received 99 courses of ZD9331 over 8 dose levels: 2.5, 5, 10, 20, 30 and 40 mg once daily for 5 days, 10 mg twice daily for 5 days and 10 mg once daily for 10 days, respectively, repeated every 3 weeks. One pt treated at 40 mg/day, 2 pts treated at 20 mg/day (bid), and 1 pt at 10 mg for 10 days developed grade 3–4 neutropenia and/or thrombocytopenia. Non-haematological toxicity was usually mild and included nausea/vomiting, stomatitis, diarrhea, myalgia/arthralgia, fever, and alopecia. Transient asymptomatic rises in liver transaminases occurred at all dose levels. Skin rash occurred in 23% of cycles. Pharmacokinetics (PK) demonstrated a saturable absorption of ZD 9331 from doses of 20 mg once daily onward, precluding further dose escalation. Twice daily dosing did not significantly increase exposure compared with a once-daily administration. PK analysis at the 10 mg × 10 days schedule is still on going. Preliminary plasma deoxyuridine data indicate that they can be used as a marker for TS-inhibition.

1168 POSTER

Phase I trial with farnesyltransferase inhibitor R115777 in patients (pts) with advanced solid tumors

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Purpose: The critical modification needed for the ras protein to exert its function is farnesylation, which can be blocked by R115777, a potent and selective orally bioavailable non-peptidomimetic inhibitor of farnesyltransferase. This study was designed to determine the MTD of a 28-day bid oral regimen.

Methods: R115777 is given according to an intra- and inter-pt dose-escalation scheme with 1–6 pts per dose level depending on toxicity. Each 28-day cycle (C) is followed by a 7–14 d restperiod. Starting dose was 200 mg bid, increased with 100 mg bid with a maximum of 2 intra-pt dose escalations. DLT was defined as grade 3–4 toxicity or treatment delay >3 wks.

Results: Sofar 7 pts have been treated, median age 58 yrs, all had received previous chemotherapy. One pt had grade 4 leucopenia at 300 mg bid in C1, and this cohort was expanded to 6 pts. One pt in this cohort had grade 4 leucopenia at 500 mg bid. At 300 mg bid one pt had grade 3 diarrhea in C2 and one pt grade 3 fatigue in C1, possibly related to R115777. One pt with gastric cancer has an ongoing SD for 8 months. PK of R115777 was assessed in C1 for the 1st 12 h dosing interval on day 1 and 28 and was measured by a validated HPLC method. Peak concentrations ranged from 431–800 ng/ml and were obtained within 2–5 h. Trough levels ranged from 29.3–98.7 ng/ml. There was little accumulation, and steady-state concentrations were maintained throughout the dosing period.

Conclusion: Recruitment continues to determine MTD and to confirm whether leucopenia is dose-limiting.

1169 POSTER

Phase I trial of a three-day schedule of cisplatin plus topotecan

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Purpose: Topotecan (tpt) is emerging as a new chemotherapy option in the treatment of lung and ovarian cancer. Preclinical data suggest a sequence dependent synergy of tpt with cisplatin but a clinically acceptable sequence-schedule of these two agents has yet to be defined. We conducted a phase I study of a convenient and logistically feasible daily ×3 schedule. By splitting the dose of cisplatin over three days we aimed to a more favourable toxicity profile and a possibly better pharmacological inter-reaction of the two agents. Main objectives were to define the maximum-tolerated dose (MTD) and dose limiting toxicity (DLT) and to characterise the toxicity profile of this regimen.

Methods: The standard for phase I entry criteria and definitions for MTD and DLT were applied. Both agents were administered intravenously on a daily ×3 basis every 3 or 4 weeks with or without G-CSF. Cisplatin was given first with hydration followed by topotecan two hours later. At present 18 patients (4 F/14 M, median age 58, range 30–72) have been treated and a total of 49 courses have been given at four dose-levels: cisplatin/tpt: 25/0.75 – 25/0.9 -25/1- 25/1.15 mg/m^2/day.

Results: Myelossupression was the DLT as expected. With cisplatin at 25 mg.m−2 daily dose the MTD of the combination was 25/1.15 at which 2/2 patients developed febrile neutropenia and grade 4 thrombocytopenia each one respectively. Febrile neutropenia also occurred in 1/6 patients at dose levels 25/0.9 and 25/1. Both were carboplatin-pretreated pts and succeeded to continue treatment with G-CSF support. At these levels a short-lived grade 2 or 3 neutropenia was seen in half of the patients and grade 3 thrombocytopenia was infrequently observed but tended to be cumulative in pretreated patients. Non-haematological toxicity was unremarkable. Efficacy was documented in 3 lung and 1 ovarian case.

Conclusion: A three-day schedule of the cisplatin plus topotecan combination is well tolerated with mainly haematological toxicity. With cisplatin at 25 mg.m−2 daily dose the MTD of the combination is 25/1.15 and the optimal 25/1. The study is in progress investigating the combination at 20 mg.m−2 fixed daily dose of cisplatin.

1170 POSTER

Phase I pharmacokinetic study of MEN-10755 in solid tumors

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Purpose: In a phase I and pharmacokinetic study the safety profile of MEN-10755 (MEN) was evaluated. MEN is a novel anthracycline showing in the animal models an improved therapeutic efficacy over doxorubicin, especially in breast, ovarian and lung cancer.

Patients & methods: Eligible patients (pts) had incurable cancer, performance status ECOG ≤ 2, no prior anthracyclines and LVEF ≥50%. MEN was administered as 15 min iv infusion once weekly for 3 weeks, followed by 1 week rest. Starting dose was 15 mg/m^2 per infusion and was escalated to 30 mg/m^2 and up to 45 mg/m^2 per infusion. Plasma and urinary MEN levels were measured by HPLC with fluorescent detection.

Results: Until now, 8 pts were entered. Anemia grade (gr) 1–3 occurred in 7 pts, anemia gr 4 in 1 pt at 30 mg/m^2, thrombocytopenia gr 1 in 1 pt at 30 mg/m^2. Two pts had leukopenia gr 1 at 30 mg/m^2. At 45 mg/m^2, in 2 pts the third infusion day 15 was omitted because of ANC ≤1000/mm^3. These pts also had leukopenia gr 3. Nausea/vomiting gr 1–2 occurred in 4 pts, gr 3 in 1 pt at 45 mg/m^2. During infusion 2 pts had flushing gr 2. Most pts experienced alopecia gr 1. No significant LVEF reduction has been observed. AUC was correlated with dose. Mean $AUC_{0\rightarrow\infty}$ for 30 mg/m^2 = 6.0 mg/L.h. Mean values (all doses) were: $t_{\frac{1}{2}\beta}$ = 15.2 ± 3.6 h, CL = 5.6 ± 0.9 L/h/m^2, Vss = 81.2 ± 23.5 L/m^2. Mean renal clearance was 4.4 ± 2.1%.

Conclusion: Neutropenia day 15 was dose limiting at 45 mg/m^2/infusion. Currently 40 mg/m^2/infusion is evaluated.

1171 POSTER

Pharmacology study of chronic oral idarubicin for breast cancer

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Purpose: To investigate new modalities of IDA administration, we designed a phase I study of IDA given orally in hyperfractionated doses. The purpose was to determine the maximum-tolerated dose (MTD), toxicity profile, and pharmacokinetics of IDA with this schedule.

Methods: Patients with metastatic breast cancer relapsed after standard therapy (including anthracyclines). The initial dose of IDA was 2 mg/d given orally in two doses every 12 hrs for 21 days every 28 days. Subsequent dose escalations were in increments of 1 mg/day. Dose limiting toxicity (DLT) was defined as G4 hematologic toxicity or any other toxicity ≥G3. Pharmacokinetic parameters were calculated using a noncompartmental model.

Results: Thirty-one patients were enrolled. IDA was escalated from 2 mg/d to 10 mg/d and MTD was reached at this dose level; DLTs were neutropenia (G4) associated with leukopenia and piastrinopenia in 1 patient and diarrhea (G3, 1 patient) out of 5 patients. Both IDOL and IDA exhibited linear pharmacokinetics over the dose range studied. The median $AUC_{(0-24)}$ of IDA increased from 3.95 μg*h/L (range, <2.4 to 6.9 μg*h/L) to 15.2 μg*h/L (range, 14.2 to 18.4 μg*h/L) when the dose was increased from 2 to 10 mg/d. The median $t_{1/2}$ for IDA was 21.2 hours (range, 11.3 to 49.7 hours), whereas $t_{1/2}$ for IDOL was much longer (median, 50.0 hours; range, 22.7 to 85.3 hours). IDA/IDOL ratio in plasma (median, 8.3; range, 5.4 to 16.5) was not dose-dependent.

Conclusion: The MTD of the schedule is 10 mg/d and the DLTs are neutropenia and diarrhea. Tolerance was good and the treatment is feasible as home therapy.

1172 PUBLICATION

A phase I study of the multitargeted antifolate (MTA) (LY 231514) in combination with oxaliplatin (LOHP) in metastatic solid tumors

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MTA is a novel multitargeted antifolate which inhibits the enzymes thymidylate synthase (TS), dihydrofolate reductase (DHFR) and glycinamide ribonucleotide formyl transferase (GARFT). LOPH is an oxalato-diaminocyclohexane platinum analogous. Previous in vitro and in vivo studies reported synergistic effects of LOPH and 5-FU a well known TS inhibitor suggesting that there may be an advantage in combining MTA and LOPH. This phase I trial aimed to determine the maximum tolerated doses (MTD) of MTA given as a 10 mn IV infusion followed 30 mn after by LOPH administered by IV infusion over 2 hours q 21 days. DLTs were assessed at first cycle and defined as grade 4 neutropenia of more than 7 days, febrile neutropenia, grade 4 trombocytopenia or grade $\geq$3 non hematologic toxicity (excluding alopecia, nausea and vomiting). To date, 9 patients (pts) median age 51, median PS 1 have received 24 courses of therapy at 3 dose levels: MTA/LOPH level 1: 300/85 (3 pts); level 2: 400/85 (4 pts); level 3: 400/100 (2 pts). Drug related toxicities include leukopenia grade 3 (1 pt), anemia grade 3 (1 pt) and transaminase grade 3 (1 pt) but no DLT is observed so far. Accrual is continuing at following levels.

1173 PUBLICATION

Gemzar® (G) and epirubicin (E) in patients (pts) with metastatic breast cancer (MBC): Final results of a phase I dose finding study

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G, a new cytidine analog has shown activity as first or second line in the treatment of MBC. E is among the most active agent with different toxicity profile. We combined G and E in a phase I dose finding trial to determine the maximum tolerated dose (MTD) and the toxicity profile of the combination. Pts with MBC, adequate organ functions and WHO performance status (PS) $\leq$ 2 were eligible. Up to one previous regimen was allowed. G was given as 30 mn IV infusion on days 1 and 8; and E as 15 min IV infusion on day 1 q 21 days. 43 pts enrolled, median age: 54 years, median WHO PS: 0.

No DLTs appeared on the 4th first levels: (G/E)
(level 1: 800/50; level 2: 800/50; level 3: 1200/50; level 4: 1200/60).

No. Level (G/E)	DLT/total pts	Dose Limiting Toxicity (pt)
5 – (1200/75)	2/6	prolonged grade 4 neutropenia (1) febrile neutropenia (1)
6 – (1300/75)	2/7	prolonged grade 4 neutropenia (1) febrile neutropenia (1)
7 – (1400/75)	0/3	
8 – (1500/75)	2/8	prolonged grade 4 neutropenia (2)
9 – (1500/90)	2/6	prolonged grade 4 neutropenia (1) febrile neutropenia (1)

A phase II trial is now opened with the recommended dose as follow: G: 1500 mg/m^2 day 1 & day 8 and E 90 mg/m^2 day 1, q 21 days

1174 PUBLICATION

Phase I study of docetaxel epirubicin and cyclophosphamide (TEC) in patients with advanced cancer (AC)

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Purpose: Docetaxel (T) has considerable activity as a single agent and epirubicin and cyclophosphamide (EC) are commonly used in breast cancer. The aim of this study is to establish the maximum tolerated dose (MTD) of TEC ± lenograstim.

Methods: Pts with AC, normal organ function, ECOG PS 0–2 and 0–1 prior chemotherapy (<300 mg/m^2 doxorubicin or equiv.) were treated every 3 weeks with E, then C 600 mg/m^2 followed 1 hr later by T (E/T doses are described below). Stepwise use of ciprofloxacin (Ci) 500 mg bid from day 5 until neutrophils $\geq$1.0 $\times$ 10^9/l or lenograstim (L) 263 μg daily from day 2 until neutrophils $\geq$1.0 $\times$ 10^9/l was used to prevent febrile neutropenia (FN).

Results: 36 pts entered to identify the MTD, median age 55 years (range: 25 to 73), prior chemo 18/36, median 6 cycles received (range 1 to 10).

Grade 3–4 Toxicity = Dose Limiting Toxicities (DLTs) experienced

E/T mg/m^2 Dose Level	60/60 1	60/60 1 + Ci	60/60 1 + L	60/75 2 + L	75/75 3 + L	90/75 4 + L	90/85 5 + L	105/85 6 + L
Total Pts	3	5	3	5	6	6	3	6
FN	2	2		1	1	2	0	2
Infection		1						
Diarrhea	2							
Vomiting								1

The MTD was defined as the dose causing DLT in 3/3 or >3/6 pts. There were 13 PR's and 3 CR's in 28 evaluable pts. (8/12 in Ca breast).

Conclusion: The MTD was reached at dose level 1 ± Ci. Lenograstim allowed escalation of TEC to dose level 6. The recommended dose for phase II/III is E 90, C 600 and T 85 mg/m^2, with lenograstim support.

1175 PUBLICATION

Synergistic effects of ZD9331 a non-polyglutamatable thymidylate synthase inhibitor in combination with SN38 in human colon cancer cells

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ZD9331, a recent quinazoline, showed potent cytotoxic effects in vitro and in vivo and manageable toxicity in phase-I/II trials. This study aims (1) to identify new drug combinations against human colon cancer, (2) to define optimal sequences combining ZD9331, and (3) to investigate the cellular and molecular mechanisms involved in drug interactions in cancer cells. Cytotoxicity and drugs interactions were studied in human HT29 colon cancer cells at both non-constant and constant ratios using the Chou and Talalay analysis based on the median-effect principle. In HT29 cells, the IC50s of ZD9331, 5-FU, SN38 and oxaliplatin were 1.3 10-8 M [range 0.7–2.3], 9.4 10-7 M [4.8–18.0], 5.6 10-9 M [3.2–9.8], and 1.1 10-6 M [0.8–1.6], respectively. The concomitant exposure to ZD9331 and SN38 (the active metabolite of CPT-11) yielded synergistic effects at low concentrations and additive effects at higher concentrations. Additive effects were observed with 5-FU but antagonism was seen with oxaliplatin. Preliminary results suggest that SN38 should be given prior to ZD9331. Our data support clinical trials combining ZD9931 with CPT-11, the prodrug of SN38, in patients with colon cancer.

1176 PUBLICATION

Single and multiple dose pharmacokinetics of letrozole (®Femara) in elderly and younger postmenopausal patients (pts) with advanced breast cancer

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A multicenter, open-label, non-randomized phase II trial was designed to compare single and multiple dose pharmacokinetic data of letrozole (2.5 mg, given orally once daily) in two age groups of postmenopausal women with advanced breast cancer: younger, aged 50–65 years (group A) and elderly, aged $\geq$70 years (group B). Pharmacokinetic profiles were collected after a single dose (dy 19) and at steady state (day 66). Sixteen pts were enrolled in group A (mean age 61 yrs, range 52–66) and 12 in group B (mean age 72, range 70–76).

Results: the mean Cmax (nmol/L ± SD) at day 1 and day 66 was 117 ± 45 and 423 ± 185 in group A and 111 ± 12 and 541 ± 319 in group B. The half-life (h ± SD) at day 1 and day 66 was 69 ± 33 and 111 ± 53 in group A