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ABSTRACTS

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Conclusions: A rapid, sensitive and reliable method has been developed for the measurement of plasma dUrd in patients receiving antifolate drugs. These data suggest that the duration of TS inhibition is dose-related and will help in the choice of dose and schedule for Phase II trials of ZD9331 and understanding the relationship of duration of target inhibition and response/toxicity.

605O Strategies for improvement in dose escalation using the continual reassessment method (CRM) in phase I clinical trials

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The CRM has been proposed as an alternative dose escalation method in the phase I clinical trial design of antineoplastic agents, with the aim of exposing a greater proportion of patients (pts) to therapeutic drug doses than traditional approaches. The statistical model utilized is a sequential Bayesian estimation scheme in which a prior distribution function of the maximum tolerated dose (MTD) and a dose toxic-response model are selected before the trial. The MTD is the dose at which a pre-determined percentage (e.g. 30%) of the pt population would experience dose-limiting toxicity (DLT, e.g. Gr 3 non-hematologic or Gr 4 hematologic). In response to the practical and safety concerns of cytotoxic chemotherapy, modifications of the CRM (MCRM) were implemented which include the use of a conventional starting dose and the fixation of dose levels a priori, customarily by applying the modified Fibonacci sequence. However, our experience with this dose escalation method has been problematic due to the dependence on non-clinical toxicity information prior to the trial, and the difficulty of predicting a fixed number of dose levels. Therefore, we have designed a "dual-stage" escalation scheme. The initial stage involves utilization of a conventional starting dose with doubling of the dose in single-pt cohorts until moderate toxicity (e.g. Gr 2 non-hematologic or Gr 3 hematologic) is encountered, at which point 2 additional pts are accured and dose escalation proceeds in a more conservative manner (e.g. at 33% to 50% increments). The second stage begins once DLT is reached, and the CRM is used to guide subsequent assignment of dose levels. Instead of the Bayesian methodology, a maximum likelihood approach (O'Quigley and Shen) is applied which offers greater flexibility without restriction by the paucity of prior data. Practical examples and simulations of models will be provided to illustrate this proposed dose escalation method.

606O Synergistic antitumor effect by novel modified oligonucleotides targeting PKAI combined with cytotoxic drugs or monoclonal antibodies

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Introduction: Protein kinase A type I (PKAI) plays a key role in neoplastic transformation and conveys mitogenic signals of different growth factors and oncogenes. Moreover, PKAI is overexpressed in cancer cells with an active TGFα-epidermal growth factor receptor (EGFR) autocrine pathway and shows a structural and functional interaction with EGFR. Inhibition of PKAI, or its regulatory subunit RIα, results in cancer growth inhibition *in vitro* and *in vivo*.

Methods: A novel class of mixed backbone oligonucleotides (MBOs) targeting PKAI (ASRIα), with improved pharmacokinetic and bioavailability, and a humanized monoclonal antibody which blocks activation of EGFR, MAb C225, have been tested *in vitro* and *in vivo* on several human cancer cells.

Results: A dose-dependent inhibition of soft agar growth was obtained in all cancer types tested with the AS RIα MBOs, as compared to mismatched control oligos. Non-inhibitory doses of each MBO resulted in a synergistic growth inhibition and increased apoptosis, when combined with taxanes, platinum-derivatives and topo II-selective drugs. When the MBOs administered either i.p. or *p.o.* were added to paclitaxel, a cooperative effect was also obtained *in vivo*, causing tumor growth inhibition and increase of survival in nude mice bearing human cancer xenografts. Finally, combined treatment of human breast and renal cancer cells, which overexpress PKAI and EGFR, with the ASRIα MBO and MAb C225, caused a cooperative antitumor effect *in vitro* and *in vivo*.

Conclusions: Since both the AS RIα MBOs and the MAb C225 are currently studied in clinical trials, the combination between them or with selected cytotoxic drugs may represent a feasible novel therapeutic strategy.

607O Pharmacokinetic (PK) interaction of the combination of doxorubicin (DOX) and Taxotere (TXT)

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Introduction: Combination of DOX with TXT has been shown to be highly effective in advanced breast cancer recently introduced into adiuvant treatment. Purpose of the present study was to detect a potential PK interaction between DOX and TXT, as already proven for Paclitaxel + DOX leading to increased DOX-AUC and enhanced cardiotoxicity (Gianni et al). Therefore PK behavior of both, DOX and TXT, was analyzed using 2 different time schedules: DOX 50mg/m² 30min inf. followed immediately (A) of after 1HR interval (B) by TXT 75mg/m² 1HR infusion.

Methods: All pts received TXT alone at cycle 1 for baseline determination followed by DOX + TXT (18 pts schedule A, 13 pts B, sampling for both DOX and TXT), followed by DOX baseline analysis (12 pts A, 6 pts B, TXT then given delayed after end of DOX sampling). Sampling period 4HR for TXT and 6HR for DOX, measured by HPLC, Win Nonlin noncompartimental analysis performed.

Results: of the respective AUC last:

AUC ng/ml.H	Taxotere				Doxorubicin			
	n	TXT	DOX/TXT	p	n	DOX	DOX/TXT	p
A	18	1484	1956	0.03	12	859	848	0.9
B	13	1703	2450	0.05	6	906	833	0.6

Conclusion: No influence of TXT on DOX-AUC documented, DOX-ol conc (n=8) with or without TXT n.s. different (p 0.2 – 0.8), thus explaining low cardiotoxicity of the combination. In contrast, TXT-AUC was significantly increased when combined with DOX, suggesting interference at the hepatic microsomal level, partly explaining high clinical efficacy. A 1HR delay between end of DOX and start of TXT does not change the respective PK behaviour of both drugs.

608P Gemcitabine (GEM) – cisplatin (CDDP): A schedule finding phase I/II study

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Introduction: Gem and CDDP are active against various solid tumors. Since preclinical studies demonstrated the efficacy of various schedules we evaluated the tolerability and clinical efficacy of 4 different Gem/CDDP schedules as part of a pharmacokinetic and -dynamic (PK/PD) study.

Methods: Gem 800 mg/m² was administered as a 30 min infusion on d 1, 8, 15, and CDDP 50 mg/m² over 1 hr on d 1, 8 every 28 days; Gem 4 hr before CDDP (10 pts), or vice versa (14) and Gem 24 hr before CDDP (9), or vice versa (9), after one cycle followed by the reversed schedule. Pts (19 male/23 female, median age 54 years [31–77], and performance status 1 [0—2]) included, 9 ovarian, 7 non-small cell lung (NSCLC), 5 head/neck squamous cell (HNSCC), 5 esophageal, 4 melanoma, 4 cervix, 3 adenocarcinoma, 2 pancreatic, 2 colon and 1 small cell lung (SCLC). 26 pts received prior chemotherapy, of which 21 platinum based.

Results: A mean of 4.2, 2.6, 3.8 and 3.5 cycles was given in the four schedules, resp. The most frequent overall grade 3/4 CTC-toxicity was thrombocytopenia, 6/10, 4/14, 2/9 and 6/9 (overall 60%), followed by leukopenia, 8/10, 5/14, 6/9 and 6/9 (43%), in the 4 schedules, resp. Therefore, Gem was not given on d 15 in 36% of pts in cycle 1. Anemia was observed in 64% of pts. No serious bleeding occurred. Myelotoxicity was cumulative, but not schedule dependent. Non-hematological toxicity consisted mainly of grade 1/2 nausea/vomiting and fatigue. One patient died of toxicity following severe neutropenia and sepsis. Creatinine clearance decreased slightly during therapy. Anti-tumor effects in 36 evaluable pts: HNSCC, 1 CR; esophageal, 1 CR/2PR; ovarian, 2 PR; NSCLC, 1 PR; melanoma, 1 PR and adenocarcinoma, 1 PR.

Conclusion: (Cumulative) myelosuppression was the major toxicity, although it was not schedule dependent. Based on toxicity, efficacy and PK/PD data a phase II study, CDDP 24 hr before Gem, has been started in pts with upper gastro-intestinal tumors.

609P MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity

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Introduction: MTA is a novel multitargeted antifolate with inhibitory activity against multiple enzymes. Phase I/II studies have shown activity in a variety of tumors. Historical data on other antifolates have suggested that a patient's nutritional status may play a role in the likelihood of experiencing severe toxicity. The purpose of this study was to assess the relationship of vitamin metabolites, drug exposure, and other prespecified baseline patient characteristics to toxicity following treatment with MTA.

Methods: Homocysteine (Hcys), cystathionine and methylmalonic acid were measured in 139 phase II patients with tumors of the colon, breast, pancreas, and esophagus at baseline and once each cycle thereafter. Stepwise regression modeling, multivariate analysis of variance, and discriminant analysis were implemented to determine which predictors might correlate with severe toxicity after one course of MTA. Prognostic factors considered were age, gen-

der, prior treatment, baseline albumin, liver enzymes, ANC, platelets, vitamin metabolites, and AUC.

Results: Statistically significant predictors of Grade 4 neutropenia (n=21 pts) were albumin ($p = 0.0006$) and Hcys ($p = 0.0012$), while Grade 4 thrombocytopenia (n=8) was highly predicted by Hcys ($p < 0.0001$) and pre-treatment AST ($p = 0.0012$). Hcys $\geq 10\mu M$ predicted Grade 4 neutropenia in cycle one 75% of the time. Grade 4 neutropenia was predicted by Hcys alone in 70% of cases. Hcys and albumin levels did not appear to change from baseline during treatment with MTA. While AUC was not found to be a predictor of toxicity, little variability was observed in AUC. Maximum values were still below AUC values related to hematologic toxicity in phase I studies.

Conclusions: Toxicities resulting from treatment with MTA appear to be predictable from pretreatment homocysteine levels. Elevated baseline homocysteine levels ($\geq 10\mu M$) highly correlate with severe hematologic and nonhematologic toxicities following treatment with MTA. Homocysteine was found to be better than albumin at predicting toxicity. These results apply to the tumor types studied. Further studies are underway in patients with renal impairment or patients who received prior cisplatin.

610P Phase I and pharmacokinetic (PK) study of Tomudex (TOM) + 5-Fluorouracil (5-FU) and levofolinic acid (LFA) in advanced head and neck and colorectal cancer

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Background: Synergism between TOM and 5-FU + LFA is observed in vitro when cells are exposed for 24 hours to TOM, followed by 5-FU + LFA. Preclinical studies support the idea that TOM might down-regulate the activity of dihydropyrimidine dehydrogenase (DPD).

Patients and methods: Patients (pts) with advanced head and neck and colorectal cancer were treated with escalating doses of TOM on day 1, and bolus 5-FU (immediately after LFA) on day 2, every 2 weeks. In the 2nd course LFA and 5-FU were administered on day 1 and TOM on day 2 with the aim of evaluating DPD and 5-FU AUC with and without pretreatment with TOM. Further treatment was given according to the sequence used in the 1st course.

Results: Available clinical data are summarized below.

Step	TOM/LFA/5FU (mg/m²)	Pts	C/HN°	DLT	Type*	Response
1	1.5/250/600	6	1/5	0/6		0/6
2	*2.0*/250/600	6	5/1	0/6		1/6 (PR)
3	2.0/250/*750*	6	5/1	0/6		1/6 (PR)
4	*2.5*/250/750	6	5/1	0/6		3/6 (2CR, 1PR)
5	2.5/250/*900*	7	6/1	0/7		0/7
6	*3.0*/250/900	8	8/0	1/8	N 4	1/8 (CR)
7	3.0/250/*1050*	16	9/7	3/15	N 4; N 4; N 4	6/13 (1CR, 5PR)
8	3.0/250/*1200*	3	2/1	2/3	N 4, M 3; R 3	1/3 (PR)
Total		58	41/17			OR

°C = colorectal cancer; HN=head & neck cancer. C = 6/39 (15%); HN = 7/16 (44%); * N = neutropenia; M = mucositis; R = Renal

DPD activity has been measured in 14 pts thus far. Pretherapy DPD activity was a median 34% higher than after TOM administration (95% C.I. −93 to +62%). PK data are available in 6 patients thus far, and 5-FU AUC basal values do not significantly differ from values obtained 24 hours after TOM.

Conclusions: The combination of TOM+ 5-FU/LFA is well tolerated every 2 weeks. Clinical activity looks very encouraging, since the majority of pts had already received prior chemotherapy. We are now treating some additional chemo-naive patients at step 7, in order to have a more reliable estimate of the activity of the regimen.

611P Radio-localization of pulmonary nodules using gamma-probe and resection by video-assisted thoracic surgery

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Video-assisted thoracic surgery (VATS) is emerging as safe procedure for diagnosis and treatment of peripheral pulmonary nodules. One limitation of thoracoscopic technique is the inability to detect those nodules which are very deep beneath the pleural surface, and could only be identified via manual palpation. Several methods are used to localize VATS occult lesions prior to excision, including methylene blue injection and introduction of hooked-wire; however, all suffer from limitations. Recent advancements in intraoperative radio-localization of non-palpable breast lesions prompt us to develop a new technique for detection of pulmonary nodules by VATS. CT-scan are used to guide perilesional injection of 0.2 – 0.5 ml of solution of 99m Tc-labeled human serum albumin microspheres (5–10 MBq) and 0.2 ml of Iodine-non-ionic contrast medium, two hours before surgery. In VATS a gamma ray detector (Scinti Probe MR 100 – Pol.hi.tech., Aquila, Italy), equipped with 11mm diameter-collimated probe, allowed us to locate that lesion for thoracoscopic resection. From June 1997 to January 1998 we treated 15 consecutive patients (pts) with sub-centimeter pulmonary nodules. Nine pts were affected by a synchronous and metachronous malignant neoplasm in other sites. Computed thomography of the chest helped in the planning of the operative procedure, the position of pts, and ideal ports. A hot-spot was easily detected, in all patients, by the probe introduced in the pleural space through a 11.5 mm trocar. The total excision of the lesion was confirmed by detection of radioactivity in the removed specimen and its absence in the resection margins of the lung. Pathological examination of specimens showed 8 benign lesions and 7 malignant lesions (4 metastases and 3 lung cancer) and it confirmed the absence of infiltration in the resection margins. The surgical procedure was extended for an average of 56.6 minutes (range 35–100 min). The average post-operative hospital stay was 3.6 days (range 3–6 days). In our experience this technique proved safe and accurate, allowing easy detection of the pleural surface projection and fast removal of the lesion. This technique offers a simple and reliable method for localization of primary and metastatic tumors by VATS.

612P Pharmacokinetic (PK) of Tomudex® (raltitrexed) (T) and oxaliplatin (O) combination: Preliminary results of an ongoing phase I study

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Introduction: The aim of this study was to evaluate the possible kinetic interactions between T and O administered to patients with advanced disease.

Methods: Patients first received T (15 min infusion), followed 45 minutes later by O (2-hour infusion). Three patients received T at a dose of 3 mg/m² and 3 at a dose of 3.5 mg/m². All of them received the same dose of 130 mg/m² of O.

Results: Plasma concentrations of T declined tri-exponentially after the end of the infusion. The terminal t1/2 derived from samples up to 28 hours post-dose varied between individuals from 9.3 to 193.2 h with average values of 73.4 and 33.7 for the two dose levels. The maximal concentrations varied between 323 and 1185 ng/ml with averages of 681 and 813 in the 3 mg/m² and 3.5 mg/m² groups respectively. The AUC varied between 720 and 3192 ng.h/ml with average of 1577 and 1378 in the two groups. The comparison between the two groups did not revealed any difference, probably due to the very large intra subject variability, however the mean AUC showed an approximately proportional increase with increasing dose. The estimated kinetic parameters were in agreement with the values previously published. Plasma concentrations of O declined bi-exponentially after the end of the infusion. The terminal t1/2 varied from 18 to 30 h (average of 25). Cmax ranged from 3.13 to 4.53 (average of 3.69) μg/ml. The AUC ranged from 74 to 120 (average of 195) μg.h/ml and the Cl varied between 1.76 and 3.43 (average of 2.47) l/h. The comparison of the kinetic parameters of O to the ones previously published in the same experimental conditions seems to indicate that T induced an increase of O Cl (from 1.32 to 2.47 l/h) with a reduction of the terminal t1/2 from 38.7 to 24.8 h and a reduction of Cmax measured at the end of the infusion from 5.11 to 3.69 μg/ml.

Conclusions: These preliminary results suggest that the expected concentrations of O obtained after administration of T may be lower that the ones observed when O is administered alone. These results indicate possible PK interaction between the two drugs.

613P A phase I and pharmacokinetic (PK) study of ET-743, a novel minor groove binder of marine origin administered on a daily × 5 schedule

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ET-743 is a novel tetrahydroisoquinoline alkaloid isolated from the marine organism *Estenaiscidian turbinata* which binds to adenine-cytosine rich regions within the minor groove of DNA. This study is evaluating the feasibility and PK behavior of ET-743 administered as a 1-hour infusion daily × 5 every 3 weeks in patients with advanced solid malignancies. Twenty-seven patients (median age 58, range 35–79; median ECOG PS-1) have received 67 courses of ET-743 at doses ranging from 6 to 380 μg/m²/day. At the 380 μg/m²day dose level, 1 patient with extensive prior treatment with 16 cycles of BCNU developed grade 4 thrombocytopenia, grade 4 neutropenia with fever, grade 3 elevation in transaminases, and acute renal failure which resulted in death. Four patients (8 cycles), at the 216 (1), 287 (1) and 380 (2) μg/m²/day dose level developed asymptomatic elevation in hepatic transaminases of grade 3 severity that typically peaked on day 8 and resolved by day 21. Mild to moderate, dosedependent nausea and vomiting, which appeared on day 4 and resolved on day 8, was observed in 14 patients. Two patients at the 380 μg/m²/day dose level suffered superficial venous thrombophlebitis at the drug infusion site. PK parameters obtained in 2 patients at the 216 μg/m²day dose level included: clearance, 137 and 589 mL/min/m²; $t_{1/2}$, 13.7 and 23.1 L/h; and,

