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

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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

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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

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In vitro methods for the validation of pet tracers for oncology

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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

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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