tumor models. G3139 (Genasense, oblimersen sodium; Genta Inc., Berkeley Heights, NJ) is a phosphorothioate oligonucleotide complementary to bcl-2 mRNA. Treatment with G3139 can reduce Bcl-2 protein levels in vivo. Since Bcl-2 overexpression is thought to contribute to chemotherapeutic resistance, Bcl-2 suppression by G3139 may enhance the anti-tumor efficacy of standard cytotoxic chemotherapy. We have previously reported that a combination of G3139 and paclitaxel led to prolonged stable disease in a small number of patients with advanced chemorefractory SCLC. Here we report initial results of a phase I study evaluating the combination of G3139, carboplatin, and etoposide in patients with previously untreated extensive stage SCLC. Eleven patients have been treated to date in 3 dose cohorts. The primary goals of this study are to assess toxicity and to determine a maximally tolerated dose for this combination. Cohort 1 initially received G3139 5 mg/kg/d IVCI days 1-8 on a 21 day cycle, with carboplatin AUC=6 on day 6 and etoposide 80 mg/m^2/d, days 6-8. Of the 4 patients evaluable for toxicity in cohort 1, 2 developed grade 4 neutropenia in cycle 1. Cohort 2 was initiated at identical G3139 and etoposide doses, with carboplatin dose reduced to AUC=5. One patient in each of the first two cohorts elected to discontinue therapy before completing cycle 1. All other patients in both dose cohorts have completed 6 cycles of therapy. In cohort 2, 0 of 4 patients experienced cycle 1 DLT. Several patients did require dose delays in later cycles due to hematologic toxicity. This may be due to the truncation of days from last chemotherapy to next cycle from 19 to 14 because of the 5-day lead-in period of G3139 administration. No non-hematologic toxicities > grade 2 have been attributed to therapy. Enrollment is continuing in cohort 3, with G3139 7 mg/kg/d, carboplatin AUC=5, and etoposide 80 mg/m^2 × 3; 2 patients in this cohort are in cycle 3 and 4, respectively. Overall, in 9 patients evaluable for response, we have documented PR in 7, and SD in 2. Final toxicity and clinical outcome data will be presented. The phase II dose will be tested in a randomized trial within the CALGB.

493B

G3139 (Genasense; Oblimersen) induces production of reactive oxygen species and hydrogen peroxide in human prostate and bladder carcinoma cells in a backbone and cpg-dependent manner

C.A. Stein[1], J. Lai[1], L. Benimetskaya[1], J. Jepsen[2]. [1] *Columbia University, Medicine and Pharmacology, New York, USA;* [2] *Danish Cancer Institute, Copenhagen, Denmark*

PC3 and T24 cells, when treated with 400 nM G3139/Lipofectin or Oligofectin, produce reactive oxygen species (ROS) and H2O2, as measured flow cytometrically by hydrethidium-ethidium and fluorescence and The production of ROS and H2O2 were measured flow cytometrically by hydroethidine to ethidium oxidiation and 2'-7'-dichlorofluorescein fluorescence, respectively. The increase in ROS and H2O2 were is as much as 500% and 250% respectively, vs. untreated cells after 72 h incubation. Maximum generation of ROS and H2O2 was observed after 72 hours, and near maximal generation as long as 5 days after initial incubation, and at a 200 nM oligo concentration, but no lower. A control oligo, 4126, (a two base mismatch of G3139 in which the two CpG motifs are eliminated), produced only a small increase in ROS and H202 production (<50%). However, the mechanism of production was unlike that in immune cells because cells treated with naked oligo (5 microM) did not increase ROS or H2O2 production. Treatment of cells with 2006, a 24mer phosphorothioate triple tandem repeat of an optimized CpG motif (GTCGTT) did not downregulate bcl-2 expression, but did induce ROS and H2O2 production to the same extent as G3139, indicating that bcl-2 downregulation did not cause the increase in production. Confirming this observation, we found that oligo 2009, which is directed to the coding region of the bcl-2 mRNA, downregulated the expression of bcl-2 protein to the same extent and with identical kinetics as G3139, yet did not induce the production of ROS and H2O2. Elimination of the increase in production of ROS and H2O2 could be accomplished by either cytosine C5-methylation, or even more dramatically by C5-propynylation of both of the CpG motifs of G3139. The rate of growth of cells treated with either of these two oligomers (which do not induce the production of ROS and H2O2) was approximately identical to those cells treated with 2009 or 4126 (both of which do not), and much faster than those cells treated with either G3139 or 2006 (both of which do, although the latter does not downregulate the expression of bcl-2). However, 4126 could be transformed into an ROS and H202 producing oligo by modification of the backbone with five LNA (locked nucleic acid) linkages at the 3' and 5' positions. Thus, it appears that there is a CpG directed, non-bcl-2 dependent induction of production of ROS and H2O2 in PC3 and T24 cells that strongly affects the rate of cell growth.

Monoclonal antibodies and immunoconjugates

494

A new Tc-99m labelled somatostatin analogue (Tc-99m EDDA-TRYCINE-HYNIC-TOC) for receptor imaging: first clinical results before and during radioreceptor therapy with Y-90 DOTATOC

R.P. Baum[1], M. Schmücking[1], S. Fischer[1], C. Przetak[1], A. Niesen[1], H.R. Mäcke[1]. [1] *Zentralklinik Bad Berka, Dept. of Nuclear Medicine / PET-Center, Bad Berka, Germany;* [2] *Kantonsspital Basel, Radiochemistry Laboratory, Basel, Switzerland*

Aim: Radioreceptor therapy using radiolabelled peptides is a promising new approach for the treatment of neuroendocrine tumors. We evaluated Tc-99m EDDA-TRYCINE-HYNIC-TOC (TET-H-TOC) in patients with somatostatin receptor (SSTR)-positive tumours (staging, dosimetry and follow-up).
Methods: The Tc-99m labelled somatostatin analogue was synthesized in our pharmaceutical lab using lyophilized kits (radiochemical purity by HPLC, TLC >95%, product stability *in vitro* 4 to 6h). So far, 46 patients (53 examinations) were studied after injection of 580-890 MBq (median 673 MBq) TET-H-TOC. The histologically proven tumours were endocrine neoplasias, renal carcinomas, bronchial carcinoma, mesothelioma and malignant fibrous histiocytoma. The imaging protocol consisted of whole-body scans and planar images of the tumor region (15 min, 1h, 2h, 4h, 8h, 24h p.i.) and additionally SPECT-images (1h und 4h p.i.). For semi-quantitative assessment, individual regions of interest (ROI) were drawn in order to generate time-activity curves and to calculate tumour-to-tissue/background ratios. Pharmacokinetic analysis was carried out (radioactivity kinetics in plasma and urine). In some selected patients, image fusion of the whole-body scans was performed with CT and/or MRT and/or PET using a HERMES computer.
Results: 7 out of 46 patients showed an intense tracer accumulation in the SSTR-positive tumours (visual 3+, tumour / background ratio >2.5). In these patients, radioreceptor therapy was carried out using Y-90 DOTATOC (simultanous injection von 150 MBq In-111 DOTATOC). All pretherapeutic scans with the Tc-99m labelled ligand (4h p.i.) showed a similar overall pattern of biodistribution and tumour uptake in comparison to the therapy scans with In-111/Y-90 DOTATOC (24h p.i.). The Tc-99m EDDA-HYNIC-TOC scans (incl. SPECT) offered superior imaging properties with earlier tumour visualisation (all lesions were detected 1h p.i.) as compared to the In-111 labelled analogue. Hence, the receptor scintigraphy with Tc-99m EDDA-TRYCINE-HYNIC-TOC enables to select patients suitable for radioreceptor therapy with Y-90 DOTATOC.
Conclusion: Our results demonstrate the ability of Tc-99m EDDA-TRYCINE-HYNIC-TOC for receptor scintigraphy of SSTR-positive tumours with superior image performance as compared to In-111 labelled SST-analogues (staging), for an individual selection of patients suitable for a radioreceptor therapy with Y-90 DOTATOC (dosimetry) and for post-therapeutic control.

495

Cetuximab (C225, Erbitux) in combination with irinotecan, infusional 5-fluorouracil (5-FU) and folinic acid (FA) is safe and active in patients (pts) with metastatic colorectal cancer (CRC) expressing epidermal growth factor-receptor (EGFR). Results of a phase I study

P. Schöffski[1], C.-H. Lutz[2], G. Folprecht[3], T. Seufferlein[2], C. Haag[3], G. Beutel[1], M. Muser[4], J.-P. Marschner[4], C.-H. Kohne[3]. [1] *Hannover Medical School, Hannover, Germany;* [2] *University Hospital Ulm, Ulm, Germany;* [3] *University Hospital Dresden, Dresden, Germany;* [4] *Merck KGaA, Darmstadt, Germany*

C225 is a chimeric antibody targeted against EGFR with activity in refractory CRC. Our current phase I trial evaluates the feasibility and safety of C225 combined with irinotecan and weekly infusional 5-FU/FA (modified AIO-regimen) as 1st-line treatment for pts with CRC. 24/27 screened tumors were found positive for EGFR by immunhistochemistry, and 21 positive pts entered the trial. None of them had previous palliative chemotherapy or relevant organ dysfunction. After a loading dose of 400 mg/m^2 i.v., C225 was given weekly at a dose of 250 mg/m^2 i.v. Chemotherapy was administered weekly × 6, followed by 1 week rest, and consisted of irinotecan 80 mg/m^2, FA 500 mg/m^2 and 5-FU 1500 mg/m^2/24h (low dose group) or 2000 mg/m^2/24h (high dose group). Dose limiting toxicity (DLT) was defined as neutropenia or skin toxicity >grade 3, neutropenia/leukopenia with fever;