SUPPLEMENTARY METHODS

Sciatic Nerve Immunofluorescence

To assess changes in gross morphological structure, nuclei, myelin and axons were identified using DAPI stain, anti-myelin basic protein, and anti-phosphoneurofilament, respectively. Using the Imaris software surfaces tool, we identified nuclei, myelin sheaths, and axons based on the fluorescent signal from their appropriate antibody or stain, manually thresholding signal to background noise. To maintain consistency in object identification in similarly treated samples, one set of threshold parameters was applied to all sections stained with the same antibody solutions and imaged with the same microscope settings. After identification, these objects were counted automatically. Signs of axon degeneration, defined as solid, circular regions of myelin lacking a phosphoneurofilament signal, were identified and counted manually and compared with the total number of axon objects identified by the software. For axon density measurements, the image stack was flattened in Fiji using the maximum intensity setting and the number of axons per region of interest (defined by phosphoneurofilament signal) quantified using Imaris. In practice, the periphery of the nerve bundle was manually traced in Imaris and a mask applied. Other axons identified within this defined mask were counted and the exact area of the mask was recorded, allowing the number of axons per unit area to be calculated.

In order to quantify changes, fluorescence values were collected and normalized within each slide first, before comparisons were made between slides. Normalization of axonal Cy2 fluorescent signals (depicted in Supplementary Figure S1) was accomplished by using the anti-phosphoneurofilament (PNF) signal to identify and mask the axonal regions, specifically differentiating axons from surrounding Schwann cells or other cell types present. The raw values of Cy2 fluorescence were determined for each axonal region within the treatment field of view. The mean Cy2 signal per axon was calculated for each treatment to give the “treatment mean.” These values were normalized by dividing each treatment mean by the sum of all four treatment means and all three vehicle control means per slide (seven means total). This method was employed in order to retain the natural variability seen in vehicle treatments. In microtubule analyses, student’s t-tests were used to identify significant differences in comparisons of the drug groups to their respective vehicles and between the two drug treatment groups. In some cases, the singular comparison of the drug to appropriate vehicle group by Student’s t-test provided additional insight.

Supplementary Figures and Legends

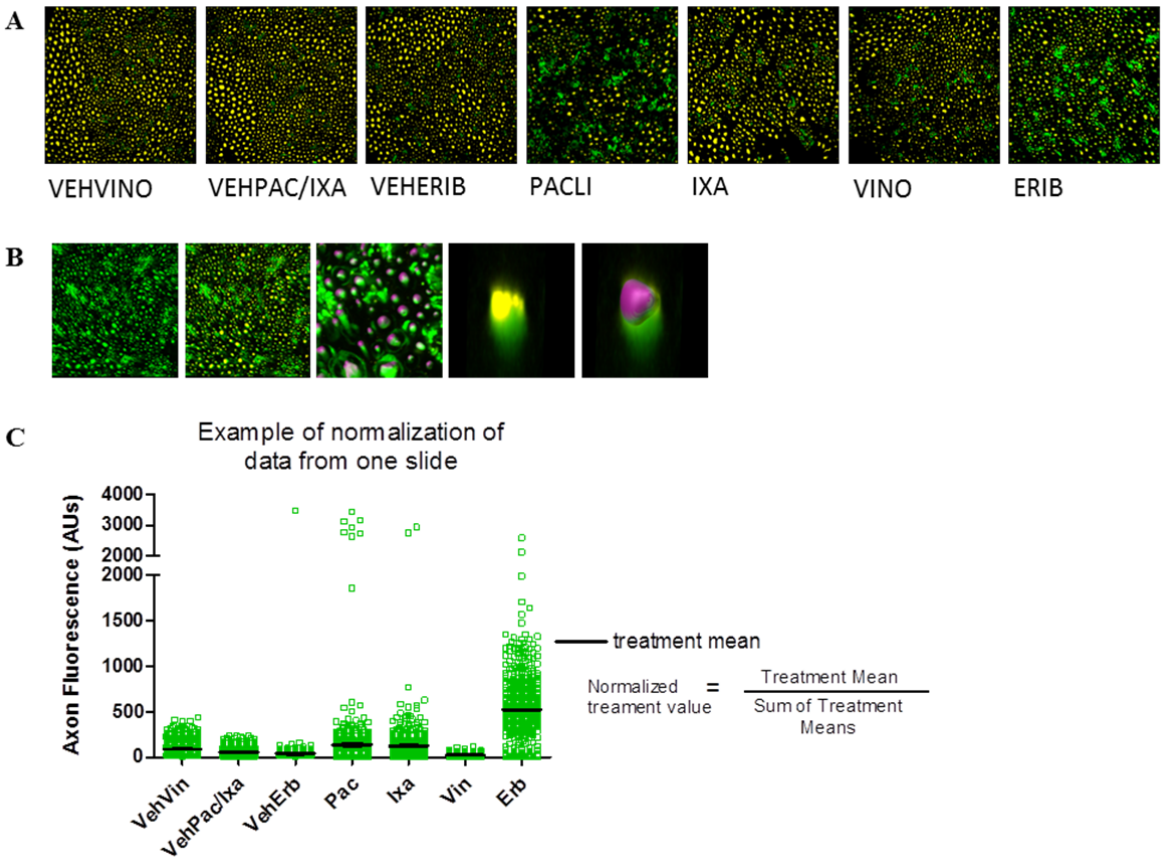

Figure 1S

Normalization of acetylated alpha tubulin fluorescent signal. **A.** Representative sections from one nerve per seven treatment groups, stained with same antibody solution and imaged using same microscope settings. Axonal (3D) region was identified by phosphoneurofilament (PNF, yellow in fluorescent images), then acetylated alpha tubulin (green) inside delimited regions were quantified. **B.** Images depicting computer identification (purple) of phosphoneurofilament delineated regions (yellow). **C.** The acetylated alpha tubulin fluorescence value identified per axon is represented by the green boxes. All axons per treatment were averaged to give the treatment mean. The treatment means were then normalized by dividing each treatment mean but the sum of treatment means observed on the slide, each normalized value was multiplied by 100, to be represented as a percent of total fluorescence observed. This was repeated twice per nerve for each of five nerves per treatment to obtain a nerve value. The mean of the five nerve values is represented in the graphs in the main figure (Figure 6). VehVino = Vehicle for Vinorelbine, VehPac/Ixa = Vehicle for Paclitaxel and Ixabepilone, VehErib = Vehicle for Eribulin, Pacli = Paclitaxel, Ixa = Ixabepilone, Vino = Vinorelbine, Erib = Eribulin

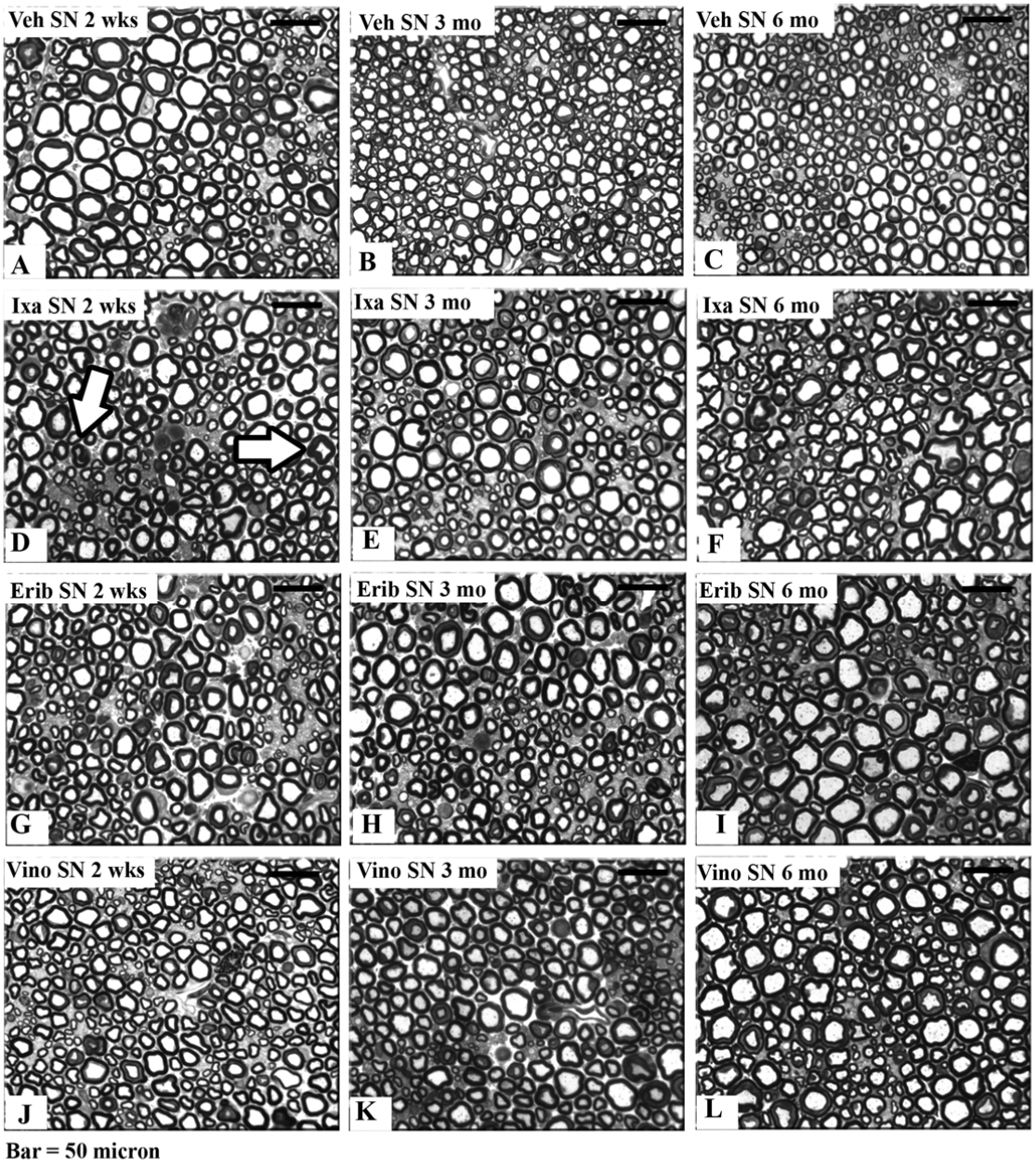

Figure 2S: Light microscopy analysis of DRG of vehicle, IXA, ERIB and VINO-treated mice found IXA induced similar but less frequent damage compared to PACLI (D), which was no longer evident at 3 months (E) and 6 months (F). No significant pathological changes were observed in vehicle (A to C), ERIB (G to H) and VINO (I to L)-treated animals.

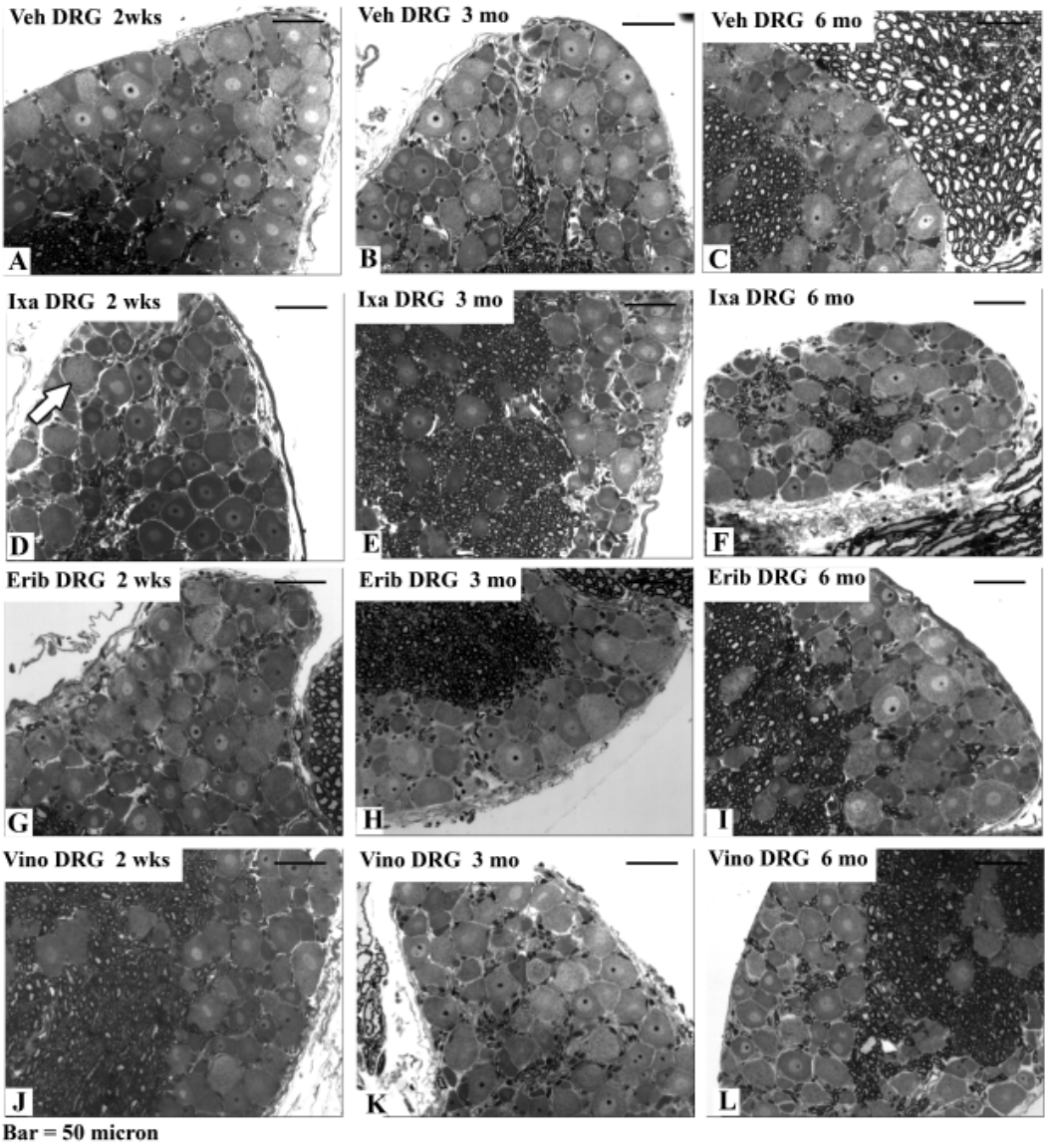

Figure 3S: Light microscopy analysis of the sciatic nerve of vehicle, IXA, ERIB and VINO-treated mice found IXA induced similar but milder morphological damage than PACLI after 2 weeks (D), changes that were no longer present at 3 or 6 months (E and F). No evident morphological alterations were present in sciatic nerves of ERIB (G to H), VINO (I to L) or vehicle (A to C)-treated animals.

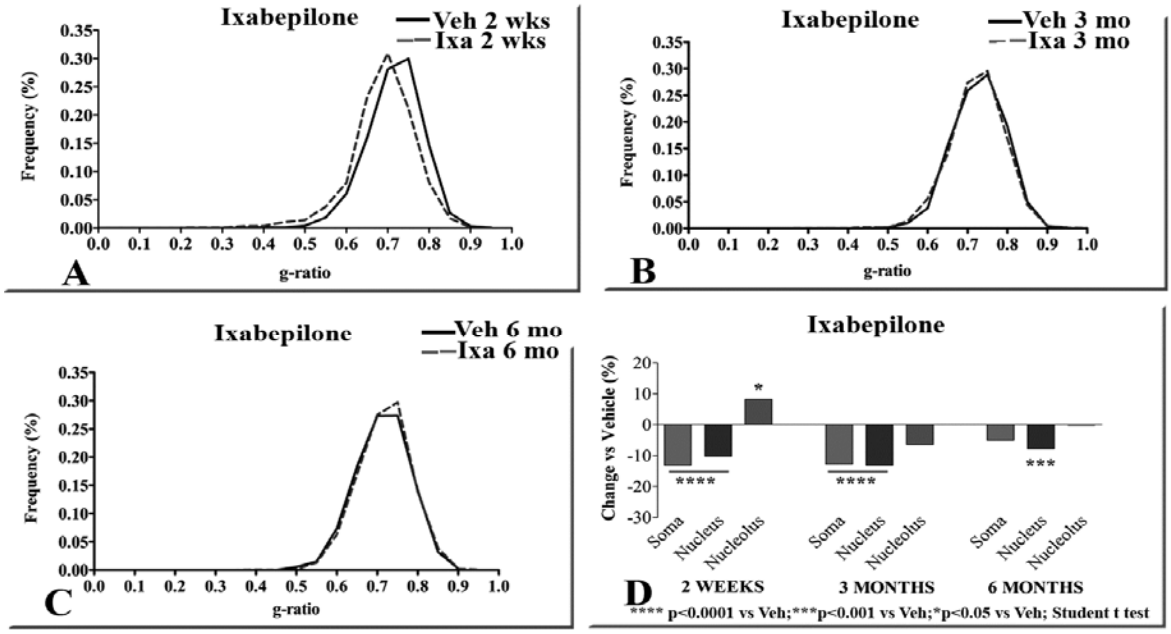

Figure 4S: The graphs in A, B, and C show the frequency distribution of myelinated fibres g-ratio (%) at 2 weeks, 3 months and 6 months, respectively. IXA, similarly to PACLI (see Figure 4N), induced a moderate shift on the left of the histograms at 2 weeks, indicating a reduction in the frequency of the largest fibers. This was no longer evident at 3 (B) and 6 (C) months.

The graphs in (D) show the rate change (%) of DRG neuronal cellular sizes of IXA versus vehicle-treated mice. IXA induced a somatic ($P<0.0001$ vs vehicle) and nuclear ($P<0.0001$ vs vehicle) reduction-in-size at 2 weeks. This persisted into 3 months ($p<0.0001$ vs vehicle for somatic, nuclear and nucleolar sizes), but recovered at 6 months ($p<0.05$ vs vehicle for nuclear size).

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	ERIBULIN	VINORELBINE	IXABEPILONE	PACLITAXEL	REFS
Mouse MTD used in this study (M, W, F dosing for 2 wks)	1.2 mg/kg	11 mg/kg	2 mg/kg	30 mg/kg	*Current paper*
Mouse AUC following single MTD dose used in this study	[1]492 ng/h/mL	[2]7332 ng/h/mL*	[1]304 ng/h/mL	[1]114,000 ng/h/mL	[1]*Cancer Res. (2016),* ***76****:3332-9* [2]*Pharm Res*. (2016), **33**:2904-2919
Patient AUC following therapeutic dosing	[3]757 ng/h/mL [4]722 ng/h/mL	[5]1992-2092 ng/h/mL	[6]124-628 ng/h/mL [7]235-268 ng/h/ml	[8]21,430-31,240 ng/h/mL [9]12,707-34,646 ng/h/mL [10]7686-40,138 ng/h/mL	[3]*Br J Clin Pharm (2013),* ***75****:507-521* [4]*Cancer Therapy: Clinical, (2009)* ***15****:4213-4219* [5]*Cancer Chemother Pharmacol (1989),* ***23****: 247-251* [6]*J Neurooncol (2010),* ***100****: 261-268* [7]http://ctr.bms.com/pdf//CA163088.pdf [8]*Br. J.Cancer (1998),* ***78****:34-39* [9]*Ann Oncol (1995),* ***6****:699-704* [10]*Clin Cancer Res (1995)* ***1****: 599-606*
GI_{50}/IC_{50} in various cancer cell lines	[11,12] 0.1-14.8 nmol/L	[13-15] 0.47-3250 nmol/L	[11,16] 2.4-197.4 nmol/L	[11,13]1.25-8760 nmol/L	[11]*Cancer Res(2016),* ***76****: 5115-23* [12]*Pediatr Blood Cancer (2013*), **60**:1325-32. [13]http://www.cancerrxgene.org/ [14]*Mol Pharm (2001),* ***60****: 225-23* [15]*J Cancer Res Clin Oncol (1992),* ***118****:249-254* [16]*Cancer Chemother Pharmacol* (2009), **63**:201–212

** after 12mg/kg dose iv vinorelbine*

SUPPLEMENTARY TABLE: 1