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)

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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

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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

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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

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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

cross resistance with cisplatin and carboplatin. We conducted a phase I study to evaluate the MTD and DLT of the GMB and L-OHP combination.

Patients and Treatment: GMB was administered on days 1 and 8 as a 30 min IV infusion at escalating doses of 1000–1600 mg/m^2 and L-OHP on day 8 as a 2-hour IV infusion at doses of 60-110 mg/m^2. Cycles were repeated every 3 weeks without growth factors. Thirty nine patients with histologically confirmed advanced stage carcinomas have been entered into the study. Median age 65 (30–76), PS (WHO) 0:11, 1:20, 2:8. Treatment was 1st line for 12 (31%), 2nd line for 9 (22%) and 3rd line for 18 (46%) pts. DLT was evaluated during the first cycle of treatment and included any grade 4 hematologic toxicity, neutropenia grade 3–4 with fever, non-hematologic toxicity grade 3–4 and any treatment delay due to toxicity.

Results: So far 8 dosing levels have been evaluated with 3 or 6 pts at each level and the DLT level (at least 50% of pts develop DLT) has not yet been reached. The evaluated doses for GMB/L-OHP in mg/m^2 have been: 1000/60, 1200/70, 1200/80, 1400/80, 1400/90, 1600/90, 1600/100, 1600/110. All patients were evaluable for toxicity. A total of 131 cycles have been administered (median 3 cycles/pt), with 11 (8%) cycles complicated with grade 3/4 neutropenia, 4 (3%) grade 3 thrombocytopenia, 5 (4%) grade 3 asthenia and 8 (6%) edema. Seventeen cycles (13%) have been delayed due to toxicity. No febrile neutropenia, cumulative hematologic or non-hematologic toxicity or toxic deaths have occurred. Among 27 pts evaluable for response we observed 3 (11%) PR and 10 (37%) SD.

Conclusion: The combination of GMB and L-OHP is well tolerated with acceptable toxicity. Whilst the study is ongoing to determine the MTD, pharmacokinetic studies are also underway.

1164 POSTER

NCIC CTG IND 98: A phase I dose escalation study of raltitrexed (Tomudex) Plus doxorubicin (DOX) in patients with advanced cancer

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Rationale: Raltitrexed (TOM), is a quinazoline antifol with good single agent activity in a range of tumor types, including gastrointestinal and is thus an interesting compound to study in combination with DOX.

Methods: A dose ranging phase I study of TOM in combination with escalating doses of DOX was performed. Patients (pts) with evaluable recurrent or metastatic inoperable solid tumors with acceptable cardiac, hematologic, renal and hepatic function were eligible. The starting dose level of TOM was 2.5 mg/m^2 followed immediately by DOX 30 mg/m^2. DOX was escalated by 10 mg/m^2 increments up to 60 mg/m^2 and thereafter TOM escalated by 0.5 mg/m^2 increments up to 3.5 mg/m^2. Cycles were repeated every 3 weeks. Dose limiting toxicity included grade 4 hematologic and grade 3/4 non-hematologic toxicity.

Results: 22 pts were accrued to 6 dose levels (DL). Median age was 59 yrs (37–76); 12 pts were male; performance status was 0 (2 pts), 1 (13 pts), or 2 (7 pts); 20 pts had gastric cancer; no pts had received chemotherapy for metastatic diseases; the most common sites of disease were stomach (10 pts), liver (10 pts), ascites (8 pts) and regional nodes (8 pts). The 22 pts have received 99 cycles with 9 pts receiving 6 or more cycles. The most common drug related toxicities included alopecia (91%), nausea (68%), fatigue (59%), vomiting (50%), anorexia (46%), stomatitis (32%), altered taste (32%) and diarrhea (23%), usually grade 1 or 2 in severity. There appeared to be no excess of cardiotoxicity. At DL 6 (TOM 3.5 mg/2 and DOX 60 mg/m^2 1 pt had febrile neutropenia while 2 pts had grade 4 myelosuppression and this dose was declared the maximum tolerated dose (MTD). Interestingly, 3 durable (7–12.8 months duration) confirmed partial responses have been seen in 13 evaluable patients at the first 4 dose levels, all in pts with gastric cancer.

Conclusions: The recommended dose for further study is TOM 3 mg/m^2 plus DOX 60 mg/m^2.

This study was supported by a grant from Zeneca Pharma Inc

1165 POSTER

Gemcitabine and Docetaxel in patients with advanced solid tumors. A GETICS phase I trial

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Gemcitabine (G) and Docetaxel (D) have a broad spectrum of clinical activity. This phase I trial was designed to identify the maximum tolerated dose (MTD) and dose limiting toxicity (DLT) of G administered days 1 and 8 plus D day 8 every 3 weeks. A minimum of 3 patients (pts) were entered per dose level.

Thirty three pts were entered in seven dose levels (G/D): I: 800/50, II: 1000/50, III: 1000/75, IV: 1000/90, V: 1000/100, VI: 1250/75, VII: 1500/75.

Demographics: 17 M/16 F, median age 59 years (range 37–77), median ECOG PS 1, prior chemotherapy: 31 pts (prior paclitaxel 19 pts, >1 regimen 24 pts). Tumor types included: NSCLC (14), breast (10), ovary (3), bladder (2), sarcoma (1), parotid (1), germ cell (1), unknown primary (1).

G was given as a 30 min. infusion on days 1 and 8, and D was given as a 1 hour infusion on day 8. Cycles were repeated every 3 weeks. All pts received oral dexamethasone for 5 days starting on day 8. Colony stimulating factors were not allowed.

DLT was leucopenia at dose level IV and V, with higher doses of G Leucopenia and Thrombocytopenia were DLTs. Non-hematologic toxicities were <grade 3 and included: nausea, fatigue, anorexia, dermatitis, myalgia and peripheral neurotoxicity. Mild to moderate peripheral edema was found in seven pts and two of them required diuretics. The suppression of G on day 15 maybe was the cause of this lower toxicity profile. Antitumor activity was observed.

We conclude that G1000 plus D90 and G1250 plus D75 are feasible to perform in this heavily pretreated population and deserve further studies.

1166 POSTER

Clinical pharmacokinetic comparative crossover study between three times a day and once a day-oral administration of etoposide

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Purpose: Based on previous studies, an etoposide concentration of approximately 1 μg/ml appears to be effective, while peak plasma levels greater than 2–3 μg/ml are thought to be associated with more severe myelosuppression. Since the drug's interpatient and intrapatient variability is large with oral dosing there are some different items in pharmacokinetic studies in the literature. This is the first study with a crossover design, to neglect the individual differences in comparing the pharmacokinetic results of three times a day and once a day-oral administration of etoposide capsule.

Methods: Two groups of four patients each received 75-mg/day oral etoposide for two days as either 75-mg once daily, or 25-mg three times daily for two days. On days 8 and 9, each group received the other form of treatment. On days 2 and 9 blood samples were collected during 24 hours to measure plasma etoposide levels. The etoposide concentrations were determined by high-performance liquid chromatography in Nippon Kayaku Co. Laboratory, in Japan.

Results: There was no significant difference between Cmean (Cmean = area under the curve/24 hr) in two treatments and no relationship between the daily dose per body surface area and Cmean. In one dose schedule peak was greater than 2 μg/ml in five (62.5%) patients (95% CI 24.5-91.5) and greater than 3 μg/ml in three (37.5%) patients (95% CI 8.5-75.5).

No patient in three-dose schedule had higher than 2 μg/ml level ($p = 0.038$). No such difference in time the concentration exceeded 1 μg/ml was observed between the mean values of the two different dosing schedules.

Conclusion: As the interpatient variability was neglected by crossover method, based on these data, the results favor fractionating a daily 75-mg etoposide dose.

1167 POSTER

Oral ZD9331, a non-polyglutamated thymidylate synthase (TS) inhibitor: A phase I and pharmacologic study

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ZD9331 is a novel selective TS-inhibitor, which does not undergo polyglutamation and therefore, might overcome resistance to other polyglutamated drugs that arise due to alterations in FPGS expression. We are performing a phase I study on the oral formulation of ZD9331. To date, 31 patients (pts), 24 male and 7 female, median age 59 years, with colorectal (17 pts), (A) CUP (2 pts), renal ca (2 pts) or miscellaneous tumours (10 pts) have