430 POSTER

Phase I and pharmacokinetic study of UCN-01 (U) in combination with irinotecan (I) in patients with solid tumors

A. Jimeno, M.A. Rudeck, W.T. Purcell, Y. Zabelina, K. Elza-Brown, T. Rogers, J.E. Dancey, S.D. Baker, M. Carducci, R. Donehower. *Johns Hopkins University, Medical Oncology, Baltimore, USA*

Background: UCN-01,7-hydroxystaurosporine, inhibits serine-threonine kinases (Ca^{2+} and phospholipid-dependent protein kinase C, cdks2,4,6, chk-1 and PDK1). UCN-01 mediates distinct effects *in vitro/in vivo*: cell cycle arrest in G1, abrogation of G2 arrest by inhibiting chk1, induction of apoptosis, and potentiation of cytotoxicity of S-phase active agents, like irinotecan (I). Due to this synergy and non-overlapping toxicity, U and I were combined in a phase I study, to determine the maximum tolerated dose (MTD), acute and chronic toxicity profile, and pharmacokinetics (PK) of U and I.
Methods: Patients with a histologically confirmed, incurable solid tumor refractory to standard therapy received I over 90 min on d1 and 8 of a 21d cycle. U was infused IV over 3 h on d1 immediately following I. All subsequent U doses were half the original dose. Starting doses of U and I were 50 and 60 mg/m^2, respectively. Initially, the U dose was increased in 20 mg/m^2 increments to its known MTD (90 mg/m^2); then the I dose would increase to 90 and 120 mg/m^2. Blood samples were collected cycle 1 for U, I, and three I metabolites (SN38, SN38G, and APC) for PK analysis. U, I, SN38, SN38G, and APC were quantitated by LC/UV and fluorescence. PK parameters were calculated by noncompartmental methods.
Results: A total of 9 patients with a variety of tumors have been enrolled on the trial at U/I doses of 50/60 mg/m^2 (n=1), 70/60 mg/m^2 (n=4) and 90/60 mg/m^2 (n=4). The long half-life ($t_{1/2}$) (541.1$\pm$320.2 h), low clearance (0.042$\pm$0.032 L/h), and volume of distribution (22.6$\pm$11.1 L) observed are consistent with prior UCN-01 data. While U PK does not appear to be affected by I, the reverse is not the case. There was a significant (P<0.01) decrease in C_{max}, AUC, and metabolite: I AUC ratio of I, SN38, SN38G, and APC, a significant (P<0.05) decrease in $t_{1/2}$ of I and APC, and an increase in SN38G exposure on d8 compared to d1. Stable disease has been documented in 4 patients, and 5 have been removed from the study (3 for PD, 1 for toxicity, and 1 by patient choice). No significant hematologic toxicity has been noted. The toxicities were hyperglycemia (2 G2, 1 G3), hyponatremia (1 G2), and hypocalcemia (2 G2). Two patients at the U/I 90/60 mg/m^2 dose level experienced a DLT (2 G3 hypophosphatemia).
Conclusion: The U/I 70/60 mg/m^2 dose level is being expanded, and escalation of I to single agent doses is planned. I dose escalation is warranted by the decrease exposure to I and SN38.

431 POSTER

Phase I and pharmacokinetic study of indisulam (E7070) in combination with carboplatin, a CESAR Central European Society for Anticancer Drug Research – EWIV report

C. Dittrich[1], M. Gneist[1], A. Zandvliet[2], C. Johnston[3], M. Yule[3]. [1]*Ludwig Boltzmann-Institute for Applied Cancer Res., 3rd Medical Department with Oncology, KFJ-Spital, Vienna, Austria;* [2]*The Netherlands Cancer Institute/Slotervaart Hospital, Dept. Pharmacy & Pharmacology, Amsterdam, The Netherlands;* [3]*EISAI Ltd., London, UK*

Background: Indisulam (E7070) is a novel sulphonamide derivative that induces dose- and time dependent G1 cell-cycle arrest as well as delay in G1/S transition and S phase progression, leading to G2 arrest followed by apoptosis. A unique anti-tumor spectrum and effects on cell cycle regulatory molecules such as cyclin E, cdk 2 and cyclin H indicate that E7070 has a novel mechanism of action when compared with existing therapies by the NCI COMPARE programme. A significant reduction in glutathione synthetase transcripts by indisulam provides a molecular basis for its combination with platinum agents. Indisulam demonstrated high activity against various non-small cell lung cancer models (NSCLC). When indisulam was tested as single agent therapy, every 3 weeks intravenously (i.v.), clinical results quite comparable to the established substances against NSCLC were observed.
Objectives of this study were: (1) to determine the recommended dose of indisulam in combination with carboplatin by dose adjustment, (2) to determine the pharmacokinetic profile of indisulam and carboplatin when administered in combination.
Materials and Methods: Patients with solid tumors refractory to standard therapy or for whom no established therapy exists, with a Karnofsky index *70%, a maximum of two previous lines of chemotherapy and normal essential organ functions were eligible. Based on prior pharmacokinetic investigations the dose of indisulam was based on the body surface area whereas that of carboplatin was calculated from the patient's glomerular filtration rate (GFR), both immediately prior to each cycle of therapy. GFR was obtained from the Cockroft-Gault formula. Indisulam was given as a one-hour i.v. infusion on day 1, carboplatin as an i.v. infusion over 30 minutes, after the end of indisulam on day 2 of a three-week cycle.
Results: The following dose levels (DL) were tested:
DL1: Indisulam 350 mg/m*, carboplatin AUC 6 mg/ml/min (3 pts; 6,7,6 cycles)
DL2: Indisulam 500 mg/m*, carboplatin AUC 6 mg/ml/min (3 pts; 5,2,1 cycles)
DL3: Indisulam 600 mg/m*, carboplatin AUC 6 mg/ml/min (4 pts; 6,1,6,3 cycles); 3 dose limiting toxicities (DLTs)
DL4: Indisulam 600 mg/m*, carboplatin AUC 5 mg/ml/min (2 pts; 1, <1 cycles); 1 DLT
Patient accrual to DL4 is still ongoing. Median 4.5 cycles (range <1–7 cycles) could be administered. Toxicity was assessed according to NCI-CTC, version 2.0. Thrombocytopenia G4 revealed to be the leading DLT (3 pts), followed by granulocytopenia G4 (1 pt). The non-hematological toxicity was minimal. The preliminary pharmacokinetic investigation let assume that carboplatin does not affect the kinetics of indisulam.
Conclusions: Hematotoxicity is dose limiting, necessitating dose reductions in four patients and almost always delay of retreatment by one week awaiting recovery from myelosuppression. The recommended dose for the further phase II study has not been identified yet.

432 POSTER

Identification of clinically relevant pharmacodynamic biomarkers in patients treated with the CDK inhibitor CYC202 (R-roscovitine)

S.R. Green, S. Frame, K. Watt, S. Anderson, I.N. Fleming, D.E. MacCallum, J. Melville, M. Watson, A. Gianella-Borradori, D.P. Lane. *Cyclacel Ltd, Dundee, UK*

CYC202 (R-roscovitine) is an inhibitor of Cyclin Dependent Kinases (CDK), which is currently in phase II clinical trials. CYC202 is a potent inhibitor of members of the CDK family with best activity against CDK2/cyclin E (IC50=80nM), CDK2/cyclin A, CDK7/cyclin H and CDK9/cyclin T. When tumour cells are treated with CYC202 there is a slight accumulation in G2/M but ultimately CYC202 causes apoptosis in tumour cells from each phase of the cell cycle. Previously CYC202 has been shown to be active against a range of human tumour cell lines both in vitro and in vivo.
CYC202 has completed two phase I studies while three phase II trials are currently ongoing: in combination with gemcitabine/cisplatin for NSCLC; in combination with capecitabine for breast cancer; and as a single agent in haematological B-cell malignancies. Samples from these clinical studies are being used for the identification of pharmacodynamic biomarkers. Three types of biomarkers are being studied: 1) markers of biological activity; 2) markers of anti-tumour activity and 3) markers of patient response. Towards this end, a broad range of approaches are being taken including: 1) analysis of CYC202 induced changes in patient plasma proteomic profiles using SELDI-TOF-MS; 2) the use of ELISAs to monitor patient plasma for markers of CYC202 induced cell death and 3) microarray analysis to monitor the effects of CYC202 on gene expression and initial experiments aimed at identifying in vitro genetic signatures that correlate with CYC202 sensitivity or resistance.
Candidate biomarkers have been identified in patient samples from the Phase I clinical trials and these markers are now being further examined in samples from the Phase II clinical trials. Results will be presented from these continuing experiments describing the identification of pharmacodynamic biomarkers to support CYC202 clinical development.

433 POSTER

A comparison of clinicopathological features and molecular markers in British and Nigerian women with breast cancer

I.D. Gukas[1], B.A. Jennings[1], B.M. Mandong[2], A. Girling[3], G. Igun[4], W. Prime[5]. [1]*University of East Anglia, School of Medicine, Health Policy and Practice, Norwich, UK;* [2]*Jos University Teaching Hospital, Department of Histopathology, Jos, Nigeria;* [3]*Norfolk and Norwich University Hospital Trust, Department of Histopatholgy, Norwich, UK;* [4]*Jos University Teaching Hospital, Department of Surgery, Jos, Nigeria;* [5]*University of Liverpool, Cancer Tissue Bank Research Centre, Liverpool, UK*

Background: Several studies have suggested that breast cancer in black women is a more aggressive disease than in white women. This study compares the clinical stage, histological grade and expression of five molecular markers in breast cancer material from Nigeria and United Kingdom.
Methods: The histological diagnoses of 178 consecutive Nigerian patients with breast cancer and 113 consecutive British patients with breast cancer were retrieved from their hospital records.
A subset of 72 age-matched Nigerian and British patients was staged and their tumours typed and graded. Immunohistochemical staining of sections