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ABSTRACTS

23rd Congress of the European Society for Medical Oncology

November 6–10, 1998 — Athens, Greece

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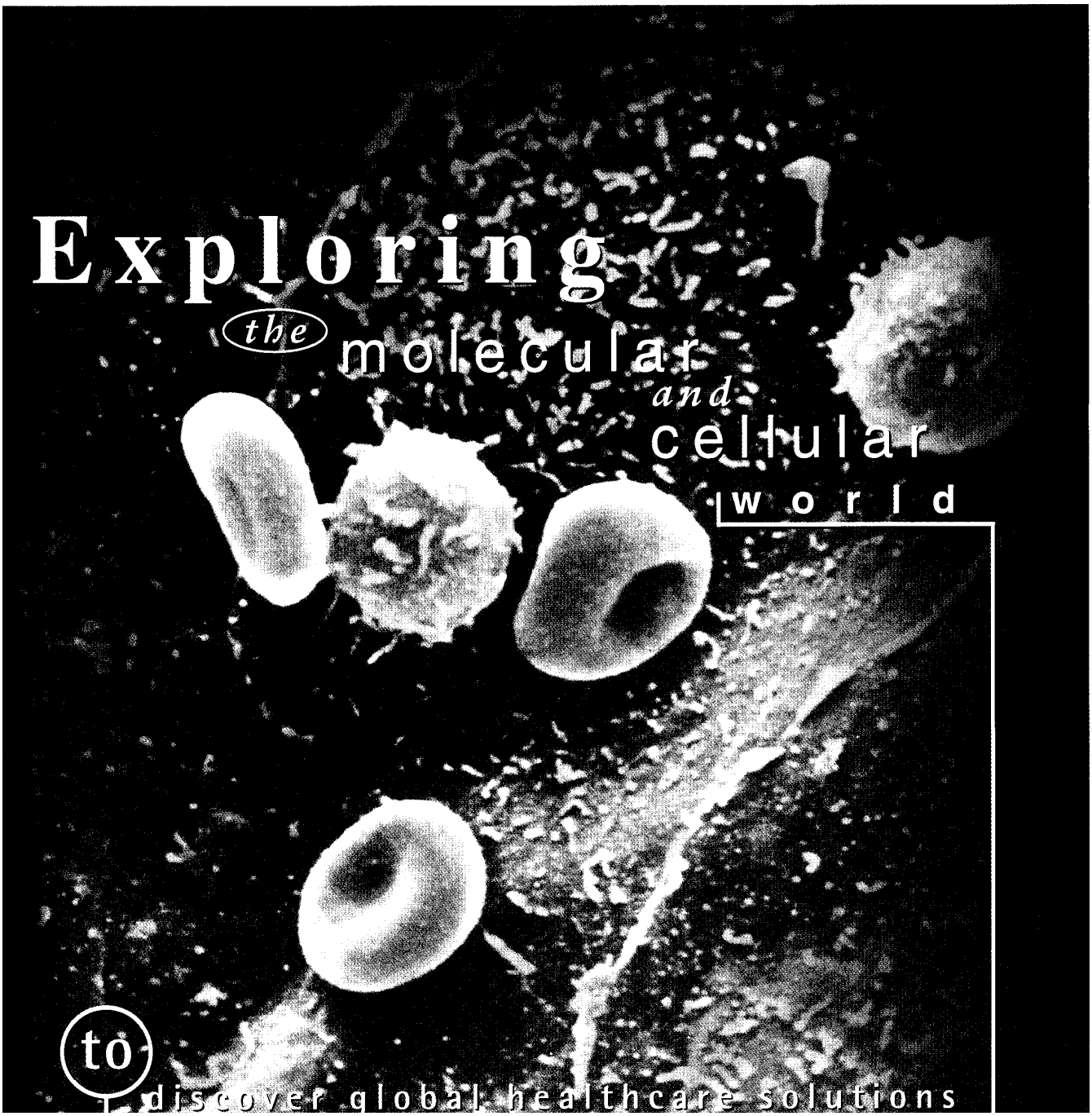

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Conclusions: A rapid, sensitive and reliable method has been developed for the measurement of plasma dUrd in patients receiving antifolate drugs. These data suggest that the duration of TS inhibition is dose-related and will help in the choice of dose 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

L.L. Siu, X. Paoletti, J. O'Quigley, E.K. Rowinsky, G.M. Clark, D.D. Von Hoff, S.G. Eckhardt. *Cancer Therapy and Research Center, San Antonio, TX, USA and U436 INSERM, Paris, France*

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

G. Tortora, V. Damiano, R. Bianco, S. Pepe, A.R. Bianco, S. Agrawal[1], J. Mendelsohn[2], F. Ciardiello. *Oncologia Medica, Univ.Federico II, Napoli, Italy; [1]Hybridon, Cambridge, MA, USA; [2]UT-MD Anderson Cancer Center, Houston, TX, USA*

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)

J. Schüller, M. Czejka, E. Krexner, K. Lehner, H. Bucher, G. Schernthaner. *Hospital Rudolfstiftung Oncol. Dep., Instit. pharma chem Vienna, Austria*

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/m^2 30min inf. followed immediately (A) of after 1HR interval (B) by TXT 75mg/m^2 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

J.R. Kroep[1], G.J. Peters[1], C.J.A. Van Moorsel[1], J.B. Vermorken[3], P.E. Postmus[2], A. Catik[1], H.M. Pinedo[1], C.J. Van Groeningen[1]. *[1]Dept. Oncol. and [2]Pulm., Univ. Hosp. VU, Amsterdam, NL and [3]Dept. Oncol., Univ. Hosp. Antwerp, B, The Netherlands*

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/m^2 was administered as a 30 min infusion on d 1, 8, 15, and CDDP 50 mg/m^2 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

C. Niyikiza, S. Baker, R. Johnson, J. Walling, D. Seitz, R. Allen. *Lilly Research Laboratories, Indiana, USA; Cancer Treatment and Research Center, Texas, USA; Univ of Colorado Health Sciences Center, Colorado, USA*

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-

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