamycin (mTOR), a class IV PI3K protein kinase, is - like PI3K itself - an important regulator of cell growth