(1), fever (1) and unspecified reason (1) accounted for the remaining delays. Toxicity data are presented in the table on p. S174.

There has been 1 therapy related death, due to malignant ulcer hemorrhage associated with G4 plts (500/40). Two patients discontinued due to toxicity: pancytopenia (1) and thrombocytopenia (1). Preliminary analysis does not reveal any overt alterations of the pemetrexed pharmacokinetic profile on coadministration with paclitaxel. Responses have been noted in thyroid, gastric, penile and renal cell cancers.

Conclusions: Overall, this schedule of pemetrexed and paclitaxel is well tolerated. The combination appears to have a broad spectrum of activity. Study enrollment is ongoing.

577 POSTER

A phase I dose-escalation study of pemetrexed and docetaxel in patients with locally advanced or metastatic cancer: preliminary results of schedule B

D.W. Fyfe[1], P. Vasey[2], P.J. Woll[1], I.C. Smith[3], R. Clark[3], J. Carmichael[4]. [1] *Nottingham City Hospital, Department of Clinical Oncology, Nottingham, United Kingdom;* [2] *Beatson Oncology Centre, CRC Department of Medical Oncology, Glasgow, Scotland;* [3] *Eli Lilly and Company, Indianapolis, IN, USA;* [4] *Astra Zeneca, UK*

Background: Both pemetrexed (Alimta), a novel multitargeted antifolate, and docetaxel, a semi-synthetic taxane, have proven to be effective antineoplastic agents. The primary study objective was determination of the maximum tolerated dose (MTD) of the pemetrexed/docetaxel combination in 2 schedules (schedules A and B); secondary objectives were to identify dose-limiting toxicities (DLTs) and recommended doses for phase II study. Preliminary results for schedule B are presented. (For schedule A, see *Mackay H et al. Proc ASCO 2002; #2120.*)

Methods: Patients (pts) who were at least 18 years of age with advanced or metastatic cancer received docetaxel on days (d) 1 and 8 and pemetrexed on d8 (before docetaxel) every 21 days, with folic acid and vitamin B_{12} supplementation to reduce pemetrexed-related toxicity. DLT was defined as the occurrence of any of the following in cycle 1: CTC grade (G) 4 neutropenia lasting > 5 days; febrile neutropenia; G4 thrombocytopenia; G3 or 4 non-hematologic toxicity (excluding nausea/vomiting, or isolated G3 ALT or AST); or treatment delay > 2 weeks due to unresolved toxicity. The MTD was reached when DLTs occurred in 2 of 6 pts. Additional pts were then treated at the previous dose level; if DLTs did not occur in * 3 of 9 pts, that dose level was the recommended dose for phase II study.

Results: Data are currently available for 15 pts (13 males, 2 females) with a median age of 61 years (range, 31-77) in 4 dose levels (pemetrexed mg/m^2/docetaxel mg/m^2): 250/25 (3 pts), 325/25 (6 pts), 325/30 (3 pts), and 400/30 (3 pts). Tumor types include mesothelioma, colon, esophagus, stomach, rectum, and head and neck cancers. An ECOG performance status of 0, 1, and 2 was reported in 4 (26.7%), 9 (60.0%), and 2 (13.3%) pts, respectively. Fourteen pts received 1 prior chemotherapy regimens. The total number of cycles reported was 42 (median 2; range, 1-6). There were 8 delays (2 of which were due to neutropenia and increased bilirubin, respectively), 1 dose reduction (at 325/25 due to G3 diarrhea), and 1 omission (at 400/30 due to decreased weight). One pt experienced G3 diarrhea (DLT) at 325/25. Other significant grade 3/4 toxicities were G3 bilirubin (1 pt), G3 neutropenia (2 pts), and G3 anemia (1 pt). No treatment-related deaths have been reported. Two pts discontinued the study due to tendonitis and decreased weight, respectively. Of the 11 pts with response data, stable disease was reported for 4 pts (in stomach, colon, and other tumor types). Based on available data, dose escalation was continued to 500/30, and the MTD was reached when DLTs (G3 fatigue) occurred in the first 2 pts.

Conclusion: The combination of pemetrexed d8 and docetaxel d1,8 is feasible and well tolerated. The MTD appears to be 500/30. Enrollment for 400/30 is ongoing to establish the recommended phase II dose

578 POSTER

Post-transcriptional regulation of P-glycoprotein expression in human colon carcinoma cell lines.

A. Gómez-Martínez[2], P. García-Morales[2], E. García-Poveda[2], M.D. Castro-Galache[2], J.A. Ferragut[2], J.L. Soto[1], A. Carrato[1,2], M. Saceda Sanchez[1,2]. [1] *Hospital General Universitario de Elche, Unidad de Investigación, Elche (Alicante), Spain;* [2] *Universidad Miguel Hernández, Instituto de Biología Molecular, Elche (Alicante), Spain*

Background: Multidrug resistance constitutes a major obstacle for success of cancer chemotherapy. The role of MDR1 gene product P-glycoprotein (Pgp) has been well established. The regulation of MDR1 expression has been mostly related to transcriptional control of the MDR1 gene expression. Recently, it has been reported that in the colon carcinoma cell line SW620, Trichostatin A (TSA), a histone deacetylase inhibitor (DHCAi), produces an increase in MDR1 transcription. This result means a major set back, because a number of histone deacetylase inhibitors inhibit tumour growth and several of them are in clinical trials. An increase in Pgp expression mediated by these compounds would made them impossible to combine with other cytotoxic agents that are Pgp substrates. We have investigated the effect of TSA on Pgp expression in the human colon carcinoma cell lines HT29 and HT29/M6.

Material and methods: Detection of mRNA levels was performed by real time RT-PCR, using specific primers and Taqman® probe. Detection of Pgp protein was analysed using three different experimental approaches: immunocytochemistry, western blot, and calcein uptake. We have also analysed by real time RT-PCR, the subcellular distribution (nuclear *vs* cytoplasmic) of Pgp mRNA. Translation of Pgp has been analysed performing the polysome profile of mRNA in sucrose gradients.

Results: We have found an increase in Pgp mRNA in human colon cancer cell lines after TSA treatment. However, this increase does not parallel an increase in Pgp protein levels or activity. We have also found that the transport of Pgp mRNA from the nucleus to the cytoplasm is quite inefficient, being this effect independent of TSA treatment. However, significant levels of Pgp mRNA reach the cytoplasm and bind to endoplasmic reticulum-associated ribosomes. We have analysed the Pgp mRNA distribution in polysomes profiles. Our results suggest a block in Pgp mRNA translation.

Conclusions: Trichostatin A increases Pgp mRNA levels in HT29 and HT29/M6 colon cancer cell lines. This increase does not correlate with a parallel increase in Pgp protein levels or activity.

The analysis of the subcellular distribution of Pgp mRNA points to an inefficient transport from nucleus to cytoplasm.

The percentage of Pgp mRNA transported to the cytoplasm, is able to bind to endoplasmic reticulum-associated ribosomes.

A translational blockade of the Pgp mRNA may occur in human colon cancer cell lines.

579 POSTER

Significant tumor growth inhibition of glioblastoma xenografts by NNC 47-0011 - a low molecular weight tricyclic tyrosine kinase modulator with anti-angiogenic activity.

R. Cao[1], Y. Cao[1], S. Dissing[2], A.J. Hansen[3], P.E.G. Kristjansen[4], U.B. Olsen[5]. [1] *Karolinska Institute, Microbiology and Tumor Biology Center, Stockholm, Sweden;* [2] *University of Copenhagen, Medical Physiology, Copenhagen, Denmark;* [3] *Novo Nordisk A/S, Cancer & ImmunoBiology, Maaloev, Denmark;* [4] *University of Copenhagen, Experimental Oncology, Copenhagen, Denmark;* [5] *Novo Nordisk A/S, Pharmacology, Maaloev, Denmark*

The Neurin series of tricyclic compounds are active against chronic inflammatory conditions (Olsen et al., Eur. J. Pharmacol. 435:43-57, 2002) in which angiogenesis plays an important role as it does in the growth of malignant tumors. NNC 47-0011 [(R)-1-(3-(6,7-Dihydro-5H-dibenz[b,g]azocin-12-yl)propyl)-3-piperidinecarboxylic acid] (MW 379) was selected due to strong anti-angiogenic effects in the chicken chorio-allantoic membrane (CAM) assay. Likewise it inhibited vessel growth induced in the mouse cornea by either VEGF or bFGF in a dose-dependent manner. We therefore assessed the effect of NNC 47-0011 on the growth of a tumor that is highly dependent on angiogenesis. MG U87 (human glioblastoma multiforme) was serially inoculated s.c. in the flanks of 7-week-old nu/nu homozygotous nude male mice of NMRI background. The tumor bearing mice and control animals were randomly allocated to receive either plain drinking water or water with 100 or 500mg/liter of NNC 47-0011 from the time of inoculation. This is equivalent to approx. 20 and 100 mg/kg/day. The mice were observed twice daily and the tumors were measured daily in two perpendicular diameters. The compound did not cause any adverse effects and produced a significant retardation of tumor growth at 100mg/kg/day (Kaplan-Meier log-rank analysis). However, in vitro NNC 47-0011 did not affect proliferation or migration of endothelial cell at concentrations attained in plasma of tumor bearing mice but it affected intracellular signalling through the P-Akt pathway. We conclude that NNC 47-0011 significantly inhibits the growth rate of the human glioblastoma line U87 at doses well tolerated. The mechanism probably involves inhibition/modulation of tyrosin kinase receptor. The Neurin family of compounds thus represents a potentially important new therapy for brain cancer.