Poster presentations (Tue, 1 Nov)
Translational research

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A phase I dose-finding study of pemetrexed combined with paclitaxel in patients with advanced solid tumors

C. Bolling[1], C. Lübbing[1], T. Graefe[1], S. Müller-Hagen[2], B. Leisner[1], J. Blatter[3], A.-R. Hanauske[1]. [1]*AK St. Georg, Hamburg, Germany;* [2]*Onkologische Gemeinschaftspraxis Hamburg, Hamburg, Germany;* [3]*Eli Lilly & Company, Indianapolis, USA*

Background: Pemetrexed (Alimta®, AL) and paclitaxel (P) show clinical activity in a variety of tumors. The primary objective of this Phase I study was to determine the maximum tolerated dose (MTD) of the ALP combination; secondary objectives included determination of dose-limiting toxicities (DLTs), recommended phase II dose, and pharmacokinetic (PK) assessments.
Methods: Escalating dose levels of P (30–120 mg/m^2, 3h infusion, d1 and d8) and AL (400–500 mg/m^2, 10 min infusion, d8 prior to P) were used in a 21d cycle. Standard taxane premedication, oral folic acid, and parenteral vitamin B_{12} were administered.
Results: 59 patients (pts) [40 M, 19 F; median age: 59 yrs (range: 31–77)] were enrolled. DLTs, not qualifying for MTD, occurred at the following ALP (mg/m^2) doses: 400/30 [1 pt: G3 bilirubin (b), 1 pt: G3 and G4 thrombocytopenia (plts)]; 500/30 (G4 plts); 500/40 (G3 b); 500/75 (G4 ANC); 500/100 (1 pt: G4 leukopenia and G4 ANC). The MTD defined as G4 leukopenia and G4 neutropenia in 4 out of 6 pts and febrile neutropenia in 1 pt, was determined at the ALP (mg/m^2) dose of 500/120, 6 more pts were enrolled at a ALP (mg/m^2) dose of 500/100 to confirm safety at this dose-level. Other clinically significant toxicities include: G3/G4 ANC (17/14), G3/G4 anemia (6/1), G3/G4 plts (2), G3 fatigue (2) and G3 stomatitis (1). 4 pts expired while on therapy (1 non-therapy related; 1 gastric ulcer hemorrhage, 1 sepsis, 1 tumor lysis and 1 pneumonia). Stable disease occurred in 18 pts [mesothelioma (3), esophagus (2), lung (1), liver (1), renal (1), stomach (1), thyroid (9)]. At present there is no clinical evidence of PK interactions. Final PK analysis is pending. Of special note, this regimen shows clear clinical activity in follicular/papillary thyroid cancer with 4/14 pts showing long lasting partial responses [duration (months) 26, 22+, 18, 15+].
Conclusions: The Alimta® / paclitaxel combination can be safely combined and shows broad clinical activity. The proposed dose for further studies of the ALP combination is 500/100 mg/m^2. Promising antitumor activity was observed in thyroid cancer, warranting further development in this indication.

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Safety, pharmacokinetics (PK), and pharmacodynamics (PD) of AMG 706 in patients (pts) with advanced solid tumors

R. Herbst[1], R. Kurzrock[1], M. Parson[2], M. Mulay[2], M. Purdom[1], M. Eschenberg[3], S. Wong[3], R. Xu[3], L. Wathen[3], L. Rosen[2]. [1]*University of Texas MD Anderson Cancer Center, Houston, TX, USA;* [2]*John Wayne Cancer Institute, Santa Monica, CA, USA;* [3]*Amgen Inc., Thousand Oaks, CA, USA*

Introduction: AMG 706 is a potent, oral, multi-kinase inhibitor with both anti-angiogenic and direct antitumor activity achieved by selectively targeting VEGF, PDGF, RET, and c-Kit receptors. An updated analysis of safety, efficacy, and the PK of AMG 706 QD and a preliminary analysis of PD from an ongoing, open-label phase 1 study are presented.
Methods: Pts with advanced solid tumors were treated with QD oral AMG 706. After determining the MTD from 5 dose cohorts (total n = 31), an additional 40 pts were enrolled and received 125 mg QD. For PK analyses, samples were obtained predose and postdose at scheduled timepoints through day 43. Baseline and post-treatment ECGs were obtained. Serum placental growth factor (PlGF) and soluble KDR were measured at baseline and predose on day 2, 8, and 22. Tumor response was evaluated at week 8 and every 12 weeks thereafter.
Results: As of April 4, 2005, 71 pts were enrolled (mean treatment duration, 140 days [range: 6 days to 566 days] with 24 pts ongoing treatment). AMG 706 was generally well tolerated up to 125 mg QD. The most common treatment-related adverse events were fatigue (n = 26 [37%]), hypertension (n = 24 [34%]), diarrhea (n = 19 [27%]) and headache (n = 17 [24%]). PK analysis showed approximately dose-proportional exposure between 50–175 mg. AMG 706 was rapidly absorbed, with an overall median t_{max} of 0.5–1.5 hours and a mean $t_{1/2,z}$ of 6.3–7.5 hours after single-dose administration. Day 1 and 21 PK parameters were similar, indicating AMG 706 does not accumulate or cause metabolic induction. The desired plasma concentration predicted from preclinical models (C_{min} >18 ng/mL) was maintained and observed to be 25–29 ng/mL with 125 mg QD dosing. ECG revealed no evidence that AMG 706 affected cardiac repolarization. Serum concentration of PlGF rose with increasing AMG 706 dose levels, suggesting that AMG 706 induces a dose-dependent biological response. Reduction in soluble KDR correlated with the change in tumor size at day 50. DCE-MRI showed up to 60% reduction in k_{trans} in target tumors. Sixty-six pts were evaluable for response and included 3 (4%) pts (RCC, sarcoma, thyroid) with PR and 40 (56%) pts with SD as their best response.
Conclusions: Continuous QD dosing of AMG 706 appeared to be safe at daily doses up to 125 mg, providing sufficient target coverage. Clinical responses were observed in refractory pt populations. These findings warrant further investigation in a broad-based clinical program.

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Patients with imatinib mesylate-resistant GIST exhibit durable responses to sunitinib malate (SU11248)

J.A. Morgan[1], G.D. Demetri[1], J.A. Fletcher[1], S. George[1], J. Desai[1], R.G. Maki[2], C.D. Fletcher[1], K. Scheu[2], C. Baum[3], M.C. Heinrich[4]. [1]*Dana-Farber Cancer Institute, Center for Bone and Soft Tissue Oncology, Boston, USA;* [2]*Memorial Hospital, New York, USA;* [3]*Pfizer Inc., La Jolla, USA;* [4]*Oregon Health & Science University Cancer Institute, Portland, USA*

Background: The purpose of this study was to establish the phase II dose and evaluate clinical responses and safety with sunitinib malate (SU) treatment in GIST patients (pts) resistant to or intolerant of imatinib mesylate (IM).
Materials and methods: After failure of IM therapy, 97 GIST pts were enrolled in an open-label phase I/II study designed to evaluate 3 different dosing schedules of SU. SU is an oral multitargeted tyrosine kinase inhibitor of VEGFR, PDGFR, KIT, RET and FLT-3 with antiangiogenic and antitumor activities. During the phase II portion of the study, SU was administered in cycles of 4 weeks on 50 mg/day followed by 2 weeks off treatment. Pts exhibiting continued clinical benefit after 6 months (PR or SD) were allowed to enter a continuation study in which further measures of tumor progression and safety were obtained. Assessments of *KIT* mutational status were performed to correlate clinical activity with tumor genotype.
Results: PR and SD were observed in 8% and 70% of pts, respectively, including 37% (36/97) who exhibited SD for ⩾6 months. Estimated TTP and OS were 7.8 and 19.8 months, respectively. Estimated TTP was significantly longer in pts with pre-IM exon 9 vs. exon 11 *KIT* mutations ($P < 0.0003$) and in pts with WT *KIT* vs. exon 11 mutations ($P = 0.01$). Estimated TTP was also significantly longer in pts with post-IM *KIT* exon 9 mutations only vs. exon 11 mutations only ($P < 0.002$) or exon 11 + secondary mutations ($P < 0.003$). Grade 1/2 fatigue, diarrhea, skin discoloration, nausea and hand–foot syndrome were the most commonly reported treatment-related AEs. Treatment-related grade 3/4 AEs included hypertension (17%), asymptomatic lipase increase (13%) and fatigue (10%). 32 pts with clinical benefit after 6 months of initial treatment entered the continuation study and received extended SU treatment. As of April 2005, 15 pts exhibited no evidence of PD while receiving extended treatment, with a median treatment time of >1.5 years. The pre-IM *KIT* mutational status of these 15 pts comprised 3 with the WT gene, 5 with exon 9 mutations, 2 with exon 11–13 mutations and 5 with unknown mutational status. The tolerability profile was similar to that of the phase I/II study.
Conclusions: SU exhibited efficacy and manageable AEs in GIST pts after failure of IM therapy. A subset of pts exhibited durable responses with extended SU treatment. Durable responses were observed in pts with WT *KIT* as well as those with exon 9 or exon 11–13 mutations.

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Mouse, rat and clinical studies with the tumour vascular disrupting agent (VDA) 5,6 dimethyl xanthenone acetic acid, DMXAA: 5-hydroxyindole-3-acetic acid (5HIAA) plasma levels as a pharmacodynamic marker of blood flow changes

L.R. Kelland[1], B.C. Baguley[2], L. Zhao[2], P. Kestell[2], L.D. McPhail[3], S.P. Robinson[3], M. Ravic[1], M.B. Jameson[4], M.J. McKeage[2]. [1]*Antisoma Research Laboratories, SGHMS, London, United Kingdom;* [2]*University of Auckland, Auckland, New Zealand;* [3]*St Georges Hospital Medical School, London, United Kingdom;* [4]*Waikato Hospital, Hamilton, New Zealand*

Background: VDAs, a class of anticancer drug distinct from angiogenesis inhibitors in that they target primarily established tumour vasculature, are now under active clinical study. They include those that interact with tubulin (e.g. combretastatins and ZD6126) and the distinct tubulin-independent based flavonoid DMXAA (AS1404). DMXAA induces direct apoptosis of tumour vascular endothelial cells and a secondary induction

of vasoactive agents including serotonin (from platelets aggregating to damaged vasculature) and tumour necrosis factor (TNFá). The study objective was to determine whether plasma levels of the serotonin metabolite, 5HIAA, correlated with DMXAA induced blood flow changes, first in preclinical mouse and rat tumour models and then in cancer patients.
Methods: 5HIAA levels from blood were determined by HPLC. Mice, bearing syngeneic colon 38 subcutaneous tumors, were given single doses of DMXAA (up to ~150 mg/m^2). Rats bearing GH3 prolactinomas were dosed with DMXAA at up to ~2200 mg/m^2. In a completed Phase I double-blind randomised study in refractory tumors; DART) plasma 5HIAA was measured in patients receiving 20 minute intravenous infusions of DMXAA at 300 to 3000 mg/m^2.
Results: 5HIAA levels in mice measured 4hr post DMXAA showed a significant linear correlation with increased extravasation of the albumin binding Evans Blue from tumours ($r = 0.82$; $P < 0.05$); extravasation significantly correlated with reduced tumour blood flow ($r = 0.88$; $P < 0.01$). Notably, in the same mice, no change in extravasation was seen in normal skin. In rats, there was a significant increase in plasma 5HIAA concentration 24hr post treatment with doses of ~1300 mg/m^2 and above. In patients, peak 5HIAA plasma levels occurred at 4hr post dosing at dose levels >600 mg/m^2. Notably, there was a positive correlation between 5HIAA plasma levels and DMXAA dose up to 1200 mg/m^2 but thereafter a plateau was observed (even though plasma levels of free DMXAA increased linearly with dose up to 3000 mg/m^2).
Conclusions: Increased plasma levels of 5HIAA appear to represent a sensitive biological marker of blood flow changes induced by the VDA, DMXAA. Dose-response data from Phase I trial patients show that the optimum biological dose of DMXAA to cause tumour blood flow/5HIAA changes is in the range of 1200 mg/m^2, that is, around only 30% of the maximum tolerated dose. This is the same dose-range at which significant changes in plasma 5HIAA were seen in tumour bearing rats. Doses in this range are being studied in Phase II combination trials with taxanes (where marked synergy was seen in various preclinical tumour models); with docetaxel in patients with prostate cancer and with paclitaxel, and carboplatin, in non small cell lung and ovarian cancer.

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Weekday on – weekend off oral capecitabine: a Phase I study of a continuous schedule better simulating protracted fluoropyrimidine therapy

G. Pentheroudakis[1], V. Golfinopoulos[1], M. Karina[2], P. Pappas[3], L. Nikiforidis[1], M. Nicolaidou[3], E. Tzamakou[1], M. Marselos[3], G. Fountzilas[2], N. Pavlidis[1]. *[1]Ioannina University Hospital, Department of Medical Oncology, Ioannina, Greece; [2]Papageorgiou General Hospital, Department of Medical Oncology, Thessaloniki, Greece; [3]Ioannina University Hospital, Department of Pharmacology, Ioannina, Greece*

Background: Although management of solid tumours with protracted 5-Fluorouracil infusion is superior to bolus regimens in terms of pharmacokinetic considerations, activity, radiosensitization and toxicity, the equivalent oral fluoropyrimidine capecitabine is administered at 2510 mg/m^2 daily for two weeks followed by a 7-day break. As attempts at continuous capecitabine dosing were offset by cumulative toxicity and low administered dose (1331 mg/m^2/day), we investigated an alternative regimen that avoided long breaks.
Materials and Methods: Oral capecitabine was administered twice daily continuously with weekend breaks (5 days on, 2 days off) until disease progression or unacceptable toxicity. Eligible patients had advanced solid tumours refractory to standard therapy, adequate organ function and performance status of 0–2. Dose escalation proceeded in levels of 1331, 1665, 2000, 2250, 2500 mg/m^2 of daily oral capecitabine according to appearance of dose-limiting toxicity (DLT) during the first six weeks. DLT consisted of any grade 3 or 4 adverse event except for alopecia and skin toxicity resolving within 7 days.
Results: Twenty heavily pretreated patients with a median age of 67 and advanced, refractory breast (7), gastric (5), colorectal (2), bile duct (2) and other cancers entered the study. Among 5, 4 and 3 patients treated in cohorts 1331, 1665 and 2000 mg/m^2 respectively, no DLT occurred. The additional patients were recruited to replace patients quitting treatment before 6 weeks due to rapid disease progression. No DLT was seen in any of the 3 and 4 patients treated at 2000 and 2250 mg/m^2 either. Four patients were recruited at 2500 mg/m^2 and 2 developed grade III diarrhoea in weeks 3–4 of therapy (DLT), resolving uneventfully in 3 days. The most common toxic episodes during all cycles of treatment in all patients were grade 1–2 fatigue (8), nausea (4), constipation (4), abdominal pain (4), skin erythema (3) and anemia (3). In this pretreated population with refractory tumours, disease stabilization with clinical benefit was seen in 10 patients. Among the 7 women with breast cancer who were treated at a dose of 2000 mg/m^2 of continuous capecitabine or higher, 3 partial responses and a disease stabilization/clinical benefit rate of 86% were seen. Pharmacokinetic studies of capecitabine and metabolites are under way in additional 6 patients at the recommended dose of 2250 mg/m^2 and will be presented.
Conclusions: Weekday on-weekend off continuous oral capecitabine better simulates protracted fluoropyrimidine therapy at a recommended dose (2250 mg/m^2) close to that of the intermittent schedule and clearly higher than the continuous one (1331 mg/m^2), with lack of severe toxicity from mucous membranes, skin or bone marrow. The regimen offers promise for activity in advanced disease as well as for incorporation in radiotherapy and adjuvant programs.

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A Phase I clinical study of weekly heptaplatin and paclitaxel in previously treated patients with advanced solid tumor

H.T. Kim[1], D.H. Lee[1], K.H. Jung[2], J.Y. Han[1], I.J. Jang[3], H.S. Lim[3], S.H. Park[1], Y.S. Park[2], J. Ro[4], J.S. Lee[1]. *[1]National Cancer Center, Center for Lung Cancer, Goyang-Si, Korea; [2]National Cancer Center, Center for Colorectal Cancer, Goyang-Si, Korea; [3]National Cancer Center, Center for Clinical Trials, Goyang-Si, Korea; [4]National Cancer Center, Center for Breast Cancer, Goyang-Si, Korea*

Background: On a 4-week schedule, the maximal tolerated dose (MTD) for single heptaplatin (H), a less toxic platinum analog, was 480 mg/m^2 with recommended dose at 360 mg/m^2 (Kim NK et al. Cancer 2001; 91: 1549–56). This study was carried out to establish the MTD and dose-limiting toxicity (DLT) of weekly administration of H in combination with weekly paclitaxel (P) in previously treated patients (pts) with advanced solid tumor.
Material and Methods: Patients with advanced solid tumor, age 20–65, ECOG PS 0–1, adequate organ function, and 1 or more prior chemotherapy regimen without prior exposure to platinum or taxanes, were eligible. P 60 mg/m^2 was given first i.v. over 1 hr followed by H i.v. over 1 hr on days 1, 8, and 15, every 4 weeks. Each cohort of 3 pts were treated with escalating doses of H at 120, 150, 200, 250, 300, 350, 400 and up to 450 mg/m^2. The DLT and MTD pertaining to first cycle only were obtained and serial blood samples were drawn for H and P pharmacokinetics (PK) during first cycle.
Results: of 30 pts enrolled, 27 pts were evaluable for toxicity. The DLT, which was noted in 2 of 6 pts, was G3 proteinuria at dose level of H 450 mg/m^2. The MTD was H 400mg/m^{2}in combination with P 60 mg/m^2. Other grade 3/4 toxicities were (no. of patients); G3/4 neutropenia (11), G3 thrombocytopenia (3), G3 constipation (1), G3 anorexia (1) and G3 elevated liver enzyme (1). Objective tumor responses (PR) were noted in 6 of 18 non-small cell lung cancers (NSCLC), 1 of 4 breast cancers and 2 of 2 gastric cancers. PK data is in progress.
Conclusion: The recommended dose of weekly H is 400 mg/m^2 combined with weekly P 60 mg/m^2. Further phase II studies of this combination regimen are warranted, particularly in NSCLC and gastric cancer.
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Metronomic oral vinorelbine (MOVIN): a dose establishing translational and pharmacokinetic study in patients with metastatic refractory cancer

E. Briasoulis[1], C. Tolis[2], P. Pappas[3], M. Marselos[3], C. Nicolaides[2], L. Nikiforidis[2], M. Nikolaidou[3], O. Siarabi[4], E. Tzamakou[2], N. Pavlidis[1]. *[1]Medical School, University of Ioannina, Medical Oncology, Ioannina, Greece; [2]Ioannina University Hospital, Medical Oncology, Ioannina, Greece; [3]Medical School, University of Ioannina, Pharmacology, Ioannina, Greece; [4]Hellenic Cooperative Oncology Group, Data Office, Ioannina, Greece*

Background: Preclinical research and clinical observations evidence that continuous administration of small dose chemotherapy (metronomic dosing scheme) may effectively target activated endothelial cells in the tumor vasculature; yet metronomic chemotherapy remains to be validated in the clinical setting and several issues such as the identification of most appropriate agents and optimal doses and schedules should be addressed. In this clinical trial we studied metronomic dosing of the oral formulation of microtubule poison vinorelbine with the aim to establish a biologically optimal metronomic dose (OMD), investigate feasibility of protracted continuous administration and describe antitumor activity.
Methods: Fixed doses of oral vinorelbine were given three times a week (TIW) non-stop until disease progression or unacceptable toxicity. The trial deployed in two phases. In phase-alpha successive cohorts of patients received escalated doses of vinorelbine (20 mg base-dose, 10 mg