greater tail moments than was observed for cells exposed to 5-FU. The results are consistent with FdUMP[10] displaying enhanced DNA-directed effects relative to 5-FU.

62

The antitumor activity of OSI-7836 (GS7836, 4'-thio-araC), a nucleoside analog, in combination with cisplatin in human NSCLC xenografts in mice

E. Brown, S. Winski, C. Nilsson, A. Franks, D. Emerson. *OSI Pharmaceuticals, Inc, Cancer Biology, Boulder, USA*

OSI-7836 (GS7836, 4'-thio-araC) is a nucleoside analog currently in Phase I trials for the treatment of solid tumors. OSI-7836 has been shown to have antitumor efficacy in a range of xenograft models, including non-small cell lung carcinoma (NSCLC). Cisplatin, a standard agent used in combination in the treatment of NSCLC, was selected for combination studies with OSI-7836 in three NSCLC xenograft models (Calu-6, H460, HOP-92). Each drug was administered alone at its predetermined optimal dose on a day 1,8 schedule (OSI-7836, 1000 mg/kg; cisplatin, 9 mg/kg) and at 60% of optimal dose of each drug for the combination (OSI-7836, 600 mg/kg; cisplatin, 5.4 mg/kg). In the H460 xenograft model, the combination of OSI-7836 and cisplatin demonstrated increased efficacy with a Log Cell Kill (LCK)= 2.4, compared to OSI-7836 alone (LCK=1.4) or cisplatin alone (LCK= 0.6). In addition, the combination produced cures in 2 of 8 animals compared to 0 of 8 animals for either single agent. In the HOP-92 xenograft model, LCK could not be determined for either group dosed with OSI-7836 due to the large number of cures, but the OSI-7836 plus cisplatin combination demonstrated improved efficacy (6 of 8 animals cured) compared to OSI-7836 alone (4 of 8 cures) and cisplatin alone (1 of 8 cures). Similarly, in the Calu-6 xenograft model, the combination of OSI-7836 and cisplatin demonstrated improved efficacy (7 of 8 cures) compared to OSI-7836 alone (2 of 8 cures) and cisplatin alone (1 of 8 cures). Further preclinical OSI-7836 and cisplatin combination studies are ongoing. These data demonstrate that OSI-7836 can be combined effectively with cisplatin to improve the antitumor efficacy in lung xenograft models, supporting the investigation of this combination in the clinic for NSCLC.

63

Phase II trial of edatrexate in adult patients with metastatic soft tissue sarcomas, an Eastern Cooperative Oncology Group (ECOG) final report

C. Schwartz[1], L. Ryan[2], J. Nwangwu[2], R. Blum[3]. *[1]St. Luke's-Roosevelt Hosp. Ctr., Dept. of Hematology and Oncology, New York, USA; [2]Dana-Farber Cancer Inst., Dept. of Biostatistical Science, Boston, USA; [3]Beth Israel Medical Ctr., Dept. of Hematology and Oncology, New York, USA*

Edatrexate (EDX) is a water soluble anti-folate, formed by modification of the N10 position of 4-amino-folate. Based on promising preclinical and clinical data for soft tissue sarcoma (STS) (Casper et al. Cancer 1993;72:766-770), ECOG performed a phase II study of EDX as first line chemotherapy in metastatic STS. Wasserheit, C. et al (ASCO, 1998) reported preliminary data. All types of adult STS were allowed, with the exception of synovial cell sarcoma (competing trial). EDX was given as an intravenous infusion of 80 mg/m^2 weekly for 5 weeks, followed by dosing every other week. Starting week 7, doses were escalated every other week by 10 mg/m^2 unless toxicity occurred. Of the 46 patients entered, two were ineligible. Patients' histologies included 16 leiomyosarcomas, 7 MFH, 5 spindle cell tumors, 4 liposarcomas, and the remainder with various other histologies. For the 44 eligible patients, based on an intent to treat analysis, the response rate was 14% (95% confidence interval 5-27%), including 5 partial responses 11% (95% confidence interval 4-27%), and 1 complete response 2%. The duration of partial responses ranged from 54 to 598 days with the complete response continuing at last follow up. At a median follow-up period of 18.2 months, the median survival was 14.5 months. For the 45 patients with toxicity data, two toxic deaths occurred, which may have been EDX related: hemorrhage; pneumonia. Grade 3 or 4 toxicity occurred in 29% of patients. Most common toxicities were liver (11%), stomatitis (9%), anemia (9%), nausea (7%), arthralgias (7%), and less than 5% included leukopenia, thrombocytopenia, vomiting, diarrhea, and fatigue. In conclusion, response rates and durations, survival and toxicity are comparable with that achieved by chemotherapy considered "standard of care." This study population had a high proportion of patients with unfavorable risk factors for response to chemotherapy, including 36% leiomyosarcoma, 42% older than 60 years and 45% with liver metastases. Further EDX study is justified given these results and the limited efficacy of currently available therapy.

64

A pharmacokinetic (PK) phase I (PI) study of ZD9331 and carboplatin in relapsed ovarian cancer (ROC) with a pharmacodynamic (PD) endpoint

T. Benepal[1], L. Pyle[2], S. Bate[2], A. Hardcastle[1], G. Aherne[1], F. Mitchell[1], R. Ruddle[1], F. Raynaud[1], A. Jackman[1], M. Gore[2]. *[1]The Institute of Cancer Research, Sutton, Surrey, United Kingdom; [2]The Royal Marsden Hospital NHS Trust, London, United Kingdom*

ZD9331 is a rationally designed, specific non-polyglutamatable thymidylate synthase (TS) inhibitor that is active against ROC in phase I/II trials (Plummer et al, Proc. Am. Soc. Clin. Onc., 1999: Rader et al, Annals Oncol, 11: 83; 2000). In light of broad sensitivity of human ovarian tumour cell lines to ZD9331 and non cross resistance to platinum based drugs (Jackman et al, Biochem Biophys Acta, in press) we studied the combination ZD9331/carboplatin in a PI PK & PD study in ROC. Eligible patients were 18 yrs or over, with a histological diagnosis and radiological evidence of ROC, and a platinum treatment - free interval of at least 6 months. Up to 3 prior lines of chemotherapy were permitted. Carboplatin was administered on day 1 of each 21day cycle (60-min IV infusion) at a fixed dose of AUC5. ZD9331 was given on day 1 (2 hrs after carboplatin, 30-min IV infusion) and day 8 of each 21day cycle. Thirteen patients have been enrolled to date (median age of 57), treated with ZD9331 at 4 dose levels, 40 mg/m^2(1), 65 mg/m^2(2), 85 mg/m^2(3)and 100 mg/m^2(4). No grade 3 or 4 toxicities were seen at dose level 1. One patient had grade 3 neutropaenia at level 2, and 1 patient had grade 3 neutropaenia at level 3. Dose limiting toxicities were seen in 2 patients at 100 mg/m^2 (grade 4 neutropaenia $>$ 7 days, and grade 4 fatigue $>$ 7 days). Plasma deoxyuridine (measured by HPLC in 6 patients in dose levels 1 and 2) was elevated indicating TS inhibition to at least day 12. Plasma ZD9331 was measured by ELISA, using a specific ZD9331 rabbit polyclonal antibody. Carboplatin was assayed by atomic absorption spectrometry. There was no PK interaction between the 2 drugs as ZD9331 PK data were similar to previous monotherapy studies, and measured AUC of carboplatin corresponded with that administered (WinNonlin professional, compartmental analysis). Antitumour activity was observed in 4/13 patients. The likely recommended phase II dose (carboplatin AUC5, ZD9331 85mg m^2) is being expanded to 6 patients with further PK and PD evaluation at this dose level. We conclude that this combination is well tolerated, TS inhibition is achieved at doses below the maximum tolerated dose, and antitumour activity is observed.

65

Phase I and pharmacokinetic study (PK) of the combination of multitargeted antifolate pemetrexed (ALIMTA) with irinotecan (CPT-11) in patients with advanced malignancies

M. Beeram[1], L. Hammond[2], G. Schwartz[3], A. Patnaik[2], A. Tolcher[2], C. Simmons[2], G. Renshaw[4], E. Rowinsky[2]. *[1]Institute For Drug Development, Univ. Of Texas Hea, Division Of Medical Oncology; [2]Institute For Drug Development, San Antonio, USA; [3]Brooks Army Medical Center, San Antonio, USA; [4]Eli Lilly Co., Indianapolis, USA*

Inhibition of key enzymes involved in folate metabolism remains an attractive therapeutic strategy. Pemetrexed, pyrrolopyridimine based antifolate is a potent inhibitor of multiple folate-dependent enzymes including thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase and has broad-spectrum antitumor activity. Preclinical evidence of synergy and minimally overlapping toxicity profiles served as the rationale for this clinical evaluation of the combination of pemetrexed and CPT-11. The feasibility of administering this combination is being evaluated in a phase I trial. Pemetrexed is given IV over 10 min followed by CPT-11 as a 90-min IV infusion every 3 weeks. 23 patients received 75 courses at the following pemetrexed/CPT-11 doses (mg/m^2) (patients/courses): 300/175 (3/13), 300/250 (6/22), 400/250 (9/21), 500/250 (5/19). Myelosuppression was the principal toxicity in this group of patients. Febrile neutropenia was seen at 300/250 (1 patient) and grade 4 vomiting at 400/250 (1 patient)(DLT). Other non-dose-limiting toxicities were diarrhea and skin rash. The protocol was then amended to include 'nutritional' quantities of folic acid (FA) (400 mcg/d) and vitamin B12 (1mg/9 weeks) supplements so as to reduce pemetrexed-induced toxicity and allow further dose-escalation. Doses explored with FA and B12 are 450/250 (4/41), 500/250 (9/61) and 500/300 (4/21). Demographics: median age- 58 (30-77); 30 M/10 F; PS 0-1(36) and PS 2(4). Primary tumors: Colorectal (10), Mesothelioma (10), Lung (6), Pancreas (3), Hepatobiliary (3) and others (8). One febrile neutropenia (DLT) was seen at 500/300 and accrual continues at this dose. One partial response in a patient with a 5-FU-refractory metastatic rectal cancer and 3 minor responses in patients with ampullary,