3 w, cutaneous side effects (hidradenitis and microkystic acnea) were the main dose limiting toxicity (DLT). In order to improve the therapeutic index, a weekly schedule D1, D8 and D15 of monthly cycles (one w rest) was initiated using an escalating dose scheme starting at 35 mg/m^2/w (4 pts level I), then 45 (5 pts level II) and 55 mg/m^2/w (3 pts level III). 12 pts were included having received from I up to 18 ad. (total 72 median 4). Main side effects were asthenia (WHO Grade 3 in 1 pt level III) and mild skin erythema (Grade 1–2 in 5 pts level II and III) and microkystic acnea (grade 1 in 1 pt level III). Nausea, vomiting and headache were prevented with setron and paracetamol premedications. MTD was not achieved but blood PK analysis showed evidence of a non linear kinetics with time between D1, D8 and D15 as shown by a 2 fold increase in clearance. Higher blood levels of the N-oxyde metabolite were found on D8 and D15 in comparison to D1. Clearance returned to base line values on D29 suggesting that a 2 week interval might be sufficient to achieve a reproducible exposure to S16020. Although the weekly schedule was well tolerated, the variability and the uncontrolled exposure to S16020 was not compatible with a development in phase II. Thus the protocol has been amended with a 2 week schedule and kinetic investigations. 5 pts have been included so far (3 at 55 and 2 at 65 mg/m^2 dose level). 2 pts developped an erythematous rash grade 2. MTD is not yet reached. Preliminary PK indicated a stable clearance over a 2 month period of treatment. A stable disease was documented in 1 pt with advanced renal carcinoma having received 18 ad. in the weekly schedule. Final results and PK analysis will be presented.

1160 POSTER

Oxaliplatin (L-OHP) + Tomudex (TOM) and levo-folinic acid (LFA) + 5-fluorouracil (5FU) every 2 weeks. A dose finding study in advanced colorectal carcinoma (ACC)

R. Casaretti[1], L. De Lucia[2], F. De Vita[3], A. Avallone[1], M. Orditura[3], A. Gravina[1], R. D'Aniello[1], P. Comella[1], G. Catalano[3], G. Comella[1]. [1]*Med. Oncol. A of Natl Tumor Inst. of Naples;* [2]*AORN of Caserta;* [3]*2nd Univ. Medical School of Naples, Italy*

Purpose: To define the MTD of L-OHP + TOM followed by LFA + 5FU, given q 2 wks in ACC patients.

Methods: L-OHP 85 mg/sqm (2 h i.v. infusion) → TOM 2.5 mg/sqm (15 min i.v. infusion) were given on d 1, LFA 250 mg/sqm (2 h i.v. infusion) → 5FU 750 mg/sqm (i.v.) were given on d 2. Courses were repeated every 2 wks. TOM and 5FU were alternately escalated if ≤4/6 patients showed the same DLT at the previous dose level. Then L-OHP will be escalated up to 130 mg/sqm. 27 pts with ACC were enrolled: 18 pretreated with 1, and 7 with 2 lines of CT. Liver/lung mets in 16/9 pts. 1/2/3 sites of disease in 9/10/8 pts.

Results: 5 dose levels have been tested so far without encountering the MTD.

L-OHP/TOM/5FU	No. pts	DLT Type	No. Cy.	N*	D*	S*	Neu*	
85/2.5/750	5	0/5		31	2	1	0	2
85/2.5/*900*	6	1/6	N4	35	2	0	0	0
85/*3.0*/900	7	3/6	N4, D3, S4	20	4	1	1	0
85/3.0/*1050*	6	0/6		20	0	0	0	0
105/3.0/1050	3	1/3	N4	7	1	0	0	0

*WHO g 3–4 neutropenia (N), diarrhea (D), stomatitis (S), neurotoxicity (Neu)

2/18 (11%) evaluable pts obtained a PR, while 13 pts showed MR (1) or SD (12).

Conclusions: Full doses of all cytotoxic drugs can be safely administered q 2 wks. G3–4 N is the main toxicity of this combination.

1161 POSTER

Phase I study of men-10755 in patients with a solid tumor as a short i.v. infusion given once every 3 weeks

M. Roelvink[2], S. Aamdal[1], P. Dombernowsky[1], J. Wanders[2], S. Peters[2], S. Bortini[3], A. Crea[3], A. Animati[3], A.-R. Hanauske[1]. [1]*EORTC-Early Clinical Studies Group, Brussels, Belgium;* [2]*Free University Hospital, New Drug Development Office, Amsterdam, Netherlands;* [3]*Menarini Research S.p.A., Clinical Research & Development, Florence, Italy*

Introduction: MEN-10755(M) is a third generation anthracycline showing better antitumor efficacy in preclinical models than doxorubicin.

A Phase I trial is currently ongoing in Denmark and Norway, investigating the feasibility of a tri-weekly schedule administering M as a short i.v. infusion. Main inclusion criteria are normal organ functions, no prior anthracyclines and LVEF >50%.

Results: Presently, thirty pts with a variety of tumor types have been enrolled, 19 M/11 F, median age 53 (range 31–69), median PS 1 (range 0–2). Twenty-one pts had no prior chemotherapy. Doses range from 4 to 110 mg/m^2. Pts were treated for a mean number of 3.8 cycles. Dose-limiting neutropenia was seen in 4 pts at dose levels 55, 80 and 110 mg/m^2 (1/6, 1/6 and 2/5, respectively). Major other grade 3–4 side-effects were nausea (13 pts) and vomiting (12 pts) without prophylactic antiemetics during the first cycle, but well controlled with oral antiemetics in consecutive cycles.

A reduction in LVEF, not correlated to cumulative dose and not accompanied by clinical symptoms was seen in 4 patients (65–49%, 72–57%, 77–60%, 70–55%). The last pt with LVEF reduction recovered after 5 weeks to baseline values. The other pts were not followed up.

No PR or CR was seen and five pts had stable disease as their best response.

M was assayed in plasma and urine using a validated HPLC method. Plasma and urine pharmacokinetics data (mean ± sd) were: CL = 6.3 ± 2.5 L/h/m^2, half-life = 19.1 ± 5.1 h, Vss = 87.6 ± 38.3 L/m^2, amount excreted unchanged in the urine = 10.2 ± 4.2% of the dose. In the range of the doses tested the kinetic of the drug is linear.

Conclusion: The maximum tolerated dose (MTD) was determined at 110 mg/m^2. A lower dose level of 100 mg/m^2 is currently under investigation.

Phase II trials will be conducted in sarcoma, non small cell lung cancer, small cell lung cancer, breast, ovarian, gastric and prostate cancer.

1162 POSTER

A Phase I study of 'Tomudex' and gemcitabine in advanced cancer

C. Cripps[1], G. Batist[2], S. Dahrouge[1], D. Fry[1], A. McQuillan[2], R. Kolendowicz[3], A.A. Abugaber[3]. [1]*Ottawa Regional Cancer Centre, Ontario;* [2]*Clinical Research Unit, Jewish General Hospital; Quebec;* [3]*Zeneca Pharmaceuticals, Canada*

Objectives: 'Tomudex' (raltitrexed) and gemcitabine are novel chemotherapeutic agents with a broad spectrum of activity and different mechanisms of action. We undertook a Phase I dose-escalation study of 'Tomudex' and gemcitabine to determine the DLT, MTD and RD for Phase II trials.

Methods: Eligibility criteria included: incurable solid cancer; [less than/= 1] prior treatment for metastatic disease; age >/= 18 yrs; ECOG performance status 0–2. Doses in cohort 1 were 'Tomudex' 2.0 mg/m[2] (15-min infusion) on day 1 followed by gemcitabine 800 mg/m[2] (30-min infusion) on days 1 and 8, q3 wks. Doses were escalated in 0.5 mg/m[2] increments for 'Tomudex' in cohorts 2, 3, and 4 and as a single increment of 200 mg/m[2] for gemcitabine in cohort 5. At least 3 pts were entered per cohort plus 3 further pts if 1/3 pts experienced a DLT. Further pts were entered at the RD to confirm tolerability.

Results: 30 pts have been treated (20 M/10 F: cohort 1, 3 pts; 2, 9 pts; 3, 5 pts; 4, 10 pts; 5, 3 pts). Primary diagnoses were: colorectal (8 pts), kidney (4 pts), stomach (3 pts), esophagus, pancreas, sarcoma, and small bowel (2 pts each), and breast, head and neck, melanoma and NSCLC (1 pt each), and unknown (3 pts). DLTs were experienced by 2/9 pts in cohort 2 (both grade III thrombocytopenia), 1/5 pts in cohort 3 (diarrhea and rash, both grade III), and 2/3 pts in cohort 5 (grade III shortness of breath, probably gemcitabine-related pneumonitis, and grade III thrombocytopenia). 1/8 evaluable pts in cohort 4 (1 further pt to be entered) experienced a DLT (diarrhea and rash, both grade III). 2/19 pts evaluable for efficacy had a PR (small bowel and colon; 1 unconfirmed), and 12 SD.

Conclusions: The likely RD is 'Tomudex' 3.5 mg/m[2] on day 1 and gemcitabine 800 mg/m[2] on days 1 and 8. This combination schedule is well tolerated and appears to have efficacy. Phase II studies of this combination will start shortly in pts with pancreatic and breast cancer.

Supported by a grant from Zeneca Pharma Inc.

'Tomudex' is a trade mark, the property of Zeneca Ltd.

1163 POSTER

A dose finding and toxicity study of the gemcitabine-oxaliplatin combination in patients with advanced solid tumors

D. Mavroudis, S. Agelaki, K. Kalbakis, Ch. Kouroussis, S. Kakolyris, N. Androulakis, J. Souglakos, N. Vardakis, G. Samonis, V. Georgoulias. *University, General Hospital of Heraklion, Dpt of Medical Oncology, Heraklion, Crete, Greece*

Background: Preclinical studies have shown synergistic activity for platinum compounds in combination with gemcitabine (GMB). Oxaliplatin (L-OHP) is a new platinum analog with better toxicity profile and partial