WHO 2 occur. Until 10/96, 56 hospitals have recruited a total of 946 pts. (FOGT 1 521 pts., FOGT 2 425 pts.). Toxicity and discontinuance rates were noted.

Results: Among the 839 pts. evaluable according to "intention to treat" (FOGT-1: 464, FOGT-2: 375), a toxic event > WHO2 occurred in 139 (17%), and treatment was stopped in 177 (21%). Toxicities > WHO2 in FOGT-1 A, B, C were 5%, 7%, 21%, in FOGT-2 20%, 16%, 38%, respectively. Discontinuance rates in Arms A, B, and C of FOGT-1 were 23%, 17%, 25%, and 20%, 20%, 23% in FOGT-2, respectively. Treatment was stopped in Arms A, B, C because of toxicity or patient's demand in 11%, 8%, 16% in FOGT-1 or 7%, 13%, 10% in FOGT-2, respectively. The overall discontinuance rate due to toxicity or patients' demand was 11%. Toxicity in ArmC seemed to be higher, and was mainly due to leukopenia and diarrhea.

Conclusion: The rate of discontinuance is within those of other trials, e.g. the Intergroup Studies (Laurie 1990, Moertel 1990), so that FOGT-1 and FOGT-2 trials are safe and acceptable concerning toxicity and patient compatibility.

1103 ORAL

Adjuvant chemotherapy in Dukes' B and C colorectal cancer. A cost-effectiveness analysis

J. Norum[1], J.A. Olsen[2], A. Revhaug[3], B. Vonen[3]. [1]*Department of Oncology;* [3]*Department of Surgery University Hospital of Tromsø* [2]*Department of Economics, University of Tromsø, Norway*

Purpose: Adjuvant chemotherapy (ACT) is now standard practice in the treatment of Duke's C colorectal carcinoma (CRC) and this has increased the financial burden on health care systems world-wide. This study was initiated to clarify the cost-effectiveness of this therapy.

Methods: Between 1993 and 1996, 95 patients (Dukes' B and C) in northern Norway were included in a national randomised CRC study, and assigned to surgery plus adjuvant chemotherapy or surgery alone. In April 1996, 94 patients were evaluable and 82 still alive. The total treatment costs were calculated and a questionnaire for assessment of the quality of life (QoL) was mailed to all survivors. 62 responded.

Results: ACT raised the total treatment costs by £3,360. The median QoL was 0.83 (0–1 scale) in both arms. Employing a 5% discount rate and an improved survival of ACT ranging from 5–15%, we calculated the cost of one quality adjusted life year (QALY) to be between £4,800 and £16,800.

Conclusion: Using a cut-off point level of £20,000 per QALY, ACT in CRC appears to be cost-effective only when the improvement in 5-year survival is ≥5%. ACT does not affect short-term QoL.

Clinical pharmacology and phase I studies

1104 ORAL

A phase I study with S-1, an oral 5-FU formulation, in patients with solid tumors

C.J. Van Groeningen[1,2], J.H. Schornagel[2,3], G.J. Peters[1,2], P. Noordhuis[1], A.B.P. Van Kuilenburg[4], T. Shirasaka[5], Y. Shimamura[5], M.J. de Vries[6], A.-R. Hanauske[7]. [1]*Academic Hospital VU;* [2]*European Cancer Centre;* [3]*Netherlands Cancer Institute;* [4]*University Hospital AMC;* [6]*New Drug Development Office;* [7]*Early Clinical Study Group of the EORTC, Amsterdam, The Netherlands;* [5]*Taiho Pharmaceutical Co., Ltd. Tokyo, Japan*

S-1 is an oral formulation of Tegafur (FT), a prodrug of 5-FU, combined with a dihydropyrimidine-dehydrogenase (DPD) inhibitor and oxonic acid (molar ratio 1: 0.4: 1), which inhibits 5-FU phosphoribosylation in the GI-tract. We determined the maximum tolerated dose (MTD), side-effects and pharmacokinetics (PK) of S-1. 23 patients (pts) with solid tumors (including 6 colorectal and 4 gastric), mean age 53 yr., median PS 1, received cycles consisting of S-1 administration during 4 weeks followed by 1 week rest. Doses of 25, 45, 35 and 40 mg/m^2 b.i.d. were successively studied in 6, 5, 6 and 6 pts resp., receiving 23, 5, 12 and 6 cycles evaluable for toxicity. The side effects were mild at 25 mg/m^2. At 45 mg/m^2 diarrhea (grade (G) 3 in 1 pt, G4 in 2 pts), anorexia (G3 in 1 pt, G4 in 1 pt) and fatigue (G3 in 2 pts) were dose limiting toxicities (DLTs). No severe toxicity was observed at 35 mg/m^2. At 40 mg/m^2 diarrhea was the DLT (G3/nausea G3 in 1 pt, G4/vomiting G4 in 1 pt). One tumor regression was observed in a pt with gastric cancer, while 13 pts are still on study. 5-FU levels reached a plateau of 0.3–2 μM after 1–2 hr; uracil levels, indicative for DPD inhibition, increased from 0.1 to 1–10 μM. In conclusion, 40 mg/m^2 b.i.d. is the MTD of S-1 with diarrhea as the most important DLT. Effective DPD inhibition results in cytotoxic 5-FU plasma levels. Phase II studies with S-1 will be performed in colorectal and gastric cancer.

1105 ORAL

A comparison of clinical pharmacodynamics of different administration schedules of oral topotecan (TPT, Hycamtin®)

C. Gerrits, J. Schellens, H. Burris, A. Planting, M. van der Burg, V. van Beurden, W. Loos, I. Hudson, S. Fields, D. Von Hoff, J. Verweij. *Rotterdam Cancer Institute and University Hospital Rotterdam, The Netherlands; Cancer Therapy and Research Center, San Antonio; SmithKline Beecham; SmithKline Beecham, USA; SmithKline Beecham, UK*

Purpose: In vitro and in vivo experiments indicated that prolonged exposure to TPT yielded the best anti-tumour efficacy. An oral formulation was developed to conveniently enable treatment schedules aiming at prolonged exposure. Bioavailability in man is 32–44%.

Methods: We performed phase I studies with once daily (OD) × 5 (29 patients (pts)), OD × 10 (19 pts), twice daily (BID) × 10 (20 pts), and BID × 21 (131 pts) schedules. Pharmacokinetic studies were performed in 55 pts.

Results: Dose limiting toxicities were observed at total daily doses of 2.7 mg/m^2, 1.6 mg/m^2, 1.6 mg/m$_2$, and 1.2 mg/m^2 respectively, and consisted of myelosuppression with OD × 5, myelosuppression and diarrhea in both 10 day schedules, and diarrhea in the 21 day schedule. AUC(t) lactone TPT was consistently higher on day 4 (OD × 5) and day 8 (10 and 21 days schedule), respectively. Intrapatient variation was (59.5 ± 51.0%) with the BID × 21 schedule (N = 13) (96.5 ± 70.1%) with BID × 10 (n = 10), (34.5 ± 25.0%) with OD × 10 and (25.4 ± 31.0%) with the OD × 5 schedule (n = 22).

The correlation between the AUC(t) day 1 TPT and the percentage of decrease of leucocytes is significant in 3 schedules of administration with correlation coefficients of R = 0.76 (p = 0.001) (OD × 5), R = 0.69 (p = 0.03) (BID × 10), and R = 0.66 (p = 0.03) (BID × 21). A similar trend was found in OD × 10 schedule with R = 0.61 (p = 0.06). The correlation with the percentage decrease of platelets was R = 0.78 (p = 0.03) (BID × 10), R = 0.83 (p = 0.01) (OD × 10), and R = 0.60 (p = 0.004) (OD × 5).

AUC per course was calculated by multiplying AUC observed after a single dose by the number of doses given per course. At MTD the resulting AUC per course did not show significant differences between schedules, being: 107.4 ± 33.7 (OD × 5), 145.3 ± 23.8 (OD × 10), 100.0 ± 41.5 (BID × 10), and 164.9 ± 92.2 (BID × 21), respectively. For all schedules a significant correlation between the AUC(t) per course of the lactone form of TPT and parameters of myelotoxicity was found, with comparable sigmoidal relationships versus percentage decrease of WBC.

Conclusion: Schedule rather than AUC per course appears to be related to the type of toxicity of oral TPT. Toxicity shifts from diarrhea with BID × 21, through a combination of myelotoxicity and diarrhea with 10 day schedules, to granulocytopenia in OD × 5. Balancing no difference in total exposure on one hand, and toxicity on the other, the once daily ×5 oral administration of TPT should get priority in further development.

1106 ORAL

Clinical and pharmacokinetic evaluation of the new bisnaphtalamide LU 79553 administered every 21 days in patients with solid tumors: An EORTC/ECSG study

R. Thödtmann[1], A. Awada[2], M. Piccart[2], F. Höppener[3], J. Wanders[3], I.-M. von Broen[4], A.-R. Hanauske[1]. [1]*Klinikum r.d. Isar Techn. Univ. München;* [4]*Knoll AG Ludwigshafen, FRG;* [2]*Institut Jules Bordet Brussels, Belgium;* [3]*EORTC/NDDO Amsterdam, The Netherlands*

Purpose: LU 79553 (L) is a new bisnaphtalamide intercalating agent with profound activity in in vitro and in vivo preclinical models. We are performing a clinical Phase I study in patients (pts) with advanced solid malignancies.

Methods: L was administered as iv infusion q 21 d with a starting dose of 10 mg/m^2, escalated to 160 mg/m^2. Infusion time was adapted to local toxicity.

Results: 37 pts have received a total of 96 courses and are evaluable for toxicity (CTC) and response (WHO). Hematologic toxicity (HT) by pts were: 3/3 pts grade (g) 3 leukopenia (WBC) at 90 mg/m^2; 1/6 pts g 3 anemia, 2/6 pts g 3 WBC, 1/6 pts g 3 thrombocytopenia, 1/6 pts g 3 and 1/6 pts g 4 neutropenia (ANC) at 120 mg/m^2; 1/3 pts g 3 and 1/3 pts g 4 ANC at 160 mg/m^2. Significant non-HT by pts were: g 2 thrombophlebitis at infusion site 1/5 pts at 50 mg/m^2, 3/6 pts at 70 mg/m^2 and 2/6 pts at 120 mg/m^2.

G 3 peripheral neuromotor toxicity occurred in 1/6 pts at 70 mg/m², 1/3 pts at 90 mg/m², 2/6 pts at 120 mg/m² and 1/3 pts at 160 mg/m². At present, 1 partial response (PR) and 2 minimal responses (MR) were observed: 1 MR at 90 mg/m² (vulva), 1 MR at 120 mg/m² (renal cell) and 1 PR at 120 mg/m² (mesothelioma).

Conclusions: The Maximum Tolerated Dose of L administered q 21 d is 120 mg/m² with peripheral neurotoxicity as Dose Limiting Toxicity. The recommended dose for Phase II trials is currently being established. L has antitumor activity and warrants further evaluation.

1107 ORAL

Phase I and pharmacokinetic study of ecteinascidin-743 (ET-743) given as a one hour infusion every 21 days

C.J. Twelves[1], J. Vermorken[2], A. Bowman[3], A. Simpson[1], J. Smyth[3], F. Höppener[4], J. Beijnen[5], J. Jimeno[6], A.-R. Hanauske. *For the Early Clinical Studies Group of the EORTC; [1]CRC Dept Medical Oncology, Glasgow; [3]ICRF Dept Medical Oncology, Edinburgh, UK; [2]University Hospitsl Vrije Universitat; [4]NDDO Amsterdam; [5]Slotervaart Hospital, Amsterdam, The Netherlands; [6]Pharma Mar, Madrid, Spain*

Introduction: ET-743 is a novel tetrahydroisoquinolone isolated from a Caribbean tunicate. ET-743 exerts antitumour activity as a DNA minor groove interacting agent. ET-743 exhibits potent *in vivo* activity in human xenograft models. Dose-limiting toxicities in all species were hepatotoxicity and myelotoxicity.

Aims and Methods: Phase I study to determine the safety and pharmacokinetics of ET-743 given i.v. in 250 mls over 60 minutes every 3 weeks. Starting dose of 50 μg/m² represents (<1/10 mouse LD_{10}) with escalation according to a modified Fibonacci scheme.

Results: At present, the 50, 100, 200 and 330 μg/m² dose levels are evaluable. Twelve patients (7 M, 5 F), median age 60.5 (range 30–77) with refractory solid tumours received 38 cycles of ET-743 (median 2.5 range 1–7). ET-743 has been well tolerated with no dose-limiting toxicities. At ≥100 μg/m², 4 pts had reversible elevation of serum transaminases (CTC grade 1/2). One pt, who refused antiemetics, had grade 3 vomiting. Preliminary pharmacokinetic data show ng/ml concentrations of ET-743 at doses ≥100 μg/m² measured by HPLC.

Conclusions: ET-743 is tolerated at doses up to 330 μg/m² and this achieves detectable plasma levels. At a dose approximating to the MTD in preclinical studies there have been only minor, transient changes in liver tests. Four patients remain on therapy and accrual continues at 440 μg/m².

1108 ORAL

Phase I study of weekly cisplatin (P) and weekly or four weekly taxol (T) in patients with advanced ovarian cancer

Mel van der Burg, R. de Wit, A. Logmans, M. van Lent, G. Stoter, J. Verweij. *Department or Medical Oncology, Rotterdam Cancer Institute (Daniel den Hoed Kliniek) and University Hospital Rotterdam, PO Box 5201, Rotterdam, NL*

Purpose: Weekly P combined with oral VP16 is highly active in 2nd line therapy in ovarian cancer (OC) (ASCO '96 abstr 772). T is more active than VP16 in patients (pts) with recurrent OC. Because of this we performed a phase I study investigating whether P could be combined with either weekly or 4-weekly T.

Methods: Nine pts with primary and 15 with recurrent/progressive OC were treated with 2 cycles of induction therapy with P 70 mg/m² on day 1, 8 and 15 combined with either T on day 1, 8, 15 (T dose 60–90 mg/m²) or T on day 1 (T dose 135–200 mg/m²), full cycle repeated day 29. followed by 6 cycles T175 mg/m² and P75 mg/m² q 3wks.

Results: 23 Pts are presently evaluable for induction therapy. One pt stopped therapy after the 5th P administration because of an increase of neurotoxicity from grade 1 to 3. All other pts received 2 full cycles. Toxicity and response are summarized in the table.

T (mg/m²)	P (mg/m²)	N Pts/ cycles	Worst toxicity CTC grade per cycle/pts*													
			WBC		Gran			Pts		N/V		nephro		neuro*		Response
			2	3	2	3	4	2	3	2	3	1	2	1	2	CR	PR
T weekly N = 11																	
60	70	3/18	5	2	6	4	0	0	2	0	1	8	0	2	0	1	2
70	70	3/18	4	1	7	1	0	0	0	1	0	1	0	1	0	1	2
80	70	5/30	7	5	2	6	0	0	0	9	2	8	1	3	0	2	2
T 4 weekly N = 12																	
135	70	3/18	4	0	7	2	0	0	0	4	0	3	0	2	0	0	3
150	70	4/23	4	3	3	4	2	0	1	10	0	5	0	2	1	2	2
175	70	3/18	4	1	3	1	1	0	0	2	0	2	0	2	0	0	3
200	70	2/12	3	3	0	4	1	1	0	1	0	3	0	0	1	1	0

1109 ORAL

Amifostine (AMI) differently influences pharmacokinetics (PK) of selected cystostatic agents (CY)

J. Schüller, M. Czejka, E. Krexner, C. Pietrzak, B. Springer, H. Kletzl, D. Borow. *Hospital Rudolfstiftung, Instit pharma chemistry, Vienna, Austria*

Purpose: For AMI, besides nephro- myeloprotection, reduction of anthracycline induced cardiotoxicity, Mitomycin C (MMC) induced thrombopenia and taxanes related neurotox. have been described in vitro or clinically. AMI has also been found to alter PK of platinum agents and doxorubicin. Therefore a potential influence of AMI on PK of MMC, Epirubicin (EPI), Paclitaxel (PAC) and Taxotere (TXT) was investigated.

Method: Using a cross over design the respective CY was applied alone at cycle I and proceeded by AMI 910 mg/m² 15 min infus at cycle II. Drug schedules consisted of EPI 120 mg/m² 30 min inf, MMC 12 mg/m² bolus, PAC 200 mg/m² 3 H inf. and TXT 100 mg/m² 1 HR inf. Different reversed phase HPLC methods were used determining CY plasma levels.

Results:

AUC ng/ml.H	n	CY	AMI/CY	p (t-test)
EPI (0–6 H)	13	895	1129	0.01
MMC (0–6 H)	15	776	758	0.44
PAC (0–24 H)	16	9780	6612	0.006
TXT (0–3 H)	11	2723	3370	0.1

Conclusion: different effects of AMI on PK of applied CY could be documented: AUC of PAC was decreased (30%) and of EPI increased (26%), latter confirming our results obtained with Doxorubicin. In contrast AUC of MMC and TXT were not significantly changed. Potential mechanisms (on protein binding, distribution, metabolism) are discussed.

1110 ORAL

Bilirubin: Baseline value and transient increase of total bilirubin (BIL) may be used as good predictor of CPT-11'S toxicity

E. Wasserman[1], A. Myara[2], M. Riofrio[1], D. Paumier[2], P. Herait[3], L. Awad[3], J.L. Misset[1], E. Cvitkovic[1]. *[1]SMST Hôp P. Brousse, Villejuif; [2]Lab. Biochimie St Joseph, Paris; [3]Rhône Poulenc Rorer, Montrouge, France*

Total bil rise between days 3 and 6 post treatment, usually reversible by days 7–10, was seen during an ongoing CPT-11/Oxaliplatin (L-OHP) combination phase I trial (see abstract Cvitkovic et al.), the rise being both direct and unconjugated bil. After 37 cycles administered, we observed 30 cycles (81%) with transient bil increase. Amongst the 30 cy, 15 cy had baseline bil <12 μmol/L (group A) and 15 cy bil >12 μmol/L. Grade 3–4 neutropenia was seen in 2 cy (13%) of group A and 9 cy (60%) of group B (p: 0.008). The predictive power of baseline bil values (≥12 μmol/L) and the transient bil increase (x 2 the baseline value) with the observation of neutropenia/diarrhea grade 3–4 (CTC-NCI) is shown below:

	Diarrhea gr 3–4		Neutropenia gr 3–4	
	Sensitivity	Specificity	Sensitivity	Specificity
Baseline bil ≥12 μmol/L	60%	52%	78%	68%
Bil increase x 2 baseline	60%	73%	50%	80%

A retrospective review of phase II single agent data of CPT-11 at 350 mg/sqm q 3 weeks elicited 43 pts where first cy of treatment had bil levels at days 3–7 available. The mean differences between baseline and maximum bil value (μmol/L) were:

	Diarrhea	p: 0.009	Neutropenia	p: 0.18
Bil values μmol/L (mean)	G 0-1-2	G 3–4	G 0-1-2	G 3–4
Baseline	14.28	12.87	8.45	19.94
Maximum	16.01	28.75	1.74	30.46
Difference	1.72	15.87	3.30	10.53

The present observation is ongoing retrospective and prospective assessment in other CPT-11 trials with the aims of optimizing individual CPT-11 doses and its safety.