

Poster presentations (Tue, 1 Nov)

Translational research

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POSTER

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

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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/m², 3h infusion, d1 and d8) and AL (400–500 mg/m², 10 min infusion, d8 prior to P) were used in a 21d cycle. Standard taxane premedication, oral folic acid, and parenteral vitamin B₁₂ 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/m²) 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/m²) dose of 500/120, 6 more pts were enrolled at a ALP (mg/m²) 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/m². 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

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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 (PIGF) 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 PIGF 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)

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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

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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