combination of C225 and L-OHP did not induced significant inhibition of tumor growth compared to single agent L-OHP or C225.
These results suggest that EGF-R blockade by C225 combined with L-OHP may be an effective therapy against some chemo refractory colorectal carcinoma tumors. In our models, the response is strictly dependent on the cell type and not correlated to the level of EGF-R expression suggesting ongoing experiments to characterize EGF-R dependant-pathway.

379 POSTER

Characterisation of a novel class I isoform selective phosphatidylinositol 3-kinase inhibitor in glioma

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The phosphatidylinositol 3-kinase (PI3K) signalling pathway regulates multiple cellular processes often deregulated in cancer, including survival, proliferation, motility and cell cycle progression. Consequently, the PI3K pathway is highly attractive for therapeutic intervention. Glioma (primary brain tumour) cell lines represent a relevant model for the investigation of PI3K inhibitors as both cell lines and patient tumours often exhibit aberrant upregulation of the pathway, with a high frequency of *PTEN* (the negative regulator of downstream PI3K signalling) and *p110* α (a class IA isoform of the PI3K catalytic subunit) mutations. In addition, there is a pressing need for new glioma therapies as current treatments only have limited success. Here we describe the effects of PI-103, a novel PI3K inhibitor with potent activity against the PI3K class I isoforms (previously described by *Patel et al.*, Proc. Am. Assoc. Can. Res. 45: supp. p111) in a panel of six high-grade human glioma cell lines with defined molecular characteristics (LN229, U87MG, U138MG, U118MG, A172 and SF268). PI-103 demonstrates potent anti-proliferative effects throughout the cell line panel, with cellular IC_{50} values at 96 hours in the 0.13–0.53 μM range by contrast with 10–15 μM for the broad spectrum PI3K inhibitor, LY294002. The sensitivity of glioma cells within the panel to PI-103 and LY294002 is independent of the *PTEN* status of the lines. However, all the lines have high constitutive levels of phospho-Akt (Ser^{473}) compared to most non-glioma derived cancer cell lines suggesting potential activation of the PI3K pathway by varied mechanisms. Treatment of the glioma lines with PI-103 for 24 hours causes inhibition of downstream signalling as demonstrated by decreased phospho-Akt (Ser^{473}) levels and Akt kinase activity. Interestingly, growth inhibition caused by PI-103 occurs by a cytostatic (G1 cell cycle block and growth arrest) mechanism whereas LY294002 tends to be both cytostatic and cytotoxic as demonstrated by flow cytometry and the cleavage of PARP by apoptotic proteases. The role of specific PI3K isoforms in glioma is currently being explored using siRNA knockdown of p110α and p110β. In summary, these results show PI-103 is a potent anti-proliferative compound in a glioma cell line panel, highlighting the promising therapeutic potential of targeting class I PI3K isoforms for the treatment of glioma.

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Analysis of complex PKB/Akt signaling pathways in human prostate cancer samples

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Background: The protein kinase B/Akt (PKB/Akt) system is of key importance for cell survival and proliferation. Due to its crucial role for survival PKB/Akt is also of major relevance for the pathogenesis and modulation of treatment response of malignant tumors. The PKB/Akt system is found to be dysregulated in several tumors in vivo and in vitro. In order to more precisely define the role of the PKB/Akt system in prostate cancer we determined the expression level and the putative activation status of PKB/Akt and downstream targets in prostatectomy specimens from 22 patients with prostate cancer (PKB/Akt; phos-PKB/Akt, FKHR-L1; phos-FKHR, mTOR; phos-mTOR; GSK3b, phos-GSK3a/b; 4E-BP1, phos-4E-BP1, p27-kip1, phos-eIF4G).
Material and Methods: Tissue samples were initially scored regarding the pathological grade (Gleason) and subsequently analyzed by immunohistochemistry using specific antibodies directed against all of the proteins and the respective specifically phosphorylated forms as listed above. The expression pattern was examined regarding any putative correlation with the Gleason grade. In addition the hierarchical composition of the assumed signaling cascade was analyzed.
Results: All tissue samples with a Gleason 5–10 displayed a significant expression and strong phosphorylation level of PKB/Akt. In some cases of Gleason 5–6 a consecutive phosphorylation of downstream targets was detectable. For this subgroup a notable overexpression but not phosphorylation of the eucaryotic initiation factor 4E binding protein was found. In the majority of specimens with more aggressive Gleason grades (7–10) the consecutive activation of most downstream targets was seen. Similarly to the low grade Gleason tumors overexpression of eucaryotic initiation factor 4E binding protein was detectable. Analysis of the surrounding normal tissue revealed a highly reproducible loss of a strongly phos-FKHR expressing basal cell layer in the malignant compared to the normal glandular structures.
Conclusions: The data prove that a dysregulation of the PKB/Akt system is a common finding in patients with prostate cancer. However, we found a substantial heterogeneity in the expression and phosphorylation levels of the upstream molecule (PKB/Akt) and even more of the putative downstream targets of the kinase. The most common denominator of the malignant gland is the loss of the phos-FKHR expressing basal cell layer and the overexpression of 4E-BP1 in malignant glandular structures.

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A phase I study of BAY 43-9006, a novel Raf kinase and VEGFR inhibitor, in combination with taxotere in patients with advanced solid tumors

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Background: The objective of this study was to determine the safety profile and pharmacokinetics (PK) of BAY 43–9006 (BAY), a novel dual action Raf kinase and VEGFR inhibitor, in combination with capecitabine (CAP).
Materials and Methods: This was a single-center, dose-escalation study. BAY was given orally bid from Day 8 until Day 21 in Cycle 1, and continuously thereafter in three doses: 200 mg bid (cohort 1), 400 mg bid (cohort 2) and 200 mg bid for the first two cycles, then 400 mg bid for subsequent cycles (cohort 3, ongoing). CAP was given orally bid (2100 mg/m* per day) from Day 1 in a 2 weeks on/1 week off schedule. PK parameters were determined on Day 21 of Cycle 1 and on Day 7 of Cycle 2 for BAY, and on Day 7 of Cycles 1 and 2. for CAP.
Results: Twenty patients were enrolled, 19 of whom were evaluable (cohort 1: n=12; cohort 2: n=4; cohort 3: n=3). Common tumor types were renal cell carcinoma (RCC; n=6) and colorectal cancer (CRC; n=4). The median number of treatment cycles for all cohorts was 5.5 (range 0–22), including one patient with RCC (22 cycles) and one patient with CRC (21 cycles). The most frequent drug-related toxicities were hand-foot syndrome (HFS), diarrhea, fatigue, mucositis and nausea. Dose-limiting toxicities included HFS grade 3 and diarrhea grade 3 (cohort 1), HFS grade 3 and mucositis grade 3 (cohort 2). All four patients in cohort 2 discontinued the planned regimen after the first or second cycle due to anorexia grade 2 and weight loss grade 2 (1 patient), HFS grade 3 and mucositis grade 3 (1 patient), epigastric pain grade 2 and HFS (1 patient), and dyspnea grade 2 (1 patient). Treatment is ongoing in all patients in cohort 3. One heavily pretreated patient from cohort 1 with breast cancer and skin lymphangitis showed tumor regression. The plasma PK of BAY were not influenced to a clinically relevant degree by concomitant administration of CAP. Multiple dosing with BAY 43–9006 200 mg bid had no relevant effect on the PK profile of CAP.
Conclusions: BAY in combination with CAP resulted in a safety profile consistent with that of the individual agents. However, CAP 2100 mg/m* per day combined with BAY 400 mg bid led to a significant rate of patient discontinuations. Therefore, two further cohorts are ongoing: CAP 2100 mg/m* per day plus BAY 200 mg bid for two cycles then 400 mg bid thereafter, and CAP 1700 mg/m* per day plus BAY 400 mg bid. Final data on four cohorts will be presented.

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Phase II antitumor activity of BAY 43-9006, a novel Raf kinase and VEGFR inhibitor, in patients with sarcoma enrolled in a randomized discontinuation study

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Introduction: BAY 43–9006 (BAY) is a novel, orally active Raf kinase and VEGFR inhibitor with broad-spectrum anti-tumor efficacy in multiple human tumor xenografts.