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3093 Publication Only

**Tariquidar (XR9576) is a potent and effective P-glycoprotein (Pgp) inhibitor that can be administered safely with chemotherapy.** *M. E. Menefee, C. Fan, M. Edgerly, D. Draper, C. Chen, R. Robey, F. Balis, W. D. Figg, S. Bates, A. T. Fojo; NIH/NCI, Bethesda, MD*

**Background:** Inhibition of P-glycoprotein (Pgp) as a means to improve chemotherapeutic efficacy remains a valid but unproven hypothesis. Two recent trials in patients with lung cancer using the Pgp inhibitor, tariquidar (XR9576), closed prematurely due to toxicity concerns. We report our experience using tariquidar with chemotherapy. **Methods:** Patients with refractory or metastatic adrenocortical cancer (ACC) received tariquidar on days 1 & 3 with a 96-hour infusion of doxorubicin, vincristine, and etoposide with mitotane (X-MAVE) every 21 days. Patients with refractory ovarian, cervical & lung cancer received tariquidar with a docetaxel infusion every 21 days. Study participants had two $^{99m}$Tc-sestamibi scans. Time-activity curves were generated and areas under the curve calculated to compare $^{99m}$Tc-sestamibi accumulation at baseline to that 1 h after tariquidar. Rhodamine efflux from CD56+ cells was measured before and after tariquidar to assess Pgp inhibition. **Results:** To date, 15 patients with ACC have received 71 cycles of X-MAVE, and 16 patients with ovarian, cervical or lung cancer have received 66 cycles of docetaxel. Grade 3 non-hematologic toxicities (# of cycles) observed with X-MAVE include: abdominal pain/constipation (4), arthralgia (4), nausea/vomiting (2), diarrhea (1), esophagitis (1), fatigue (6), hand-foot reaction (1), and hyponatremia (3); those with docetaxel include: diarrhea (1), dyspnea (1) fatigue (6), hyponatremia (3), pain (3) and tearing (2). $^{99m}$Tc-sestamibi accumulation increased 39 to 129%, compared to a mean increase of 106% in the liver, in 6 of 8 patients with ACC whose lesions could be visualized. Quantitation for the 10 such patients with ovarian, cervical or lung cancer is ongoing. Rhodamine efflux from CD56+ cells assayed in 30 patients was reduced by a mean of 85% after tariquidar and was sustained even after 48 h. Pharmacokinetic sampling before and after tariquidar has been performed. **Conclusions:** Tariquidar is a potent and highly effective Pgp inhibitor that can be administered safely with a combination of doxorubicin, etoposide and vincristine or with docetaxel. The efficacy in patients with refractory cancers continues to be evaluated.

3094 Publication Only

**Phase I pharmacokinetic-pharmacodynamic trial of weekly MS-275, an oral histone deacetylase inhibitor.** *E. A. Donovan, Q. Ryan, M. Acharya, E. Chung, J. Trepel, K. Maynard, E. Sausville, A. Murgo, G. Melillo, B. Conley; National Cancer Institute, Bethesda, MD*

**Background:** MS-275, a synthetic benzamide derivative, is a histone deacetylase (HDAC) inhibitor with in vitro & in vivo antitumor activity. Based on our q2 week dosing results, we explored maximum tolerable dose (MTD) & dose limiting toxicity (DLT) for a weekly schedule with 2 oral formulations & 2 administration conditions. **Methods:** MS-275 uncoated ("A" with meal) or coated ("B" fasting) tablets were given weekly x4 q6 weeks to patients (pts) with advanced malignancy & PS≤2, LFTs≤2.5x normal, adequate hematopoetic & renal function, & normal resting MUGA. Pharmacokinetics (PK) (validated LCMS method) & histone H3 acetylation (H3Ac) in peripheral blood mononuclear cells (PBMC) (IHC image analysis and novel flow cytometric assay for protein acetylation) were assessed. **Results:** 13 pts, ECOG PS =1 (0–2) received median of 1 (1–4) course. 4 "A" (4–6 mg/m2) pts & 7 "B" (2–4 mg/m2) pts were evaluable for cycle 1 toxicity (CTC v2.0). "A" grade 3 toxicities were hypoalbuminemia, neutropenia & vomiting. On "B", 2 pts had DLT at 4 mg/m2, one with grade 4 dyspnea/grade 3 pleuritic pain & dyspepsia & one with right heart failure, diarrhea & hypoalbuminemia. Grade 1–2 toxicities in >1 pt for A or B were thrombocytopenia, fatigue, hyperglycemia, taste disturbance, hypoalbuminemia, hypocalcemia, hypomagnesemia, hypophosphatemia, leucopenia, neutropenia, nausea, anorexia, headache, dyspepsia, flatulence, myalgias & insomnia. Enrollment is ongoing on "B" 2 mg/m2 fasting. Median Tmax was 0.5h (0.5–6h). At 4 mg/m2, mean Cmax was 38.2 ng/mL (14–71 ng/mL) in "B" vs 4.8 ng/mL (4–6 ng/mL) in "A. Mean AUC at 2, 4, & 6 mg/m2: 190, 284, & 358 ng*h/mL, respectively. PBMC H3Ac was seen at all dose levels. 3 pts had stable disease, 2 at 4 mg/m2 (colon, CTCL) & 1 at 2 mg/m2 (CTCL). **Conclusions:** The MTD for coated MS-275 given fasting on this schedule was exceeded at 4 mg/m2 p.o. weekly x4 q6 weeks. AUC increased with dose. Drug-related hyperacetylation was observed.

3095 Publication Only

**A phase I dose-escalation study of weekly multiple dose intravenously administered SR271425 in patients with refractory solid tumors.** *E. Calvo, A. C. Lockhart, A. W. Tolcher, E. K. Rowinsky, G. Shackleton, J.-G. Morrison, R. Rafi, M. L. Rothenberg; Cancer Therapy & Research Ctr, San Antonio, TX; Vanderbilt-Ingram Cancer Ctr, Nashville, TN; Sanofi-Synthelabo Research, Malvem, PA; Sanofi-Synthelabo Research, Malvem, PA*

**Background:** The thioxanthone analog, SR271425, is a novel cytotoxic DNA-interacting agent with a broad spectrum of antitumor activity in preclinical murine tumor models. This clinical trial aims to determine tolerability and toxicities of SR271425 as a 1-hour single intravenous dose repeated weekly for 2 weeks followed by 1 week rest, to determine the maximum tolerated dose (MTD), recommended phase II dose (RPIID), and to assess its pharmacokinetic profile. **Methods:** A modified Fibonacci dose escalation design is being used. A single intravenous dose of SR271425 is administered over 1-hour weekly for 2 weeks, followed by 1 week rest, in a variety of refractory solid tumors. Of note, in the rabbit model, QTc prolongation, related to Cmax, has been reported at doses >660mg/m$^2$. Therefore, all patients are undergoing cardiology assessment with serial ECGs, which are assessed by a central reviewer. **Results:** To date, 17 patients have been treated at 5 dose levels (ranges, 64–675 mg/m$^2$/week). The mean age is 53 (range 24 -74 years) and ECOG performance status is 0–2. Grade 1–2 toxicities including QTc prolongation, nausea/vomiting/constipation, and fatigue have been observed. The pharmacokinetics of SR271425 following weekly dosing were consistent with that observed previously in a single dose ascending study with SR271425. Both Cmax and AUC (day 1) increased in a dose dependent manner. As would be predicted from the drugs short half-life (6.7 h), no systemic accumulation was observed as assessed by Cmax and $C_{6h}$ values on Day 1 versus Day 8. Stable disease has been observed in 3 patients. **Conclusions:** Preliminary data on this ongoing study suggests that SR271425 administered at split, weekly doses will likely allow greater cumulative exposure without significant toxicity.

3096 Publication Only

**A phase II trial of temsirolimus in metastatic neuroendocrine carcinomas (NECs).** *I. Duran, L. Le, D. Saltman, J. Kortmansky, W. Kocha, D. Singh, G. R. Pond, J. M. Peralba, J. Dancey, L. L. Siu; Princess Margaret Hosp Phase II Consortium, Toronto, ON, Canada; Memorial Sloan-Kettering Cancer Ctr, New York, NY; Univ of Chicago, Chicago, IL; Johns Hopkins Univ Sch of Medicine, Baltimore, MD; National Cancer Institute, Bethesda, MD*

**Background:** NECs are a varied group of endocrine neoplasms characterized by neurosecretory granules and cell surface markers. Except for islet cell carcinomas, NECs are resistant to conventional cytotoxics. Hormonal therapy such as somatostatin analogs or local therapies such as hepatic resection or arterial embolization are generally delivered to palliate symptoms. Temsirolimus is a novel mTOR inhibitor that downregulates cascades activated by loss of the tumor suppressor protein PTEN, a defect reported in moderately differentiated NECs. Due to the lack of effective systemic therapy for NECs, loss of PTEN detected in some cases, and a report of a partial response in this tumor type from phase I trials, a multi-centre 2-stage phase II trial in NECs was conducted. **Methods:** Patients were eligible if they demonstrated 25% increase in tumor volume, clinical deterioration or new tumor focus in the last 6 months. Temsirolimus 25 mg was administered intravenously over 30 minutes on a weekly basis. **Results:** To date, 23 patients (pts) with progressive NECs have been enrolled with the following demographics from 18 pts with baseline data: median age=55, range=36–68, M:F=9:9, ECOG 0:1:2= 8:9:1, and 11 pts had prior chemotherapy. Toxicity information is available from 15 pts in 50 four weekly cycles. The most frequently encountered grade 3–4 toxicities expressed as % of treatment cycles are: hypophosphatemia (14%), hyperglycemia (10%), cough (10%), hypokalemia (8%), hypercholesterolemia (8%), and hypertension (8%). The most frequent toxicities considering all grades are: fatigue (86%), anemia (76%) and lymphopenia (70%). Among 15 pts evaluable for response thus far, 10 have achieved prolonged stable disease (range: 3–11 cycles), including 1 pt with a 24% tumor shrinkage by RECIST criteria after 4 cycles, and 2 pts who have experienced significant clinical benefit and are on cycles 9 and 11, respectively. Levels of p70S6kinase in peripheral blood mononuclear cells at 24 hours post treatment have not shown correlation with clinical outcome in the majority of pts. Markers of cell cycle inhibition and apoptosis in paired tumor biopsies will be reported. **Conclusions:** Temsirolimus appears to have antitumor activity in NECs, study accrual is ongoing.