

Methods: ZD1839 was given as a single, oral, daily dose from day 2 onwards, at one of two dose levels (250 or 500 mg). Gemcitabine (1250 mg/m²) was administered as a 30-min infusion on days 1 and 8, and cisplatin (80 mg/m²) as a 2-h infusion on day 1, after gemcitabine. Cycles were repeated every 3 weeks for a maximum of 6 cycles, or until disease progression, toxicity or patient (pt) refusal. Recruitment of 6-12 pts was planned at each ZD1839 dose level. Pharmacokinetic analyses were done during cycles 1 and 2.

Results: Between November 2000 and February 2001, 18 pts were enrolled (M:F 11:7; median [range] age, 59 [30-71] years; WHO performance status, 0 [4 pts], 1 [11] and 2 [3]). Primary tumours: non-small cell lung cancer (NSCLC) (8 pts), adenocarcinoma of unknown primary (ACUP) (3), oesophageal (3) and other (4). All pts were chemonaive for advanced or metastatic disease. Nine pts were included at each ZD1839 dose level and all pts were assessable for toxicity. Toxicity at the 250 mg dose level comprised: G1 skin rash (3 pts), G1 diarrhoea (3), G3 asthenia (1), G3 thrombocytopenia (1), G3 vomiting (1) and G4 asymptomatic short-lasting (2 days) elevated hepatic transaminases (1). At 500 mg, 4 pts experienced G3 diarrhoea and 1 pt had G4 asymptomatic elevation of hepatic transaminases. Skin rash was observed in 7 pts but was generally mild (G1 [3 pts], G2 [3] and G3 [1]). No other severe toxicity or treatment-related deaths were observed. Fifteen pts are evaluable for efficacy, to date (1 pt withdrew after 1 cycle, 1 pt had only pleural effusion and 1 pt too early). Six pts had PRs (NSCLC [4 pts], ACUP [1] and pancreatic [1]), 7 pts had SD, including 2 pts with MRs (mesothelioma and oesophagus) and 1 pt with an unconfirmed PR (NSCLC); 2 patients progressed. Pharmacokinetic results will be available by September 2001.

Conclusion: p The combination of ZD1839 with gemcitabine and cisplatin is feasible and well tolerated, and appears highly active. A three-arm, multicentre, Phase III trial of the same combination, in patients with advanced NSCLC, has completed accrual with >1000 patients having been enrolled.

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ORAL

A phase I dose escalation pharmacokinetic (PK) study of BAY 38-3441 administered as a short infusion once every three weeks

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Rationale: BAY 38-3441 is a camptothecin glycoconjugate that was designed to stabilize the lactone form of camptothecin in blood, thereby increasing the proportion of the lactone available for uptake by tumor cells.

Methods: BAY 38-3441 was administered as a single 30-minute intravenous infusion once every three weeks (q3wks) to patients with advanced refractory cancer. Patients received 20 (n = 3), 40 (n = 6), 67 (n = 3), 100 (n = 6), 140 (n = 3) and 210 (n = 3) mg/m²/day q3wks BAY 38-3441. Plasma samples were taken at pre-defined time points for the determination of pharmacokinetic parameters, including C_{max}, AUC, t_{max}, t_{1/2}, and CL.

Results: Twenty-four patients (pts) with different solid tumor types have been accrued so far. The median age was 60 yrs (27-71). At 20 mg/m² 1 pt developed brain metastases 16 days after dosing with BAY 38-3441. At 40 mg/m² 1 pt with mCRC developed an increase of liver enzymes after the first dosing, but was considered disease-related rather than drug-related. At 67 mg/m² no TOX was observed. At 100 mg/m² 1 pt developed bradycardia, hypotension, and loss of consciousness during drug infusion, and these conditions were considered possibly drug-related. No further TOX was seen. At 140 and 210 mg/m² no TOX has been observed so far. The following pharmacokinetic results were obtained.

PK parameters of BAY 56-3722 (free base of BAY 38-3441) and Camptothecin (means/SD)

Dose [mg/m ²]	20	40	67	100	140
BAY 56-3722					
C _{max} [mg/L]	1.85/1.47	4.27/1.33	9.38/1.27	7.39/1.36	13.1/1.63
AUC [mg* ^h /L]	1.50/1.71	4.83/2.20	20.3/2.02	8.52/1.73	16.2/3.03
t _{1/2} [h]	1.10/1.69	2.65/1.44	9.20/2.51	4.31/1.69	10.2/1.28
CL [L/h]	19.2/1.67	13.8/2.16	5.26/1.85	21.4/1.60	13.3/3.16
Camptothecin					
C _{max} [μg/L]	3.39/1.58	16.8/2.50	15.3*	17.7/1.42	28.1/2.05
AUC (0-t _n) [μg* ^h /L]	53.3/2.74	537/2.70	410*	346/2.34	591/3.88
t _{1/2} [h]	22.9/1.33	33.4/1.23	-	26.8/2.74	37.8/1.67

+): median

Conclusion: BAY 38-3441 administered intravenously once every 3 weeks is generally well tolerated up to the 210 mg/m² dose level. The PK parameters show large interpatient variation; the MTD has not been reached.

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ORAL

Pharmacokinetic (PK) and Pharmacodynamic Analysis of Aspirin Administered with Multi-targeted Antifolate (ALIMTA)

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Purpose: ALIMTA (pemetrexed disodium, LY231514) is an antimetabolite, which inhibits three folate dependent enzymes. ALIMTA has a similar structure to methotrexate and both are excreted unchanged in the urine. Salicylates have been shown to impair the renal clearance and enhance the toxicity of methotrexate and thus patients (pts) taking non-steroidal anti-inflammatory drugs have been excluded from ALIMTA trials. Myelosuppression with ALIMTA is most pronounced in pts with folic acid or B12 deficiency.

Methods: Pts with normal renal function (as determined by glomerular filtration rate) were randomized to receive aspirin (ASA) either with the first cycle of ALIMTA (Group 1) or with the second cycle (Group 2). After the first cycle the pt was crossed-over to the alternate treatment. ALIMTA was dosed at 500 mg/m² day 1 of a 3 week cycle. Vitamin supplementation was mandated: Folic acid, at least 350 μg per day, beginning at least one week prior to the first dose of ALIMTA; 1000 μg of intramuscular vitamin B12 one to two weeks prior to first day of treatment then every 9 to 12 weeks. ASA 325 mg was given orally every 6 hours starting 2 days prior to ALIMTA with the 9th dose taken 1 hour prior to infusion. Samples for PK analysis were obtained with the first and second cycles.

Results: 24 pts (15 men and 9 women) with solid tumors, a median number of 2 prior therapies and a median age of 52 years (range: 34 - 71) received at least two cycles. ASA was administered to 12 pts in their first cycle and 12 pts took ASA with their second cycle. Preliminary PK analysis was performed on the first 7 pts in each group and showed that ASA ingestion did not appear to alter the clearance, mean steady state volume of distribution (Vss - L/m²), or area under the curve (AUC - μg/mL*hr). The median nadir neutrophil count for Group 1 after the 1st and 2nd cycles were 2.0 and 1.44 respectively and were 2.85 and 1.81 respectively for Group 2. A paired analysis of each individual pt's nadir neutrophil count from cycles 1 and 2 demonstrates that ASA did not augment the myelosuppression of ALIMTA (p=0.199). There were 3 episodes of grade 3/4 granulocytopenia and all occurred in cycles without ASA. There were no episodes of febrile neutropenia.

Conclusions: ALIMTA administered with folic acid has minimal myelosuppression and is well tolerated even when administered with ASA. Preliminary PK analysis suggest that ASA ingestion does not alter the disposition profile of ALIMTA

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Extended temozolomide (TMZ) dosing schedules permit the administration of higher TMZ dose intensities and inhibit the DNA repair enzyme O6-alkylguanine DNA alkyltransferase (AGAT)

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Purpose: AGAT has been implicated in the development of resistance to alkylating agents such as TMZ. Preclinical studies of prolonged exposure to TMZ have shown progressive depletion of AGAT. Extended TMZ dosing schedules may therefore decrease resistance and enhance cytotoxicity. We have conducted two dose-escalation studies to evaluate extended TMZ dosing.

Methods: Two TMZ dosing schedules were studied: 7-days on/7-days off (7/7) and 21-days on/7-days off (21/7). All patients received escalating doses of TMZ from 50 mg/m² up to 150 mg/m² per day; patients on the 7/7 schedule were titrated to a maximum dose of 175 mg/m² per day.