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.