growth inhibition occurred on the schedule of 0.15 mg/kg followed by 0.3 (T/C of 30%), with optimal tolerance achieved using a 7-day gap between treatments.
These results suggest that tumour IFP reduction may be harnessed to guide clinical dosing regimens of ABJ879 or other epothilones aimed at optimizing their therapeutic index.

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ILX651 inhibits polymerization of alpha beta III tubulin and is cytotoxic to beta tubulin mutant tumor cell lines that overexpress beta III tubulin

M. Kavallaris[1], R. Luduena[2], M. Lu[1], V. Prasaad[2], L. Hammond[3], K. Stephenson[3], L. Arthaud[3], S. Weitman[3]. *[1]Children's Cancer Institute Australia for Medical Research, Biochemistry, Randwick, Australia; [2]University of Texas Health Science Center, San Antonio, USA; [3]Ilex Products, Inc., San Antonio, USA*

Background: ILX651 is a synthetic dolastatin 15 analog with a unique mechanism of action that potentially differs from that of other tubulin interacting agents. ILX651 has been chemically modified to provide improved pharmacological properties and is orally bioavailable with a potentially enhanced therapeutic window over previous generations of dolastatins. Based on preclinical and Phase I data, ILX651 has potential activity across a wide number of solid tumors. ILX651 inhibits the extent of microtubule assembly and induces a long lag time which is a unique finding for anti-tubulin drugs. It is possible that ILX651 acts by slowing down the rate of microtubule nucleation or elongation which may disrupt mitotic spindle function by this unique mechanism of action.
Methods: As the expression of specific β tubulin isotypes may play a significant role in cellular sensitivity or resistance to tubulin interacting agents, the effects of ILX651 on microtubule assembly of purified bovine brain tubulin isotypes (αβII, αβIII and αβIV) were examined. In addition, ILX651 response in drug-resistant cell lines with tubulin mutations was investigated. β tubulin isotypes were purified by immunodepletion chromatography and microtubule assembly was assessed by turbidimetry. Growth inhibition was evaluated by the alamar blue dye assay.
Results: ILX651 strongly inhibited microtubule assembly at concentrations as low as 1 μM in the presence of purified αβIII tubulin. Epothilone-resistant human acute lymphoblastic CCRF-CEM cell lines, CEM/dEpoB140 and CEM/dEpoB300, which overexpress βIII tubulin and harbor mutations in β tubulin, were exquisitely sensitive to ILX651 treatment with IC50 values of 0.9 nM and 0.4 nM, respectively, compared to an IC50 value of 11.4 nM for parental CCRF-CEM cells.
Conclusions: These results indicate that ILX651 has a profound inhibitory effect on polymerization of αβIII that may correlate, in part, to the cytotoxicity observed in β tubulin mutant cell lines that also overexpress βIII tubulin isotype. Tubulin mutations in the dEPO-resistant cells also affect microtubule stability and therefore may contribute to the hypersensitivity to ILX651. Because aberrant or modulated expression of class III β tubulin is associated with paclitaxel resistance, ILX651 may be active against paclitaxel-refractory tumors that overexpress βIII tubulin. Further studies are currently underway to elucidate ILX651 interactions with tubulin isotypes and MAP's.

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The orally effective taxane DJ-927 has little ability to induce drug resistance in human non-small cell lung cancer cells

Y. Ochi, M. Minami, A. Togho. *Daiichi Pharmaceutical Co., Ltd, New Product Research Laboratories III, Tokyo, Japan*

DJ-927 is an orally active taxane with higher solubility, lower neurotoxicity, and superior preclinical efficacy than the clinical taxanes docetaxel (DTX) and paclitaxel (PTX). In particular, DJ-927 shows marked efficacy in vitro and in vivo against intrinsic or acquired multidrug-resistant tumor cells that express P-glycoprotein (P-gp). In the present study, we established sublines resistant to DJ-927, DTX, or PTX from the human non-small cell lung cancer (NSCLC) cell line NCI-H460, and investigated their characteristics and mechanisms of resistance. Additionally, the antitumor effect of DJ-927 against a PTX-resistant clone was confirmed in vivo.
Drug-resistant sublines were selected by stepwise exposure of NCI-H460 cells to DJ-927, DTX, or PTX. Acquisition of 10-fold resistance against DTX required 58 days and against PTX required 86 days, while acquisition of DJ-927 resistance required more than 200 days. Both DTX- and PTX-resistant cell lines exhibited multidrug-resistant phenotypes and overexpressed P-gp. In contrast, the DJ-927-resistant cell line exhibited not only cross-resistance to DTX and PTX, but also increased sensitivity to tubulin-interacting agents such as navelbine and vincristine. Additionally, the amount of P-gp and α-, β-, and acetylated α-tubulin proteins in DJ-927-resistant cells were the same as the amount of control cells. Single clones were successfully derived from DTX- and PTX-resistant sublines (yields: >30%), but not from the DJ-927-resistant line (yield: <0.1%). In vivo antitumor effects of DJ-927, DTX, and PTX were examined using NCI-H460/PTX13 (PTX13), one of the PTX-resistant clones with confirmed tumorigenicity in nude mice. In this system, DJ-927 treatment at a total dose of 19.6 mg/kg exhibited significant antitumor activity (inhibition rate [IR] = 74.9%) even though one mouse died of toxicity. In contrast, neither DTX at toxic doses that caused severe body weight loss (a total dose of 75 mg/kg) nor PTX at its MTD (a total dose of 180 mg/kg) exhibited antitumor effects against PTX13 tumors (IR = 31.2% for DTX and 34.7% for PTX).
These results indicate that DJ-927 has little ability to induce P-gp-mediated multidrug-resistance, and that DJ-927 inhibits growth of human NSCLC cells that are resistant to current clinically available taxanes. Studies to elucidate the mechanisms of DJ-927-induced resistance are in progress.

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Nonlinear pharmacokinetic modeling of XAA296 administered to patients with advanced solid tumors once every 3 weeks (q3w) intravenously (IV) in a phase I clinical trial

C. Hsu[1], T. Chen[1], A. Mita[2], A.C. Lockhart[3], M. Moricz[1], L. Alland[1], G. Taccard[4], E. Rowinsky[2], M.L. Rothenberg[3], S. Sharma[1]. *[1]Novartis Pharmaceuticals, East Hanover, USA; [2]Institute for Drug Development, Cancer Therapy and Research Center, San Antonio, USA; [3]Vanderbilt-Ingram Cancer Center, Nashville, USA; [4]Novartis AG, Basel, Switzerland*

Background: XAA296, a natural product isolated from the marine sponge *Discoderma dissoluta*, stabilizes microtubules more potently than paclitaxel and demonstrates activity against paclitaxel-refractory xenografts.
Methods: In a phase I dose-escalation study, we investigated the MTD, safety, and PK profiles of XAA296. Patients (pts) with advanced solid tumors received XAA296 via IV q3w at a fixed rate of 0.77 mg/mL/min. Blood samples were drawn at various time points in a 3-week interval. Blood XAA296 levels were determined by an LC/MS/MS method with a quantification limit of 0.5 ng/mL using 0.25 mL of blood.
Results: Twenty-five pts (15 m/10 f; ages 19–79 yrs) provided complete blood samples after the first dose. The dose escalation was 0.6, 1.2, 2.4, 4.8, 9.6, 14.4, 19.2, and 25 mg/m^2. After a short infusion, XAA296 levels declined rapidly followed by a prolonged terminal phase. Nonlinear pharmacokinetics, evidenced by a secondary peak and a convexity on a semi-log scale of the terminal phase, was observed in all patients. The disposition of XAA296 was characterized by a 2-compartment model and an additional drug repository compartment. Following the short infusion, the drug was distributed to the peripheral compartment (Vp) and eliminated from the central compartment (Vc) by a first-order process ($\leqslant$2.4 mg/m^2) or by a Michaelis-Menten process (>2.4 mg/m^2). When recirculation took place, a fraction of the drug stored in the repository compartment was released back to the central compartment. The model was parameterized with volumes of Vc and Vp, inter-compartment diffusion parameters (Q2 and Q3), K_m, V_{max}, K_{10}, and a lag time (t_{lag}) for delayed recirculation. Saturable elimination was evident in pts receiving >2.4 mg/m^2 of XAA296 whereas pseudo-linear disposition profiles were observed in pts receiving $\leqslant$2.4 mg/m^2. Drug clearance rate in the central compartment and $t_{1/2}$ are concentration-variant parameters. PK parameters by model fitting are summarized in the table.

Dose	Vc (L)	Vp (L)	Q2 (L/h)	Q3 (L/h)	K_m (ng/mL)	V_{max} (ng/mL/h)	K_{10}	t_{lag} (h)
$\leqslant$2.4 mg/m^2, n=9	8.3 ±3.9	543 ±341	92 ±53	5 ±1.9	–	–	2.2 ±2.0	28 ±16
>2.4 mg/m^2, n=16	11.1 ±5.2	755 ±231	198 ±206	59 ±187	34 ±61	21±19	–	18 ±20

Conclusion: XAA296 administered to pts q3w has demonstrated non-linear pharmacokinetics at >2.4 mg/m^2, which is well described by a 2-compartment model and an additional drug repository compartment.

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Oxi 4503: a novel combretastatin analog with both single agent activity and the abilty to enhance radiation response

M.R. Horsman. *Aarhus University Hospital, Dept. Experimental Clinical Oncology, Aarhus C, Denmark*

Background: The aim of this study was to test the anti-tumour activity of the novel tubulin-binding agent, Oxi 4503, when used alone or in combination with radiation therapy, in a murine tumour model that generally shows a limited response to such agents.