618P Phase I study of different sequences of MTA (LY231514) in combination with cisplatin in patients with solid tumours

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Introduction: The novel multi-targeted antifolate (MTA) is a potent inhibitor of thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyltransferase. MTA has shown encouraging antitumour activity in vitro and in vivo and in single-agent phase I and phase II trials. The purpose of this study was to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT), pharmacokinetics and antitumour activity of MTA in combination with cisplatin (C).

Patients and Methods: Patients (pts) with solid tumours with no proven treatment options were entered into this trial. In cohort 1, both drugs were administered on day 1; in cohort 2 MTA on day 1 and C on day 2. Treatment was repeated every 3 weeks. In cohort 1 the starting dose was MTA 300 mg/m^2 and C 60 mg/m^2; in cohort 2 the starting dose was MTA 500 mg/m^2 and C 75 mg/m^2.

Results: In cohort 1, 40 pts were evaluable for toxicity. The MTD was reached at MTA 600 mg/m^2 and C 100 mg/m^2, with thrombocytopenia and febrile neutropenia as DLTs. In cohort 2, 11 pts were evaluable for toxicity. In this schedule, thrombocytopenia grade 4 occurred in 1 pt at MTA 500 mg/m^2 and C 75 mg/m^2, and in 1 pt at MTA 600 mg/m^2 and C 75 mg/m^2. Grade 4 infection was observed in 1 pt at each dose level, rash grade 3 in 1 pt at each dose level. Grade 4 diarrhoea occurred in 1 pt at MTA 500 mg/m^2 and C 75 mg/m^2, and grade 4 mucositis in 1 pt at MTA 600 mg/m^2 and C 75 mg/m^2. At both dose levels 1 pt died due to therapy-related toxicities. Pharmacokinetic parameters of MTA were not influenced by C administration and hydration. Several responses were observed: in cohort 1, 11 pts, including 4 of 7 pts with mesothelioma; in cohort 2, 3 pts had minimal responses, and remain on study.

Conclusion: The MTD of this combination is MTA 600 mg/m^2 and C 100 mg/m^2, if administered on day 1, with myelosuppression as the DLT. The day 1 schedule was clinically superior. This combination of MTA and cisplatin shows encouraging antitumour activity.

619P Reduction of micrometastatic tumor load by monoclonal antibody therapy: influence of tumor antigen heterogeneity

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Introduction: Disseminated cancer cells in bone marrow (BM), are regarded as suitable targets for adjuvant immunotherapy, because they are easily accessible for both immunoglobulins and immune effector cells. This pilot study was designed to examine the influence of the individual antigen profile of such target cells on the potential treatment efficacy.

Methods: Individual breast cancer cells in BM were identified by the anti-cytokeratin (CK) monoclonal antibody (mAb) A45-B/B3. To evaluate the antigen profile of these cells, we applied a quantitative double-marker assay and typed for four potential therapeutic targets (17-1A, MUC-1, Lewis^Y, c-erbB-2). In a pilot study, five breast cancer patients with a CK$^+$ BM finding were treated with a single dose of 500 mg Panorex™, and were monitored for the elimination of 17-1A co-expressing CK$^+$ cancer cells after 5–7 days.

Results: CK$^+$ cells from 20 breast cancer patients typed in this study for the expression of the four antigenic targets were found to represent a heterogeneous cellular population. The mean percentage of double-positive cells per total no. of CK$^+$ cells was 44% (0–75%) for 17-1A, 41% (0–67%) for MUC-1, 34% (0–59%) for Lewis^Y, and 42% (0–92%) for c-erbB-2. This was contrasted by a mean count of 70% (34–100%) cocktail$^+$/CK$^+$ cells if all four antigens were targeted simultaneously by the antibody-cocktail consisting of all four antigens. Thus, we considered tumor antigen heterogeneity a potential cause for incomplete tumor cell elimination by monovalent therapeutic approaches. This assumption was supported by our pilot study. Prior to treatment patients presented with 17, 67, 97, 115, 524 CK$^+$ cells per 10^6 BM cells, and a mean percentage of 61% (range: 41–100%) CO17-1A$^+$/CK$^+$ double-positive cells per total no. of CK$^+$ cells. In all five patients we assessed a remarkable reduction in both the no. of CK$^+$ cells (17→5, 67→11, 97→2, 115→20, 524→26) per 10^6 BM cells, and the percentage of 17-1A$^+$/CK$^+$ cells (41%→0%, 48%→0%, 54%→10%, 60%→15%, 100%→17%) per total no. of CK$^+$ cells after the administration of Panorex™.

Conclusion: Genomic instability of carcinoma cells resulting in the reported polyclonal phenotype of the disseminated tumor cell population may limit the efficacy of monovalent immunogenetic treatment strategies. Individual immunocytochemical monitoring of therapeutic tumor cell elimination is feasible and suggest that Panorex™ might be able to eliminate 17-1A$^+$ breast cancer cells.

620P A phase I and pharmacokinetic (PK) study of the multitargeted antifolate (MTA, LY231514) with folic acid (FA)

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Introduction: MTA, a new antifolate that inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyl transferase, demonstrated notable broad antitumour activity when infused 10 min i.v. every 21 days. Myelosuppression precluded dose escalation above 500–600 mg/m^2. As preclinical evaluations indicate that FA supplementation increases the therapeutic index of MTA, this study was initiated to determine if FA supplementation permits significant dose-escalation above the recommended phase II dose of MTA alone. Vitamin metabolites were measured to determine their value as potential prognostic markers with this combination.

Methods: So far, 33 minimally- and heavily-pretreated pts received 90 courses of FA (5 mg/day) for 5 days starting 2 days before MTA at 600, 700, 800 925 mg/m^2. Vitamin metabolites were evaluated during cycles 1 and 2 as potential determinants of principal toxicities and effects.

Results: Principal drug-related toxicities include neutropenia, anaemia and thrombocytopenia, which were more severe in heavily-pretreated pts. Other toxicities (grade (G) 1–2) include rash, somnolence, fatigue, leg oedema, and a decrease in creatinine clearance (CrCl). Severe toxicities in 2 pts, 1 who had taken a non steroidal anti-inflammatory agent and 1 with severe hypoalbuminaemia, resolved after administration of leucovorin and thymidine. Preliminary vitamin metabolites in 26 pts reveal: 2 and 3 of 11 pts with homocysteine ≥ 10 had G4 thrombocytopenia and neutropenia, respectively; 1 and 2 of 15 pts with homocysteine < 10 had G4 thrombocytopenia and neutropenia, respectively; 1 and 2 of 9 pts with elevated cystathionine levels (cystathionine upper limit of normal 342 nM/L) had G2 somnolence and G1–2 fatigue, respectively; 1 and 10 of 16 pts with normal cystathionine levels had G2 somnolence and G1–2 fatigue, respectively; 1 of 4 pts with elevated methylmalonic acid (methylmalonic acid upper limit of normal 271 nM/L) had G2 fatigue while 12 of 22 pts with normal levels had G1–2 fatigue. 7 of 15 pts with elevated homocysteine, cystathionine, or methylmalonic acid levels had a significant decrease in CrCl. Based on information from these 15 pts, addition of FA may reduce the usefulness of vitamin metabolites as predictors of toxicity.

Conclusions: FA supplementation appears to permit MTA dose escalation by ameliorating toxicity. Heavily- and minimally-pretreated pts tolerate MTA at 700 and 925 mg/m^2 and accrual continues at 800 and 925 mg/m^2, respectively.

621P Pharmacokinetic (PK) and pharmacodynamic (PD) analysis of a phase-I study of Taxol®(T), Carboplatin (C) with P-glycoprotein (P-gp) modulator PSC-833 (PSC)

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Introduction: Cyclosporine analogues such as PSC reduce the clearance of P-gp substrates (i.e. T) and their maximum tolerated dose (MTD). This trial was designed to assess the MTD, PK and PD of T and C with oral PSC in patients (pts) with refractory solid tumors.

Methods: All patients were planned to receive a fixed dose of PSC (5 mg/kg, p.o, 6 hr × 12, days 0–3) and T (baseline dose 54 mg/m^2, 13.5mg/m^2 increments, 3 hr infusion, day 1) and C (target AUC 6–9 mg/mL.min, day 1), 3-weekly. C AUCs derived from a limited sampling model, and T PK parameters fitted to a 2-compartment model.

Results: 58 pts entered into 7 dose levels (DL), 41 had previous chemotherapy, (34, 1 prior regimen). PK for DL 1–7 summarized below.

DL	T Dose mg/m^2	Target C·AUC mg/m.hr	# pts	C-AUC mg/ml.hr	T-AUC μM.hr	T-Cl L/hr/m^2	Time (hr) T > 0.05μM
1	54	6	3	5.4	4.8	13.19	20.46
2, 6, 7	67 5	6, 7.5, 9	28	6.3, 7 15, 7.55	5.94	13.31	26.52
3, 5	81	6	23	5.2	7.46	13.47	28.0
4	94 5	6	4	6.7	12.1	9.14	37.32

No PK interaction was noted between C & T or PSC & C. The T and C doses showed a linear correlation with % change nadir ANC (R^2 = 0.95 respectively), their AUCs correlated less well with % change nadir ANC or platelets. PSC prolonged the time T > 0.05 μM at T 94.5 mg/m^2 > than T 175 mg/m^2 alone. DL-2 and DL-5 were the MTDs of prior treated & chemonaive pts respectively.

Conclusions: PSC by reducing T's clearance, prolongs the time T > 0.05 μM, without influence on C PK. PSC reduced the MTD of the T & C combination.

