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#282 Phase I and pharmacokinetics (PK) study of RPR 116258A given as a weekly 1-hour infusion at day 1, day 8, day 15, day 22 every 5 weeks in patients (pts) with advanced solid tumors. P. Fumoleau, J. Trigo, M. Campone, J. Baselga, F. Sistac, P. Gimenez, L. Manos, H. Fontaine, D. Semiond, G. Sanderink, D. Perard, M. Besenval. *Ctr Rene Gauducheau, Nantes, France; Hosp Vall d'Hebron, Barcelona, Spain; Aventis Pharma Spain, Barcelona, Spain; Aventis Pharma France, Antony, France; Aventis Pharma France, Alforville, France.*

RPR 116258A is a new taxoid with a broad spectrum of activity: activity on mdr-1 expressing tumor cells *in vitro* and against B16/TXT resistant melanoma and ability to cross blood brain barrier. This new compound was tested in phase I study using Simon's design 4A. The drug was administered as a weekly 1-hour infusion during 4 consecutive weeks (D1, D8, D15 and D22) every 5 weeks, without premedication. The dose-limiting toxicities (DLTs) were evaluated after cycle 1 (5 weeks) to establish the Maximum Tolerated Dose (MTD). PK samples were collected during the first 48 or 72 hours post infusion at day 1 and day 22 of cycles 1 and 2 when possible. Twenty-five patients (6 males, 19 females, median age: 52) were included. Most of pts presented advanced breast cancer (15/25 pts). Seventeen patients were treated in the dose escalation phase at 1.5 (1 pt), 3 (1 pt), 6 (4 pts), 8.4 (5 pts) and 12 mg/m^2 (6 pts). A total of 48 cycles (1-8) was administered with treatment duration ranges from 2 to 40 weeks. The MTD was reached at the 12 mg/m^2 dose level at which 2 out of 6 pts experienced DLTs at cycle 1. These DLTs consisted of diarrhea gr 3 (time of occurrence: day 7-18/duration: 3-4 days). At the subsequent cycles, other DLTs were reported at 12 mg/m^2: 2 fatigue gr 3, 1 diarrhea gr 3, 1 neutropenia gr 4 > 5 days, 1 febrile neutropenia and at 8.4 mg/m^2: 1 fatigue gr 3. Eight additional patients were treated at 8.4 mg/m^2 to well establish the recommended dose for future phase II studies. Neutropenia was the main hematologic toxicity and reached gr 3 (1 pt) at the dose of 8.4 mg/m^2. The main non hematologic toxicities were: diarrhea: 36.4% pts including 3 gr 3, fatigue: 36.4% pts including 3 gr 3 and neurosensory: 22.7% pts with only 1 gr 3. No neurocentral toxicity was reported. Only 3 cases of mild hypersensitivity reaction (gr 1) were observed. The preliminary PK results indicated that AUC(0-t) increased proportionally with the dose from 1.5 to 12 mg/m^2 on day 1 at cycle 1. At 8.4 mg/m^2, the drug had a high total body clearance (50 L/h/m^2), a very large volume of distribution (1424 L/m^2) and a quite long terminal half life (31h). There was a trend towards higher plasma levels at later sampling times on day 22 than on day 1 at cycle 1. However, no drug was detected at predose on day 22. Two confirmed partial responses in breast cancer patients after taxoid failure were reported at 8.4 and 12 mg/m^2 dose levels and 12 stable diseases were observed in different indications, such as: breast (7 pts), gastric, ovary, cholanglocarcinoma, carcinoid tumor, NSCL cancers. An intermediate dose level of 10 mg/m^2 is being explored.

PK Parameter Estimates

	Parameters				
Dose in mg/m^2	Maximum Concentration Cmax; ng/mL	Volume of distribution at steady state Vss; L	Clearance CL; L/hr	Terminal Half-life $T_{1/2}$; hrs	Area-Under-Curve AUC; ng·hr/mL
130 (1)	108	1669	100	22.4	3419
215 (6)	248±50	457±180	57±11.9	10.8±3.2	6513±1540
325 (2)	384	446	51	12.7	10953

#281 Inhibition of H-ras membrane binding and topoisomerase-1 in a phase I trial of topotecan combined with the farnesyl transferase inhibitor, R115777 (Zarnestra). H. Hochster, L. Liebes, M. Buckley, J. Sorich, D. Fry, A. Hamilton, J. Wright, F. Muggia. *New York Univ Sch of Medicine, New York, NY; CTEP, NCI, Bethesda, MD.*

Pre-clinical studies have suggested synergistic activity of the farnesyl transferase inhibitor, R115777, when given together with topotecan, a topoisomerase-1 inhibitor. This phase I study combined topotecan given on a daily x 5 regimen (days 1-5) together with R115777 given orally bid days 1-21 every 28 days. Methods: Eligibility included histologically documented, advanced cancer, ≤3 prior chemotherapy regimens, RT to less than 25% of bone marrow, ECOG PS 0-2. Organ function had to meet typical criteria and bowel function had to be normal. Twelve patients were entered including 8M, 4 F; PS 1 =9, 2 = 3; median age 54 (range 35-67 years); disease sites: colon 4, pancreas 2, gastric 2, NSCLC, MM, sarcoma, peritoneal @1; prior RT = 3, prior chemo 12 (1 prior = 3, 2 = 3, >3 = 6). Dose levels were (topo/FTI) = 1.0/200, 1.25/200 and 1.0/300. Dose limiting neutropenia and thrombocytopenia was seen at levels II and III. PK and PD studies were performed for topotecan blood levels, PBMC free topo-1, and PBMC membrane-bound fraction of H-ras. Studies were performed on day 1 (topotecan alone) and compared to day 5 (topotecan plus R115777, which was started on day 2 of treatment first cycle). Topotecan blood levels and PBMC topo-1 were determined by published methods (Liebes, et. al. Clinical Cancer Res. 4:545-557, 1998). To determine fraction of membrane-bound ras, PBMCs were pelleted and then phase separated using Triton-X 1% to isolate cytoplasmic vs membrane fractions. These were quantitated by scanning densitometry from Western Blots using anti-H-ras 259 antibody (Santa Cruz Biotech). Results: 1) PK modeling of topo-1 AUC showed no difference for day 1 (topotecan alone) compared to day 5 (topotecan plus R115777); 2) AUC (4-hour sampling) for free topo-1 (in PBMCs) decreased from mean value of 11.4 x 10^5 copies per cell on day 1 compared to 3.5 on day 5 (n=10, p<0.001, paired t-test); and 3) Membrane bound H-ras decreased from mean value of 48±11% (day 1) to 24±7% (day 5) (p<0.001 paired t-test, n=5). Conclusions: 1) Enhanced myelosuppression was seen when a topo-1 inhibitor was combined with R115777, such that neither drug could be given at full doses; 2) Inhibition of topo-1 is dramatically increased on day 5 compared to day 1, which may be due to cumulative topotecan effect or enhancement of topotecan binding to cleavable complex by the FTI. This is not accounted for by a pharmacologic interaction; and 3) R115777 plus topotecan causes inhibition of ras farnesylation by approximately 50% as evidenced by the decrease in the ratio of membrane bound compared to cytoplasmic H-ras. We are continuing these studies using topotecan administered by the less myelosuppressive 21-day infusion with R115777 given orally x 21 days. Supported in part by P30 CA16087, M-01 RR00096, and U-01 76642.

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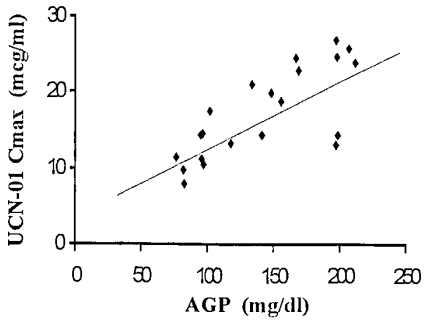
#283 A phase I/pharmacologic study of UCN-01 in combination with 5-fluorouracil in patients with advanced solid tumors. M. A. Shah, J. Kortmansky, D. P. Kelsen, C. Hseuh, A. Kaubisch, D. Spriggs, M. Gonen, W. Tong, S. Endres, G. K. Schwartz. *Memorial Sloan Kettering Cancer Ctr, New York, NY.*

Background: UCN-01 (UCN) is a potent inhibitor of protein kinase C and cyclin dependent kinases. Single agent Phase I toxicities have included headache and hyperglycemia (HG). We have previously reported that, UCN significantly enhances the induction of apoptosis by 5-Fluorouracil(F) *in vitro*, associated with a decrease in the transcription factor E2F-1, and a subsequent reduction in thymidylate synthase expression [Clinical Cancer Res,1998]. Therefore, to initiate the clinical evaluation of this novel drug combination, we began a Phase I clinical trial of UCN in combination with F. Methods: Escalating doses of weekly 24 hour infusional F (250→2600 mg/m^2) were given in combination with a fixed monthly dose of UCN (45 mg/m^2/d). Based on the single agent maximum tolerated dose, UCN infusion began on day #2 of each 28 day cycle over 72 hours for cycle 1 and over 36 hours for subsequent cycles. Peripheral blood samples were taken for thymidylate synthase assessments. Results: 24 patients have enrolled thus far; 22 are evaluable for toxicity and 18 for pharmacology. UCN associated toxicities have included grade 3 headache in 1 patient and grade 3/4 HG (1 and 2 patients). All incidents of grade 3/4 HG occurred in patients with a history of diabetes mellitus, and those with grade 4 HG required continuous insulin infusions. We have therefore modified the inclusion criteria to exclude diabetic patients, and since have seen no further episodes of grade 3/4 HG. UCN peak plasma concentrations (Cmax) did not change from cycle 1 to cycle 2 and did not change with increasing F. As UCN is tightly bound to serum α-1 acid glycoprotein (AGP), AGP levels were measured. As shown below, we found a significant linear correlation between serum AGP and UCN Cmax (Spearman's rank correlation, r=0.79, p=0.0015). The regression line is estimated as Cmax=0.09*AGP+5.53. In addition, plasma UCN concentrations achieved (20.2-53.5 μM) are associated with potentiation of F *in vitro*. Thus far, we have observed 3 patients with stable disease (range 4-7 months duration), and a minor respone in 1 patient with colon cancer refractory to irinotecan and F. Conclusions: From the regression analysis, UCN Cmax can be predicted from AGP determinations. This allows for UCN determinations by a simple protein immunoturbidity assay. Since we have yet to reach the maximal tolerated dose for this exciting drug combination, accrual continues with escalating F doses. TS assessments will be presented. Supported by Grant UO1 CA6985-6.



#284 Changes in plasma levels of hypoxia-induced secreted proteins as markers of response to a tirapazamine-containing regimen: Molecular endpoints of a California Cancer Consortium phase I trial of tirapazamine (TPZ) plus carboplatin/paclitaxel. P. C. Mack, P. N. Lara, I. V. Galvin, D. H. Lau, H. J. Lenz, J. H. Doroshow, D. R. Gandara, P. H. Gumerlock. *Univ of CA, Davis Cancer Ctr, Sacramento, CA; Univ of Southern CA, Los Angeles, CA; City of Hope, Duarte, CA.*

Tumor-related hypoxia is associated with increased resistance to conventional anticancer therapies, and thus, patients may benefit from combining an