fever, non-hematologic toxicity grade 3–4 and any treatment delay due to toxicity.

Results: All patients were evaluable for toxicity and the DLT dose level has not yet been reached. A total of 61 cycles have been administered (median 2 cycles/pt), with 5 (8%) cycles complicated by grade 2 neutropenia, 3 (5%) grade 2–4 anemia, no grade 2–4 thrombocytopenia, 12 (20%) grade 2–3 asthenia and 2 (3%) grade 3 neurotoxicity. Seven cycles (11%) have been delayed due to toxicity. No febrile neutropenia has been observed.

Dose level	Caelyx	L-OHP	Pts	DLT	Toxicities
1	25	80	3	–	–
2	30	80	3	–	–
3	30	90	3	–	–
4	35	90	6	2	G2 neutropenia (Tx delay)
5	35	100	3	1	G3 neurotoxicity

Conclusion: The combination of Caelyx and L-OHP is well tolerated with acceptable toxicity. The study is ongoing to determine the MTD.

269 POSTER

Gemcitabine, Docetaxel and Carboplatin triplet: a phase I dose-finding study with and without filgrastim (G-CSF) support

C. Belani, G. Long, R. Ramanathan, T. Evans, M. Earle, M. Capozzoli, D. Trump. [1] *University of Pittsburgh Cancer Institute, Medicine, Pittsburgh, USA*

Gemcitabine(G), docetaxel(D), and carboplatin(C) have a wide spectrum of activity against solid tumors. This phase I study was designed to determine the maximally tolerated dose (MTD) and dose-limiting toxicity (DLT) of G+D+C chemotherapy administered with and without G-CSF support. G(day1,8) + D(day1) + C(day1) were administered every 21 days. Twenty patients (7F, 13M), median age 57 (28-77 years), with a variety of solid tumors have been treated. At dose level I(G 600mg/m2 + D 65/mg/m2 + C AUC=5), the first 2 pts experienced DLT

(grade [gr] 4 thrombocytopenia, with one febrile neutropenia [FN] and fatal sepsis). Dose level 0 was then established with reduction of the D dose (55mg/m2); 1/6 evaluable pts experienced DLT (gr. 4 thrombocytopenia & FN). Gr. 4 neutropenia was frequently observed at this level, but was generally short lasting. With G-CSF, dose level I was safely administered (0/3 DLT). At dose level II + G-CSF, 2/6 evaluable patients experienced DLT with gr. 4 thrombocytopenia. Of 12 evaluable pts, there were 4 partial responses, two in patients with pancreatic cancer, one in a patient with SCLC, and one in a patient with unknown primary. Eight patients are not evaluable for response (5 with DLT, 1 death from progressive disease within 1 week of treatment, 1 refused further treatment after D1, and 1 patient is currently being treated). This regimen is associated with notable myelosuppression, but is otherwise fairly well tolerated and is highly active. The recommended phase II doses in this combination regimen without G-CSF, are D 55 mg/m2, G 600 mg/m2 and C AUC=5. With the addition of G-CSF, the recommended phase II doses are D 65 mg/m2, G 600 mg/m2 and C AUC=5. Supported in part by Eli-Lilly, Aventis and Amgen.

270 POSTER

A Phase I/II study of dose-escalated docetaxel given two weekly in combination with a fixed dose of G-CSF

K. Hoekman[1], H.M. Pinedo[2]. [1] *VUmc, Dpt. of Medical Oncology, 10-East, Amsterdam, The Netherlands;* [2] *VUmc, Dpt. of Medical Oncology, 10-East, Amsterdam, The Netherlands*

Docetaxel has an established activity in different cancer types. Dose limiting toxicity is neutropenia and asthenia, which is reason to investigate the toxicity of different treatment schedules and the effect of specific support.

Purpose: To determine the MTD of docetaxel q 2wks in combination with G-CSF.

Patients and Methods: 25 patients with progressive and advanced malignancies and an anticipated sensitivity to docetaxel were included. Tumor distribution: breast cancer(15) bladder cancer(6),lung cancer(2),stomach cancer(1) and ovarian cancer(4). All patients were pretreated, one patient with paclitaxel. Further patient characteristics: 20 female/5 male; median age 52 years; PS was 0, 1 or 2. Docetaxel was administered q 2wks in a 1hr infusion. The dosis of docetaxel was escalated from 60 (7 patients), to 70 (7 patients) to 80 (11 patients) mg/m2. G-CSF (Lenograstim) 263 mcg s.c.was given from day 2-12. On day -1, 0 and +1 dexamethason 8 mg was taken two times daily orally. A minimum of 6 cycles was scheduled, unless disease progression or unacceptable toxicity occurred earlier. Every 3 cycles evaluation of response was performed.

Results: 16 patients completed at least 6 cycles; 6 stopped earlier because of progressive disease, 2 stopped after 4 courses because of toxicity (1SD,1PR), and 1 because of sepsis, most probably not related with docetaxel therapy. Hematological toxicity grade 3-4 was not observed in any patient during 160 cycles docetaxel. Alopecia was present in all patients after 3 cycles and nail changes cumulated with further treatment. At level 60 mg/m2 1/7 patient experienced asthenia grade 3 after 3 cycles, but completed 6 cycles. At level 70 mg/m2 1/7 patient experienced asthenia grade 2-3, but completed 6 cycles, and another patient stopped after 2 cycles because of sepsis. At level 80 mg/m2 4 patients (1PR/1SD/2PD) stopped therapy after 2, 3, 4, and 4 cycles, one patient because of toxicity. The other 7 patients except one experienced grade 2-3 asthenia, 2 developed edema in the arm at the mastectomy side, and 2 peripheral edema. These toxicities became evident after 6 cycles and prohibited further dose escalation. 9/15 patients with breast cancer and 2/2 with lung cancer had a PR; the patients with other tumor types did not response.

Conclusions: 2-weekly schedule of docetaxel supported by G-CSF resulted in a MTD of 80 mg/m2 consisting of asthenia and edema which became apparent particularly after 6 cycles.

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A Phase I Study of combined modality Fever-Range, Long-Duration, Low-Temperature Whole-Body Hyperthermia (LL-WBH) optimally-timed with Cisplatin (CIS)-Gemcitabine (GEM) & Interferon-a (IFN-a)

J. Bull, G. Scott, V. Nagle, F. Strebel, S. Koch. *University of Texas Medical School, Medical Oncology, Houston, TX, USA*

Background: We have shown in an in vivo model that antitumor efficacy & normal tissue toxicity are highly time & sequence dependent when combining CIS with GEM, or either drug with whole-body hyperthermia.

Purpose: From our pre-clinical data, we designed a clinical protocol combining optimally timed & sequenced CIS with LL-WBH + GEM + low dose IFN-a. This Phase I study was designed to determine the MTD of cisplatin in the regimen of LL-WBH + GEM + IFN-a.

Patients and Methods: A total of 22 Pts. with drug resistant, advanced-bulky or metastatic cancers (median age 60y, [range 25-78y], 10 females/12 males were treated. 19 pts are evaluable; 4 pts recently started treatment). The therapeutic regimen was an escalating dose of CIS (50 to 80 mg/M2) d1, LL-WBH (40.0 ± 0.2 °C for 6h) + GEM (600 mg/M2 over 60 min during LL-WBH) d3, and GEM d10 + daily s.c. IFN-a (1 x 106 i.u.). Cycles were repeated at d28. LL-WBH was induced using the Heckel radiant heat device.

Results: The number of treatment cycles were 1-9 (median 3). Time to reach target core temperature was median 75 min. (range 60-185 min). Grade III thrombocytopenia occurred in 2/3 pts at CIS 70 mg/M2, 2/3 pts developed grade II thrombocytopenia after 3 cycles at CIS 70 mg/M2. Three pts experienced grade 1 leukopenia, 1 pt a grade III ototoxicity at CIS 70 mg/M2. We established the MTD of CIS to be 60 mg/M2. In 19 evaluable pts we documented 14 objective responses: 10 PRs (3 pancreas, 2 gastric, 1 renal, 1 lung, 1 adrenal, 1 bladder, 1 sarcoma), (3/10 PRs were >90%) and 4 SDs lasting > 5 mos.

Conclusions: i) the recommended phase-II dose of CIS in this multi-modality regimen is 60 mg/M2. ii) The thermobiochemotherapy regimen is safe, and well tolerated. iii) Although not a primary endpoint of analysis, the regimen induces clinical benefit in a high proportion of pts with advanced, chemotherapy-resistant tumors. iv). We will begin Phase II trials in a) pts with pancreatic; b) lung; and c) gastric cancer.

272 POSTER

Dose escalation and pharmacokinetic study of capecitabine and irinotecan (CPT-11) in gastro-intestinal (GI) tumors

J. Delord[1], J. Pierga[2], F. Berthault-Cvitkovic[3], S. Abadie-Lacourtoisie[1], F. Lokiec[3], P. Canal[1], V. Dieras[2], F. Turpin[3], Z. Mouri[4], R. Bugat[1]. [1] *Institut Claudius Regaud, Medical Oncology, Toulouse, France;* [2] *Insitut Curie, Medical Oncology, Paris, France;* [3] *Centre Rene Huguenin, Medical Oncology, Saint Cloud, France;* [4] *Roche Pharmaceuticals, Neuilly sur Seine, France*

Capecitabine (Xeloda) is an oral tumor-activated fluoropyrimidine and has demonstrated superior activity and improved safety compared to the Mayo regimen in metastatic colorectal cancer (CRC). CPT11, a topoisomerase I inhibitor is an active drug in GI tumors. Capecitabine and CPT11 demon-

strated at least additivity in vivo. Based on these data, we conduct a study of capecitabine combined with CPT-11 in patients (pts) with GI tumors. The aim of this study was to define the dose-limiting toxicities (DLTs) of the combination, the doses of CPT11 and Capecitabine for further phase II studies and the pharmacokinetic behavior of both drugs.

CPT-11 was administered as a 90 minute intravenous infusion at doses of 200 to 350 mg/m* on day 1 every 3 weeks, followed by Capecitabine 700 to 1250 mg/m* twice daily for 14 days followed by a one week rest period.

Seven dose levels are planned (see table). No intra-patient dose escalation was allowed. We defined DLTs as toxicities occurring during the first two cycles.

So far, 18 pts with GI malignancies have been included. 15 patients were evaluable for safety with diarrhea as the main side effect. One patient (out of seven) at level 4 (250, 1000) experienced a DLT. Other toxicities were mild: nausea (grade 1/2) in 10 patients, neutropenia (grade 1/2) in 7 patients, hand-foot syndrome (grade 1/2) in 2 patients. The study is currently ongoing at level 5.

Conclusions: These preliminary data suggest that oral capecitabine and CPT-11 present a favorable toxicity profile and can be combined in a three-weekly regimen. An update of toxicity profile, dose escalation, pharmacokinetic data and efficacy will be presented at the congress.

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Phase I study of ZD0473 and liposomal doxorubicin in advanced refractory solid tumor malignancies

D.S. Dizon[1], F. Maluf[1], C. Aghajanian[1], A. Daud[1], P. Sabbatini[1], S. Soignet[1], L. Krug[1], S. Pezzulli[1], D.R. Spriggs[1], P. Beale[2]. [1] *Memorial Sloan-Kettering Cancer Center, New York, NY, USA;* [2] *Royal Prince Alfred Hospital, Camperdown, NSW, Australia*

The prognosis for patients with advanced solid tumors remains poor. This has been the major drive in the search of new modalities of therapy. ZD0473 is a new generation platinum drug that appears to differ from cisplatin in its specificity toward DNA. In addition, preclinical studies show it circumvents cellular changes in drug uptake and retention, DNA repair, and glutathione uptake associated with acquired platinum resistance. Liposomal doxorubicin is a new formulation of doxorubicin which confers extended pharmacokinetics and differing toxicity profile compared with the intravenous formulation. We conducted a phase I trial of l-doxorubicin followed by ZD0473 administered once every 4 weeks in patients with advanced solid tumor malignancies. The objective of the study was to determine the recommended doses and toxicity profile of ZD0473 in combination with l-doxorubicin. Dose-limiting toxicity was defined as one of the following: febrile neutropenia, Grade 4 hematologic toxicity, or ≥ Grade 3 non-hematologic toxicity excluding alopecia. To date, nine patients with advanced solid tumor malignancies have been enrolled on 3 dose levels: l-doxorubicin (mg/m2)/ZD0473 (mg/m2) 20/100, 30/100, 40/100. The malignancies represented are ovarian (4), bladder (2), melanoma (1), head and neck (1), and lymphoepithelioma (1). The median number of treatments prior to enrollment was 1.6 (range, 0-3). Two patients underwent definitive radiation therapy. Of the evaluable patients, there has been no DLT reported to date. One mixed response in a patient with lymphoepithelioma was noted. Two patients have had stabilization of disease with one ovarian carcinoma patient normalizing her CA-125. We are actively accruing patients to this trial. Updated data will be presented on our cohort.

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Phase I trial of ZD0473 in combination with vinorelbine for patients with advanced cancer

J. Douillard[1], J. Cosaert[2], V. Barbarot[1]. [1] *CRLCC Nantes-Atlantique, Nantes-Saint Herblain, France;* [2] *AstraZeneca, Macclesfield, UK*

Aims: ZD0473 is a new generation platinum drug designed to have an extended spectrum of antitumour activity and overcome platinum resistance mechanisms. Single-agent Phase I evaluation of ZD0473 has demonstrated a manageable safety profile. This abstract outlines the interim results of a Phase I open-label, dose-escalation trial, which was designed to assess maximum tolerated doses of ZD0473 and vinorelbine when used in combination, in patients with advanced cancers.

Methods: Each patient received 15 mg/m2 vinorelbine as a 6- to 10-min iv infusion on days 1 and 8, followed 30 min later by either a 60 mg/m2 or 90 mg/m2 1-h iv infusion of ZD0473, on day 1 only; this cycle was repeated every 21 days. Six dose levels of the combination are planned, with the doses of ZD0473 ranging from 60 to 120 mg/m2 (day 1), and the doses of vinorelbine ranging from 15 to 30 mg/m2 (day 1 and day 8).

Results: To date, six patients (M:F, 3:3; median age 57 years [range 51-75]) have been recruited into the study. Patients had a range of tumour types: non-small cell lung (1 patient), colorectal (1), prostate (1), carcinomatosis (1), hepatocellular carcinoma (1) and neoplasm of the bladder (1). Five patients had received prior chemotherapy/immunotherapy or hormonal therapy with radiotherapy or surgery, including four who had received previous platinum drugs. One patient had undergone only prior surgery. Three patients received a dose of 60/15 mg/m2 (ZD0473/vinorelbine) and three received 90/15 mg/m2, with one patient increasing from 60/15 mg/m2 to 90/15 mg/m2 after 3 cycles. The median number of 60/15 mg/m2 and 90/15 mg/m2 cycles received were 2 (range 2-3) and 1.5 (range 1-2), respectively. Patients did not require dose reductions or delays and, so far, no dose-limiting toxicity has been observed. Haematological toxicities rated as grade 3/4 were neutropenia (2) and thrombocytopenia (1). There were no grade 3/4 haematological toxicities in patients receiving a dose of 60/15 mg/m2. Non-haematological toxicity was mild to moderate and included nausea and vomiting, which was easily controlled. No drug-related deaths occurred and no adverse events led to withdrawal.

Conclusion: The combination of ZD0473 and vinorelbine in this schedule is well tolerated and no dose-limiting toxicity was observed. Patients are currently being treated at dose level 3 (120/15 mg/m2 [ZD0473/vinorelbine]). Further results are awaited and will be presented at this meeting.

Preclinical drug development

275 POSTER

In vitro methods for the validation of pet tracers for oncology

M. Bergström, E. Bergström-Pettermann, L. Lu, F. Wu, G. Lendvai, J. Mälman, K. Fasth, U. Yngve, B. Långström. *Uppsala University, PET Centre, Uppsala, Sweden*

Purpose: New chemical entities are labelled with positron emitting radionuclides, with the purpose of being used in PET examinations. Such studies aim at defining drug pharmacokinetics, drug interaction, improved diagnosis or characterisation of tumor biology.

Before application into man, a preclinical assessment is needed to exclude candidates with limited chance of success in vivo.

Methods: Tumour cell culture, preferably as multicellular aggregates is used for studies of drug interaction and secondary physiology to screen among surrogate PET tracers. Frozen section autoradiography helps in defining a tracers binding characteristics and to screen among cancer types for the expression of a specific target. Small animal tumour models are used for drug distribution, target validation and assessment of surrogate marker PET methods. Animal PET camera makes animal experiments more efficient.

Results: The development of PET methods via preclinical assessment are illustrated with the development of a specific imaging tracer for adrenocortical cancer: 11C-metomidate, a surrogate PET method for the assessment of effect of a farnesyl-transferase inhibitor, a labelled drug for pharmacokinetic studies: 11C-alpha-amino-buturic acid, the development of a method for the assessment of antiproliferative effects, using 76Br-bromo-fluoro-deoxyuridine, and attempts to develop labelled anti-sense oligonuclides for the recording of gene expression.

Conclusion: In vitro methods are essential for the development of new PET tracers and allow rejection of candidates or new routes of development. These methods are additionally easy to use and give possibilities for oncology researchers to probe the PET methodology under cheaper and easier conditions.

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Differencial effects of choline kinase inhibitors in tumoral and primary human cells

A. Rodríguez-González[1], F. Fernández[1], J. Campos[2], A. Espinosa[2], J.C. Lacal[1]. [1] *Biomedical Research Institute (CSIC), Cellular and Molecular Biology of Cancer, Madrid, Spain;* [2] *University of Granada, Organic and pharmacology, Granada, Spain*

Purpose: Lipid metabolic pathways are frequently altered during carcinogenesis. Some of them play an important role in mitogenic signalling such as diacylglycerol and phosphoinositoides. Phosphoscholine (PCho) is generated by choline kinase (ChoK) after mitogenic stimulation by growth factors, and it is found elevated in human tumors. We have investigated the requirement of PCho in the regulation of cell cycle progression and the