increased midazolam AUC by 1.2 fold compared with midazolam alone (Table). The upper limits of the 90% CIs for the AUC and C_{max} ratios were below 1.5, indicating no clinically relevant effect on midazolam exposure according to the predefined criteria. Zibotentan had no marked effect on the PK of 1-hydroxy and 4-hydroxy midazolam. Tolerability was as expected, with fatigue and headache being the most common adverse events associated with midazolam and zibotentan treatment, respectively.

Parameter	GLSMean		Ratio (90% CI)
	Midazolam + zibotentan	Midazolam	
AUC, ng×h/ml	109.5	91.5	1.20 (1.05–1.37)
AUC_{0-t}, ng×h/ml	107.9	89.8	1.20 (1.05–1.38)
C_{max}, ng/ml	39.4	37.5	1.05 (0.84–1.32)

Conclusion: These results indicate that zibotentan 10 mg once daily has no clinically relevant potential to inhibit CYP3A4.
Trial sponsored by AstraZeneca (AZ code D4320C00010).

1245 POSTER

Zoledronic acid and Taxotere (ZANTE) metronomic and sequential administration in patients with hormone refractory prostate cancer (HRPC) – final results of phase I study

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Background: Docetaxel (DTX) is an active agent for HRPC. Zoledronic acid (ZOL) has demonstrated efficacy in the treatment of bone metastases in patients with prostate cancer. In vitro data suggest that ZOL and DTX have a synergistic effect on growth inhibition of prostate cancer cells and that such synergism is sequence-dependent. On the basis of these considerations, a phase I clinical trial of ZOL and DTX administered in 2 different sequences was conducted in HRPC.
Patients and Methods: Inclusion criteria were: HRPC, bone metastases, ECOG PS 0−2, no previous chemotherapy, adequate organ function, written informed consent. Cohorts of three to six patients were sequentially enrolled to receive one of three escalated doses of docetaxel (30, 40 and 50 mg/m^2) in combination with a fixed dose of ZOL (2 mg), both administered every 14 days in two different sequences. Sequence A: DTX at the day 1 followed by ZOL at the day 2. Sequence B: ZOL at the day 1 followed by DTX at the day 2. DLT was defined as the occurrence during the first 3 cycles (6 weeks) of therapy of febrile or long lasting G4 neutropenia, G3−4 thrombocytopenia, G3−4 non hematologic toxicity (except nausea and vomiting), any toxicity inducing a delay of treatment longer than 2 weeks. Angiogenic factors, cytokines and T lymphocyte subpopulation distribution were evaluated prior and after treatment.
Results: The study enrolled 22 patients (median age 73 years; range 43−80). The MTD was not achieved with sequence A. Two patients at third level of sequence B developed DLT that consisted of G3 thromboflebitis and cardiac ischemia. A reduction ⩾50% of PSA levels was observed in four patients (levels 2A and 3A). Angiogenic factors, cytokines and T lymphocyte subpopulation distribution were evaluated in 19/22 patients. Data will be reported at the congress.
Conclusions: The recommended dose of docetaxel was 40 mg/m^2 for sequence ZOL → DTX and 50 mg/m^2 for sequence DTX → ZOL.

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Oral oncology drugs: how do patients view their effectiveness?

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Background: While standard chemotherapeutic agents are usually administered intravenously, the growing number of oral agents is progressively gaining prominence. Many possess new mechanisms of action and specific targets that result in different adverse effect profiles from those associated with traditional chemotherapies. Oral administration of chemotherapy (CT) offers considerable advantages over the parenteral route. This study sets out to analyze patient opinion on different aspects of oral and intravenous (IV) treatment.
Material and Methods: This prospective study was carried out by means of a survey of patients to compare differences in preference, tolerance, effectiveness and security between oral and IV chemotherapy. 190 patients who had received both treatments were enrolled from September to November 2008.
Results: Seventy percent of the patients were women and the median age at diagnosis was 60 years (range, 28 to 91 years). Fifty percent had gynaecological tumours (mainly breast cancer); thirty percent, digestive tumours; eighteen percent, lung cancer and two percent, other neoplasm, with a median of 3 different CT schemes received (range, 1 to 9).
Patients preferred the oral route to the IV route (76% vs. 20% respectively; $P < 0.001$). Four percent had no preference. Tolerance was better with oral therapy (64%) than with IV chemotherapy (36%; $P < 0.001$) and became lower as the number of treatment cycles increased. With respect to effectiveness, sixty percent of patients considered the IV chemotherapy more effective, while eleven percent chose oral therapy and twenty nine percent found both equally effective ($p < 0.001$). Sixty one percent of patients felt more secure receiving intravenous CT, while eight percent felt more secure with oral therapy. Thirty one percent felt that there were no differences between the two routes of administration ($p < 0.001$).
Conclusions: Oral agents open up new possibilities with respect to convenience and patient satisfaction. Nonetheless, some aspects of the use of oral CT need to be examined. This study shows better tolerance of oral administration and a patient preference for oral therapy. However, when asked about important issues such as the effectiveness or security offered by the different treatment types, most patients expressed a preference for the IV route, irrespective of tolerance.

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Phase I study of nimotuzumab, a humanized anti-epidermal growth factor receptor (EGFR) IgG1 monoclonal antibody in Japanese patients with solid tumors

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Background: Nimotuzumab is a humanized IgG1 monoclonal antibody to epidermal growth factor receptor (EGFR). The antibody has demonstrated absence of severe skin toxicity commonly caused by other EGFR-targeting antibodies. The primary objective of this phase I open-label dose escalation study was to evaluate safety of nimotuzumab in Japanese patients with solid tumors. Secondary endpoints included tumor response and human antibody against nimotuzumab (HAHA), and pharmacokinetics (PK), pharmacodynamics (PD) and biomarker.
Methods: Thirteen patients with advanced solid tumors who had failed in prior standard therapies were enrolled in two centers. Nimotuzumab was given intravenously weekly at the dose levels of 100, 200 and 400 mg/body. Skin biopsies and serum samples were collected for PD analysis before treatment and after fourth infusion. For biomarker analysis, blood and formalin fixed and paraffin embedded tumor samples before treatment were collected
Results: Twelve patients were treated except 1 patient who received other therapy. Median treatment cycle (4 weeks per cycle) was 4 (range 1−10) in these 12 patients. Neither dose limiting toxicity nor grade 3 drug-related adverse events including infusion reaction were observed, and maximum tolerated dose was not reached. Common drug-related adverse events were grade 1 or 2 skin rash (58%), which were localized and did not show relation to the dose levels. No HAHA appeared during the whole treatment course. AUC_{0-inf}, C_{max} and $t_{1/2}$ increased and the clearance decreased in a dose dependent manner. While neither complete nor partial response was obtained, 8 patients (67%) showed stable disease (⩾4 weeks). Median time to progression (TTP) was 14 weeks. Among 8 patients whose pre-treatment tumor samples were obtained, 5 patients with amplified gene copy number of EGFR showed longer TTP than the other 3 patients.
Conclusions: Nimotuzumab was well tolerated up to 400 mg/body weekly in Japanese patients with advanced solid tumors. Additional biomarker analysis is currently ongoing.