

solid tumor panels. Using a time to event measure of efficacy, AZD2171 had intermediate and high levels of activity against 10 and 1 of 26 solid tumor xenografts evaluable for this measure, respectively. Intermediate activity was observed in 4 of 5 rhabdomyosarcoma, 3 of 3 Ewing sarcoma, and 2 of 3 Wilms tumor (WT) xenografts, with high level activity observed in 1 of 2 evaluable rhabdoid tumor (RT) xenografts. AZD2171 induced CR against 1 of 3 osteosarcoma (OS), 1 of 3 RT, and 1 of 3 WT xenografts, but had no effect on *in vivo* growth of any ALL xenografts. Kasumi-1, the only PPTP *in vitro* panel cell line with an EC₅₀ < 1 μM (EC₅₀ 0.175 μM) is known to have a gain-of-function KIT^{Asn822Lys} mutation.

Conclusions: AZD2171 demonstrated broad activity against the PPTP's solid tumor panel. Antitumor activity was manifested primarily as tumor growth delay, although tumor regressions were observed in the OS, RT, and WT panels. Further preclinical evaluation of AZD2171 is warranted and will include studies of AZD2171 in combination with clinically relevant agents for selected xenografts in which activity was observed. The Pediatric Brain Tumor Consortium is planning clinical evaluations of AZD2171 in children. Supported by NCI NO1CM42216.

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POSTER

A phase II study of enzastaurin as second- or third-line treatment of non-small cell lung cancer (NSCLC)

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Background: Enzastaurin, an oral serine/threonine kinase inhibitor, targets the PKC and PI3K/AKT pathways to inhibit tumor cell survival and proliferation and tumor-induced angiogenesis. PKC isoforms and PI3K/AKT are over-expressed and active in NSCLC and are associated with poor prognosis and treatment resistance. Based on preclinical and phase I trial data, this multicenter phase II trial was conducted to evaluate enzastaurin as second- and third-line treatment of NSCLC. The primary objective was to determine the rate of progression-free survival (PFS) at 6 months. Secondary objectives included safety, antitumor activity, and the rate of survival at 12 months.

Methods: Patients with advanced (stage IIIB) or metastatic (stage IV) NSCLC, who had failed at least 1 prior therapy, received 500 mg of oral enzastaurin (tablets), once daily after breakfast, every 28 days until disease progression or unacceptable toxicity occurred. All patients had to have failed prior platinum-based chemotherapy and had to be considered eligible for second- or third-line treatment.

Results: Fifty-three patients (55% male, 45% female; ECOG ≤2), were enrolled. All patients had prior chemotherapy, including 28% with EGFR inhibitor treatment. At the time of interim analysis, 34 (64%) patients were alive. The median PFS time was 1.84 months (95% limits: 1.68–1.87 months) and the rate of PFS at 6 months was 10.4% (95% limits: 8.4%–10.9%). Eighteen patients (34%) had a best response of stable disease, while no patients had a partial or complete response. Of the 53 patients, 10 (19%) received therapy for ≥6 cycles, 3 of whom are currently receiving enzastaurin beyond 9 cycles of treatment. The most common toxicity was fatigue (n=21), noted within 1 week of starting treatment, but was not reported in patients with disease stabilization.

Conclusion: Although no objective tumor responses were observed in this study, 10.4% of the patients were progression-free at 6 months. Additional evaluations are ongoing to better understand the use of enzastaurin in the treatment of NSCLC, including studies to determine how to best combine enzastaurin with other agents active in NSCLC.

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POSTER

Simultaneous blockade of VEGF and HGF receptors results in potent anti-angiogenic and anti-tumor effects

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Vascular endothelial growth factor (VEGF) and its tyrosine kinase receptors, VEGFR1 and VEGFR2, are expressed on the surface of vascular endothelial cells and play a central role in the promotion of tumor angiogenesis. Hepatocyte growth factor (HGF) and its tyrosine kinase receptor Met are overexpressed or activated in a wide variety of tumor types, promoting tumor growth. Additionally, HGF and VEGF interact synergistically to promote endothelial cell proliferation, tubule formation, and growth of new vessels *in vivo*. EXEL-7184 (XL184) is a small molecule tyrosine kinase inhibitor that targets the VEGF and HGF receptor tyrosine kinases.

In enzymatic assays, EXEL-7184 is a potent inhibitor of VEGFR2 and Met tyrosine kinase activities, with IC₅₀ values in the sub-nanomolar and single digit nanomolar range, respectively. EXEL-7184 also exhibits potent activity in cell based assays, inhibiting VEGF-induced activation

of ERK in endothelial cells, and HGF-induced activation of Met in tumor cells. EXEL-7184 also inhibits endothelial tubule formation stimulated by VEGF or by conditioned media derived from tumor cell lines, and HGF induced responses in tumor cells (e.g. invasion, chemotaxis). In pharmacodynamic assays, oral administration of EXEL-7184 resulted in dose-dependent and reversible inhibition of VEGFR2 in mouse lung, and of Met in xenograft tumors and in mouse liver. Following acute administration to xenograft tumor-bearing mice, EXEL-7184 caused rapid disruption of the tumor vasculature, and apoptosis of both tumor and endothelial cells. Administration of EXEL-7184 using both once-daily and less frequent oral dosing schedules resulted in significant efficacy in a range of solid tumor models, with substantial regression of large tumors. Immunohistochemical analysis at the end of efficacy studies demonstrated potent inhibitory effects on the tumor vasculature, and strong induction of tumor cell death. In summary, EXEL-7184 is a potent inhibitor of VEGFR2 and Met, and exhibits potent anti-tumor and anti-angiogenic activity in preclinical models. A phase I clinical trial for EXEL-7184 is in progress.

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POSTER

A prospective study of the cutaneous side effects of sorafenib, a novel multi-kinase inhibitor

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Background: This study investigated the incidence, severity and management of cutaneous reactions to the oral multi-kinase inhibitor sorafenib (Nexavar®) (SOR) in advanced renal cell carcinoma (RCC) patients. Additional objectives were to determine the effect of SOR on nevi and on ERK phosphorylation in normal skin.

Materials and Methods: During a 16 month period from Nov. 2003 to Feb. 2005, all consecutive patients included in our center in the Phase III TARGETs RCC trial were enrolled in this dermatologic sub-study. Patients were randomized to receive either SOR 400 mg twice daily (bid) or placebo. Dermatologic examination was performed before treatment, every 3 weeks during the first four cycles, and every 4 weeks thereafter.

Results: Ninety-six patients with unresectable or metastatic RCC and failure of one systemic therapy were enrolled, and 85 received either SOR (n=43) or placebo (n=42). Thirty-nine patients (90.7%) on SOR, and three (7.1%) on placebo, had ≥ one cutaneous adverse event. Most cutaneous adverse events were mild or moderate; only two SOR patients had grade 3 toxicity (hand-foot skin reaction [HFSR]). No patient discontinued due to cutaneous side effects. HFSR was typically less severe and more localized than the form associated with traditional chemotherapies. HFSR (grade 3) led to dose reductions in two patients (50%), but resolved in 3–4 weeks without sequelae. After restoration of full-dose treatment, HFSR recurred in only one of these patients. SOR-induced nevi modification was not observed and no clear difference in ERK phosphorylation was reported between treated and non-treated patients. Dermatologic symptoms were easily managed with topical treatments.

Conclusions: Despite a high frequency of SOR-induced cutaneous toxicities, most were mild to moderate in severity and easily manageable. The majority of SOR-induced grade 2 HFSR can be treated symptomatically without dose decrease or interruption. For grade 3 HFSR, dose reduction (by 50%) or interruption for 5–7 days, plus symptomatic treatment, usually leads to rapid symptom relief. In this study, treatment discontinuation for HFSR was not necessary. Further experience at our center shows that even when discontinuation is necessary for severe HFSR, reinstitution at the same dose is often possible without reoccurrence of this grade of toxicity. Final clinical and pharmacodynamic results, including correlation of cutaneous events with patient response, will be reported.

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POSTER

Methylnaltrexone inhibits S1P, VEGF and PDGF-induced angiogenesis: role of receptor transactivation

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Background: The role of opioids in angiogenesis is largely unknown. The peripheral mu opioid antagonist, methylnaltrexone (MNTX), allows exploration of the role of opioids in angiogenesis. We have shown in human dermal microvascular endothelial cells (EC) that clinically relevant concentrations of morphine sulfate (MS) cause EC migration, inhibited by pretreatment with MNTX at therapeutically relevant levels (0.1 μM). To confirm the angiogenic effect of opioids and determine its mechanism, we examined MNTX in agonist-induced human pulmonary microvascular EC (HPMVEC) proliferation (P) and migration (M), two key elements in angiogenesis.