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— SUPPLEMENT TO —

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2004 ASCO Annual Meeting Proceedings (Post-Meeting Edition)

40th Annual Meeting
June 5-8, 2004
Ernest N. Morial Convention Center
New Orleans, LA

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Official Journal of the American Society of Clinical Oncology

ASCO®

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3146 **Publish Only**

Study of vascular endothelial growth factor (VEGF) serial blood levels as predictor of response to chemotherapy. *A. Irigoyen, J.-R. Delgado, P. Ballesteros, I. Rodriguez, E. Gonzalez, R. Luque, V. Conde, P. Belon, M. Sanchez-Moreno, J. Belon; Hospital Virgen Nieves, Granada, Spain; Science Faculty, University, Granada, Spain*

Background: The molecular profile of a cancer may give information pertinent to response to chemotherapeutic agents. Vascular endothelial growth factor is a endothelial mitogen, survival factor and permeability inducer produced by many types of tumor cells. A rational approach is to study the sequential expression in peripheral blood of biomarkers during the treatment in order to select an individualized therapy. **Methods:** From February 2002 we have determined the serial levels of VEGF in the serum of cancer patients , with a life expectancy superior to 12 weeks, with a Karnofsky index superior to 60, which have received chemotherapy. The VEGF expression has been measured before the starting of treatment, after 2 courses, at the end of therapy, and when the disease progression was documented, using the enzyme-linked inmunosorbent assay technique (Oncogene Research Products kits). Until now 119 patients have completed 2 extractions **Results:** We have observed 2 groups according to the levels of VEGF in peripheral blood: The first group includes non small cell lung and gastric cancer, in which we have observed concentrations in the rank of 500 to 2000 pg/ml, and the second group is made up of ovarian, breast, colorectal, head and neck cancer where the lowest values are found over 100 pg/ml and the maximum does not reach 500 pg/ml. In most cases of lung cancer there is a relationship between the VEGF evolution and the response to treatment. The more advanced is the disease stage the bigger are the VEGF values at the first extraction. The VEGF values have been predictive of the disease evolution during the treatment in patients with gastric and ovarian cancer. VEGF confirmed their predictive value in case of discrepancy with computed tomography. **Conclusions:** The determinations of VEGF levels in peripheral blood before the chemotherapy and after the second course could predict the individual response to treatment in non small cell lung, gastric and ovarian cancer

3147 **Publish Only**

Gene expression changes during acquired resistance to tamoxifen; a preclinical model of post-menopausal breast cancer. *N. Macpherson, S. Moore, A. Brodie, T. Olivotto, A. Thiantanawat, B. Long, D. Jelovac, C. Nelson; BC Cancer Agency, Victoria, BC, Canada; The Prostate Centre, Vancouver, BC, Canada; Dept of Pharmacology, University of Maryland, Baltimore, MD*

Background: Most metastatic breast cancers initially respond to hormonal treatment but all become resistant to these treatments over time. The genetic events that occur during acquired resistance are unknown. To examine the gene expression changes during acquired hormonal resistance, we used a model that mimics ER positive breast cancers in the post-menopausal setting with the tumors responsive to both Tamoxifen (TAM) and aromatase inhibitors. Tumors were analyzed with high density cDNA microarrays to identify genes associated with TAM resistance. **Methods:** Aromatase-transfected MCF-7Ca human breast cancer cells were grown as tumor xenografts in female ovariectomized athymic nude mice in which an androstenedione supplement was converted to estrogen to stimulate tumor growth. When tumor volume was approximately 300 mm^3, the animals were grouped (4 groups, each with n=20) for continued supplementation with androstenedione (Δ4A) only (control), Letrozole (an aromatase inhibitor) 10 μg/day + Δ4A, TAM 100 μg/day + Δ4A, or vehicle. Tumors were then retrieved at various time points during the development of hormone resistance. Tumor RNA samples were compared to reference RNA from Stratagene and incubated with 14K microarrays (Array-Ready Oligo Set, Qiagen). Expression results were analyzed with Genespring 6.1 (Silicon Genetics). **Results:** We have identified 15 TAM-resistant associated genes that are over-expressed by at least 2-fold, after controlling for genes associated with house-keeping function (vehicle and short term control), proliferation (freely growing tumors without TAM), and TAM inducible genes. They include; cystatin A, TGFbeta1-induced anti-apoptotic factor, cadherin1 E-cadherin, Snf2-related CBP activator protein, and chromatin-remodelling genes. At the meeting we will also present data on the expression changes seen in the Her-regulin family, cyclin family and MAP kinase genes during acquired TAM resistance. Patient biopsies are currently being collected and analyzed to validate these observations. **Conclusions:** Chromatin remodeling genes are over-expressed in acquired TAM-resistance.

3149 **Publish Only**

Effects of 5-fluorouracil on endothelial nitric oxide synthase in endothelial cells in different states of confluence. *V. M. Casado-Echarren, C. Abarrategui, R. Alvarez, G. Rubio, A. León, M. Dómine, I. Calvo, L. G. Estévez, A. López-Farré, F. Lobo; Fundacion Jimenez Diaz, Madrid, Spain*

Background: Some studies suggest a direct effect of 5-fluoruracil (5-FU) on vascular endothelium. The enzyme endothelial nitric-oxide synthase (eNOS) produces nitric oxide (NO) in the endothelium. It is known that NO has multiple physiological functions one of which is involved in the interaction of circulating tumour cells with the endothelium. On the other hand, endothelial cells (E.C) can be found in two different states of proliferation: confluence (quiescent) and subconfluence (proliferating). Our objetives are to study the effect of 5-FU on the eNOS expression and to analyse if there is a direct relationship between the effect of 5-FU and eNOs expression and the state of endothelial growth. **Methods:** Culture of bovine aortal endothelial cells (B.A.E.C). The dosage of 5-FU was 20 ugr/mL. The enzyme eNOS was measured using Western-blot method. **Results:** We observed an increase in eNOs expression in subconfluent E.C with respect to confluent E.C (14.6 densitometric units as opposed 8.97 DU;$p<0.003$; t Student method).The presence of 5-FU reduces eNOS expression in subconfluent E.C with respect to control subconfluent endothelial cells (14.6 DU as opposed to 9.47; $p< 0.023$). **Conclusions:** 5-FU reduces eNOs expression in E.C in subconfluence state. This finding suggests a direct effect of 5-FU on the proliferating endothelium and as well a possible effect on tumoral endothelium.

3150 **Publish Only**

A phase I trial of a novel mTOR inhibitor AP23573 administered weekly (wkly) in patients (pts) with refractory or advanced malignancies: A pharmacokinetic (PK) and pharmacodynamic (PD) analysis. *A. A. Desai, L. Janisch, L. R. Berk, H. L. Knowles, V. M. Rivera, C. L. Bedrosian, M. J. Ratain; University of Chicago, Chicago, IL; ARIAD Pharmaceuticals, Cambridge, MA; ARIAD Pharmaceuticals, Inc., Cambridge, MA*

Background:AP23573 is a non-prodrug rapamycin analog that potently inhibits mTOR, a downstream effector of the PI3K/Akt and nutrient pathways. AP23573 demonstrated powerful antiproliferative activity *in vitro* and antitumor activity in mouse xenograft studies. **Methods:** This trial is utilizing an accelerated dose escalation scheme to determine safety and tolerability, establish a maximum tolerated dose, and characterize the PK and PD of AP23573. AP23573 is administered as 30-minute IV infusion wkly on 4-week cycles, and tumor responses are evaluated every 2 cycles. Potential PD markers are being assessed using western blot analysis of peripheral blood mononuclear cells. **Results:** As of 12/01/03: 9 pts (4M/5F), median age 55 yrs (range 27 – 79 yrs), have received doses ranging from 6.25 to 25 mg in 3 dose level cohorts (total cycles, 15; median cycles, 2/pt). No dose limiting toxicities or AP23573-related serious adverse events have been observed. Common reversible side effects for first cycle have been grade 1 chills, diarrhea, fatigue, rash, anorexia, mucositis, and one pt had grade 2 anemia. PK analyses (doses 6.25 and 12.5 mg) suggest a mean AP23573 half-life of 46 – 52 hours, with AP23573 concentration levels generally remaining above *in vitro* antiproliferation IC50 levels until the next wkly dose. PD analyses (doses 12.5 and 25 mg) show inhibition of mTOR activity until the next wkly dose as measured by decrease in phosphorylated 4EBP1 levels. One of 5 evaluable pts has stable medullary thyroid cancer for > 2 months. **Conclusions:** AP23573 can be administered safely using this schedule. There is evidence of a substantial PD effect at dose levels associated with minimal toxicity, and early evidence of antitumor activity. Given the promising PD findings, further dose escalation and new pt enrollment will include evaluation of maximum effective dose of AP23573 based on PK/PD relationship. If substantial interindividual PK variability is observed, the trial also is prospectively designed to evaluate the relevance of genetic variants in candidate drug metabolism genes.