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#5 Phase I clinical and pharmacokinetic (PK) trial of E7070, a novel sulphonamide, administered daily × 5 every 3 weeks in patients with solid tumors. Fumoleau, P., Punt, C.J.A., Priou, F., de Mulder, P.H.M., Bourcier, C., Van de Walle, B., Wanders, J., Faber, M.N., Hanauske, A.R., Ravic, M., Finnegan, V., from *EORTC/ECSG, NDDO Oncology and EISAI Ltd-London, UK.*

Introduction: E7070 is a new chloroindolyl sulfonamide inhibiting the activation of cdk2 and cyclin E in cancer cells at concentrations ranging from 1.4–131.4 μg/ml *in vitro* and inducing cell cycle arrest in G1 and apoptosis. E7070 showed an original cytotoxicity profile suggesting a unique mechanism of action using the NCI-COMPARE program. Study design: E7070 was given as a 1 h. i.v. infusion (IV) on 5 consecutive days (d), repeated every 3 weeks. The total E7070 dose was escalated from 50 to 1000 mg/m^2/course through 7 dose levels using a standard Phase I design (3–6 pts cohort). PK study was performed during the 1st course (cr). Patient characteristics: to date, 25 patients with miscellaneous solid tumors: 17 females/8 males, median age (yrs): 53 (27–69), median PS: 1 (0–2). Study results: data is summarized for 25 pts and 69 crs (1–6).

Dose-Level	No. of pts	No. of crs	DLT's
10 mg/m^2 × 5	6	17	1/6 -atrial fibrillation at 2nd course
13 mg/m^2 × 5	3	6	0/3
26 mg/m^2 × 5	3	6	0/3
52 mg/m^2 × 5	3	14	0/3
104 mg/m^2 × 5	3	7	0/3
200 mg/m^2 × 5 (MTD)	3	9	2/3 -febrile neutropenia, -gd 4 neutropenia & thrombocytopenia
160 mg/m^2 × 5 (currently explored)	4	10	1/4 -gd 4 neutropenia & thrombocytopenia & gd 4 mucositis

Preliminary PK results indicate that E7070 displays a long half-life T½ and a large volume of distribution. At dose-levels above 52 × 5 mg/m^2 Cmax increases proportionally while AUC increases more than dose-proportional and the clearance & Vd_{ss} tend to decrease suggesting a non linearity in the PK's. So far, no response is reported.

#6 Phase I study of PS-341, a novel proteasome inhibitor, in patients with advanced malignancies. Papandreou Christos N, Pagliaro Lance, Millikan Randall, Daliani Danai, Herrmann John, Hong Yang, Smith Mathew, Adams Julian, Elliott Peter, Lightcap Eric, McCormack Teresa, Pien Chris, Newman Robert, Logothetis Christopher J. *Department of Genitourinary Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, TX, 77030 and Leukosite, Inc., Boston, MA 02139*

The ubiquitin-proteasome pathway plays an important role in neoplastic growth and metastasis through regulation of cell-cycle regulatory proteins (p53, p21/^{waf1}, and p27^{Kip1}). In addition, it regulates the activation of the nuclear factor NF-kB, a key transcriptional regulator of cell adhesion molecules {E-Selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1)}, which are involved in tumor metastasis and angiogenesis *in vivo*. We are currently conducting a Phase I trial with PS-341, a proteasome inhibitor, in patients with advanced malignancies. **Objectives:** 1) Define maximum tolerated dose and dose limiting toxicity of PS-341 as an intravenous (i.v.) push administration over a range of doses (0.13–0.75 mg/m^2) in patients with advanced malignancies. 2) Correlate toxicity with proteasome inhibition in peripheral blood. **Methods:** To date, 12 patients (9: androgen-independent prostate cancer, 2: metastatic renal cell carcinoma, 1: metastatic colon cancer) have been treated (4 at: 0.13 mg/m^2 and 2 each at: 0.25, 0.4, 0.6, 0.75 mg/m^2) with i.v. PS-341 weekly for 4 weeks in a 6-week cycle. Dose escalation is defined by the continuous reassessment method. Proteasome activity in patients' peripheral blood is measured ex-vivo using fluorogenic peptide substrates. **Results:** All patients completed at least one cycle of treatment. Four of 12 patients received 2 or more cycles of PS-341. No toxicity has been observed so far. One patient achieved partial response {major radiographic response of retroperitoneal lymph nodes (RPLN) without PSA change} and a second patient had radiographic stabilization of RPLN with unchanged PSA. A 55–60% proteasome inhibition in peripheral blood has been achieved at the current dose level (0.75 mg/m^2). **Conclusion:** 1) Up to the current dose of PS-341, no toxicity was observed. 2) At 24 hrs after drug infusion, proteasome inhibition was achieved as predicted. 3) Responses were seen even at low levels of proteasome inhibition. Further dose escalation (with pharmacokinetics and proteasome inhibition studies) is in progress. This early evidence of clinical activity without toxicity justifies further development of this agent with a novel mechanism of action. This work was supported by awards from the Association for the Cure of Cancer of the Prostate (CaPCURE) to C.N.P. and C.J.L.

#7 CCI-779, A new Rapamycin analog, Has Antitumor Activity at Doses Inducing Only Mild Cutaneous Effects and Mucositis: Early Results of an Ongoing Phase I Study. J. Alexandre*, E. Raymond*, H. Depenbrock°, S. Mekhaldi*, E. Angevin*, C. Paillet*, A. Hanauske°, J. Frisch, A. Feussner, J.P. Armand*. *Department of Medecine, Institut Gustave-Roussy, 94805 Villejuif cedex, France, Onkologische Tagesklinik°, Münich, Germany, Genetics Institute, Münich, Germany.*

Like rapamycin, CCI-779 interacts with the protein kinase mTOR thus preventing the phosphorylation of eIF4E-BP1 and p70S6K thereby inhibiting the initiation of the translation of messenger RNAs. We report the early results of a phase I study of CCI-779 given as a weekly 30 min. i.v. infusion in patients (pts) with advanced solid tumors. So far, 12 patients (pts) have been treated at the doses of 7.5, 15.0, 22.5, 34.0, 45.0, and 60.0 mg/m^2/w using a modify continuous reassessment method for dose escalation. CCI-779 does not appear so far to have any significant immunosuppressive effect. No opportunistic infection was observed. The immunophenotype of peripheral lymphocytes (CD3, CD4, CD8, CD45, CD14, and CD56) and the mitogen proliferation assays (phytohemaglutinin, concanavaline A, PWM) did not reveal any significant modifications. However, a reactivation of peri-oral herpes lesions was observed in 5 pts within the first month of treatment and rapidly resolved under oral acyclovir. Interestingly, significant tumor regressions were rapidly observed in 2 pts with lung metastasis of renal cell carcinomas both treated with 15 mg/m^2/w and in one patient with a neuroendocrine tumor of the lung treated with 22.5 mg/m^2/w. Responses occurred after 8 weekly doses. Additionally, 2 patients experienced tumor stabilization. Neither grade III–IV nor dose-limiting toxicity have been reported so far. Only mild grade I–II skin reactions and mucositis were observed at each dose level but did not increase in intensity while the dose-escalation was performed. Dryness of the skin with mild itching, fine scaling, and mild facial erythema occurred in 6 pts after the 1st infusion and lasted during the overall period of treatment. Mild hypersensitivity reactions were observed in all the pts including: (1) sub-acute urticaria in 1 pt immediately after the 1st infusion which did not reoccurred during subsequent cycles, (2) ≪Eczema-like≫ lesions on the anterior side of arms in 2 pts, and (3) aseptic follicles were associated with self-limited erythematous papules with central vesiculations occurring in bold areas in 7 pts. In the latest 7 pts, concomitantly to the skin reactions, grades I or II mucositis were observed associated with genital mucous membrane erosion in 1 pt. Skin biopsies were performed in all the pts experiencing skin reactions and consistently showed an aspect of folliculitis with infiltrate of neutrophils associated with non-specific superficial peri-capillar dermatitis. With repeated dosing transient regressions were usual, accelerated in some patients by topical steroid therapy and antiseptics. No alopecia was reported. Nails changes consisting of thickness and dystrophia progressively increased in pts receiving more than 8 doses. The study is ongoing to determine the dose limiting toxicity and the dose to be recommended for phase II studies.

#8 Phase I clinical and pharmacokinetic (PK) study of the Cryptophycin analog LY 355703 administered on an every 3 weeks (wks) schedule. Pagani, O., Greim, G., Weigang, K., Westphal, K., Van den Bosch, S., DePas, T., Burgess, M., Weimer, I. and Sessa, C. *IOSI, Bellinzona, CH; Klinikum Nürnberg, Nürnberg, D; EIO, Milano, I; Lilly Research Centre, Windlesham, UK.*

Cryptophycins are antimitotic antitumor agents from blue-green algae which inhibit microtubule dynamics with characteristics partially like vinblastine and partially like paclitaxel. The synthetic Cryptophycin LY355703 is highly potent (*in vitro* activity at picomolar concentrations) has antitumor activity in murine and human tumour xenografts, and high activity in tumours expressing the MDR phenotype, including models resistant to paclitaxel. In toxicology studies dose-limiting toxicities (DLT) were neutropenia in rats and diarrhea in dogs, the latter being the most sensitive species. The starting dose for this study on a single q 3wks schedule was 0.1 mg/m^2, corresponding to 1/10 of the Maximum Tolerated Dose in dogs; doses were escalated according to a modified Continual Reassessment Method. LY355703 was administered as 2 h i.v. infusion. Premedication with i.v. Dexamethasone, H_1 and H_2 antagonists 30 min before LY dose was given starting from the 0.88 mg/m^2 dose because of moderate hypersensitivity reactions to Cremophor EL observed at the previous dose (0.68 mg/m^2). The plasma concentration of LY355703 was investigated by LC-MS-MS method with a detection limit of 0.25 ng/mL. Twenty-nine patients (pts) with a variety of solid tumours (soft tissue sarcoma 8, renal 5, colon 4) and 10 dose levels have been evaluated so far. At the highest dose level of 1.92 mg/m^2, 2 of 5 pts presented self-limiting DLTs (G3 neuropathic pain in 1 pt, G3 myalgia and constipation in the other) which appeared within 3 days of the infusion and required opioids. The dose of 1.7 mg/m^2 was then tested in 2 pts with occurrence of self-limiting G3 myalgia within 48 hours in both, in spite of prophylactic analgesia. Overall, peripheral neuropathy was mainly sensory and of moderate degree and not necessarily dose related nor cumulative; neutropenia was sporadic and only moderate; total alopecia was observed only in pts who presented DLTs. PK was linear from 0.1 mg/m^2 to 1.92 mg/m^2 with mean (±SD) t½ of 2.6 hr (±1.02), Clp of 90.4 L/hr (±50.3) and no apparent correlation to