shown responses ranging from regression to tumor stasis and growth delay. CHIR 200131 has an absolute oral bioavailability of > 90% in mice and rats, 17% in dogs, and 28% in monkeys. The apparent elimination t* ranged from 1.5 to 5.5 hours in plasma following an IV dose. In general, this compound exhibited high plasma clearance relative to hepatic plasma flow and was also widely distributed as indicated by a large V_{ss} relative to total body water in each species evaluated. Tissue concentrations were higher than those in plasma following a single or multiple oral doses in mice and rats. Maximum plasma and tissue concentrations occurred between 2 and 4.5 hours and following T_{max}, tissue concentrations declined in parallel with those in plasma. After multiple dosing in a human colon tumor xenograft model at 30 mg/kg (ED_{50}), plasma concentrations of approximately 500 ng/mL were obtained 2 hr post-dose and by 24 hr were generally undetectable. However, tumor concentrations of CHIR 200131 were 15 fold higher than plasma at 2 hr and at 24 hr significant levels remained. Multiple dose plasma pharmacokinetics in mice, rats, and monkeys demonstrated time- and dose-independent pharmacokinetics. These data indicate that CHIR 200131, with its combined cytostatic and antiangiogenic activities, has potential as an effective therapy for solid and metastatic tumors.

197

Potent *in vivo* activity of MCR peptides against chemotherapy-resistant human small cell lung cancer (SCLC)

R.T. Radulescu[1], G. Jaques[2]. [1]*Molecular Concepts Research (Mcr), Muenchen, Germany;* [2]*Philipps-Universitaet, Marburg, Germany*

Previous studies had shown that MCR peptides containing retinoblastoma protein (RB) fragment LFYKKV suppress human non-small cell lung cancer growth (NSCLC) *in vivo*. Since the current prospects for an efficient treatment of human small cell lung cancer (SCLC) are even poorer than those for an effective therapy of NSCLC, we have now also investigated the performance of MCR peptides against human SCLC xenografts in nude mice. As such, we chose the human RB-negative SCLC cell line H82 as a model. A first *in vivo* experiment performed with the MCR peptide coined MCR-4 (sequence: (all-D) LFYKKVRQIKIWFQNRRMKWKK, molecular weight (MW): 3026) showed that this compound is active against s.c. H82 tumors that had been allowed to reach a large size (ca. 400 mm3) before treatment was initiated (this tumor size was attained after 12 days from the initial inoculation of 10 million H82 cells s.c. into each nude mouse). Specifically, MCR-4 achieved 67% tumor growth inhibition vs. controls when injected i.p. at 10 mg/kg every other day over a 2-week-period (i.e. in altogether only 7 doses). In contrast, the chemotherapeutic etoposide (MW: 589), also known as VP-16, when administered at 1 mg/kg i.p. every other day over the same time period was found to have no significant activity in this *in vivo* test. In a different experiment, another MCR peptide termed MCR-14 (sequence: (all-D) KRKRSPVRSLFYKKVYRLAPKT, MW: 2722) at a dose of 5 mg/kg and given via the i.p. route daily over 10 days also performed excellently against s.c. H82 lung tumors by causing about a 70% growth inhibition whereas the chemotherapeutic VP-16 at 1 mg/kg i.p. was again completely inactive. This MCR-14 performance is particularly remarkable given that the 5 mg/kg dose is usually rather a suboptimal dose for an MCR peptide. In contrast, VP-16 failed against H82 tumors which markedly differs from its effectiveness at the same dose against A549 NSCLC tumors in previous tests we had conducted and reported. Taken together, our data suggest that RB-negative SCLC could be a well-suited target tumor for a successful MCR peptide therapy in a clinical setting. Furthermore, our results indicate that MCR peptides should be tested as therapeutics against other RB-negative tumors as well since these tumors frequently display chemoresistance and, moreover, are not treatable with the novel type of agents termed cyclin-dependent kinase (cdk) inhibitors that, by their nature, are active only in RB-positive tumor cells.

198

Antitumor activity of the epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) ZD1839 ('Iressa'), alone or combined with gemcitabine and vinorelbine platinum-based chemotherapy, in human non-small-cell lung cancer (NSCLC) xenografts

R. Bras-Gonçalves[1], K. Boye[2], A. Livartowski[1], A. Chapelier[3], H. Magdelenat[1], P. de Cremoux[1], R. Defrance[4], M.-F. Poupon[2]. [1]*Institut Curie, Section Médicale, Paris, France;* [2]*Institut Curie, Section de Recherche, Paris, France;* [3]*Hôpital Marie Lannelongue, Plessis-Robinson, France;* [4]*AstraZeneca, Rueil-Malmaison, France*

Objectives: The benefit of chemotherapy in NSCLC remains modest. High expression of EGFR in NSCLC provides an opportunity to improve chemotherapy by combination with anti-EGFR compounds. ZD1839 ('Iressa') is an orally active, selective EGFR-TKI undergoing clinical evaluation in a range of tumor types, including NSCLC. This *in vivo* study aimed to evaluate the benefits of ZD1839, alone or combined with standard platinum-based chemotherapy, using NSCLC human xenografts.
Methods: Five NSCLC biopsies with different levels of EGFR mRNA (1 squamous carcinoma and 4 adenocarcinomas) were obtained from pts and grown as subcutaneous xenografts in nude mice. Two chemotherapy regimens were used: either cisplatin (CDDP, q 3 wks) + gemcitabine (GZ, wkly) at doses of 0.5 and 60 mg/kg ip, respectively, or CDDP (q 3 wks) + vinorelbine (VNR, q 10 d) at 0.5 and 1 mg/kg ip, respectively. ZD1839 was given po at doses of 40 or 120 mg/kg daily for 2 wks, alone, or at 120 mg/kg when combined with chemotherapy. Individual tumor growth rate was measured and % tumor growth inhibition (TGI) was calculated by comparison with control mice.
Results: ZD1839 alone produced significant responses in 4/5 tumors, with mean TGIs of the tumor IC8 of 63 and 40% at high and low dose, respectively. At the high dose, TGIs of the other NSCLCs were 27, 54, 64 and 80%. Response to ZD1839 occurred independently of EGFR expression or histology. Three NSCLCs (IC8, LC131, IC9) responded to CDDP/GZ with TGIs of 40, 41 and 90%, 1 (LC131) was improved by ZD1839. Two NSCLCs did not respond to CDDP/GZ alone, but 1 (IC14) showed marked response to CDDP/GZ + ZD1839 (mean TGI 77%). The CDDP/VNR regimen alone produced a significant response in only 1 NSCLC (IC8), not improved by ZD1839. A marked TGI of LC131 was observed when CDDP/VNR was given with ZD1839 (mean TGI 63% vs 12 or 54% with CDDP/VNR or ZD1839 alone, respectively). No improvement of TGI of IC1 was obtained by combination with ZD1839.
Conclusions: These results suggest that ZD1839 has a significant benefit in NSCLC, independent of histological type and EGFR expression levels of the tumor. The NSCLC xenografts selected had different although modest responses to standard chemotherapy. The CDDP/GZ regimen was the most active, but ZD1839 did not potentiate its efficacy except in tumors insensitive to chemotherapy alone. The CDDP/VNR regimen was inactive, even when combined with ZD1839. 'Iressa' is a trademark of the AstraZeneca group of companies

199

Functional characterization of novel epidermal growth factor receptor(EGFR) and HER2 inhibitors based on pyrrolo[2,3-d]pyrimidinone structure

S. Gilbert[1], C. Schaechtele[2], H. Weinberger[3], T. Reissmann[4]. [1]*Baxter Oncology GmbH, Pharmacology/Molecular Biology, Frankfurt / Main, Germany;* [2]*ProQinase GmbH, Freiburg, Germany;* [3]*Baxter Oncology GmbH, OCE, Frankfurt / Main, Germany;* [4]*Baxter Oncology GmbH, Pharmacology/ Molecular Biology, Frankfurt / Main, Germany*

Overexpression of epidermal growth factor receptor family members has been implicated in a variety of tumors including breast, lung and ovarian. This overexpression is associated with tumor aggressiveness and poor patients prognosis, partly due to an impaired response of cancer patients to chemotherapy. Therefore blockage of EGFR (HER1) and HER2 signaling by small-molecule compounds is a beneficial therapeutic approach to induce growth inhibition of human carcinoma cells. We have investigated the potency and specificity of two 5,7-dihydro-pyrrolo[2,3-d]pyrimidin-6-one derivatives, namely D-69491 and D-70166, in respect of tyrosine kinase inhibition and carcinoma cell proliferation. In biochemical assays the kinase activities of HER1, HER2 and HER4 were inhibited with IC_{50} values in nanomolar range. Inhibition of HER1 and HER2 phosphorylation was confirmed by western blot analysis of inhibitor-treated A431 epidermoid carcinoma cells and HER2-overexpressing NIH3T3 cells. Both inhibitors impaired ligand-stimulated HER1 and HER2 phosphorylation in a