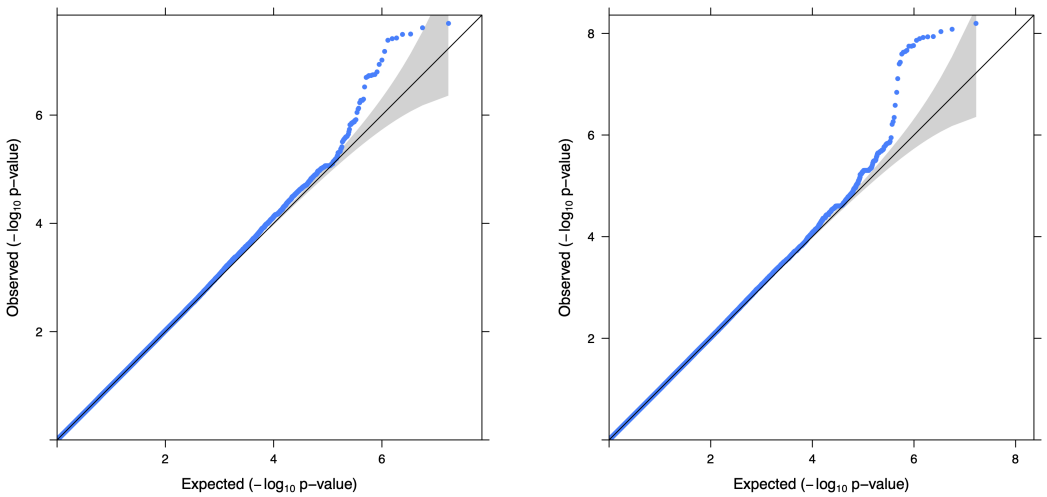

Figure S1. QQ-plot of p-values from a common variant GWAS of time to first peripheral neuropathy for all patients N=4,900 (left) and for the taxane treated subcohort, N=2,535.(right). Each point represents a single variant. Genomic inflation factor λ_{gc}=1.004 (all patients) and λ_{gc}=1.005 (taxane treated subcohort). Gray region designates the 95% confidence interval around the null distribution of p-values.

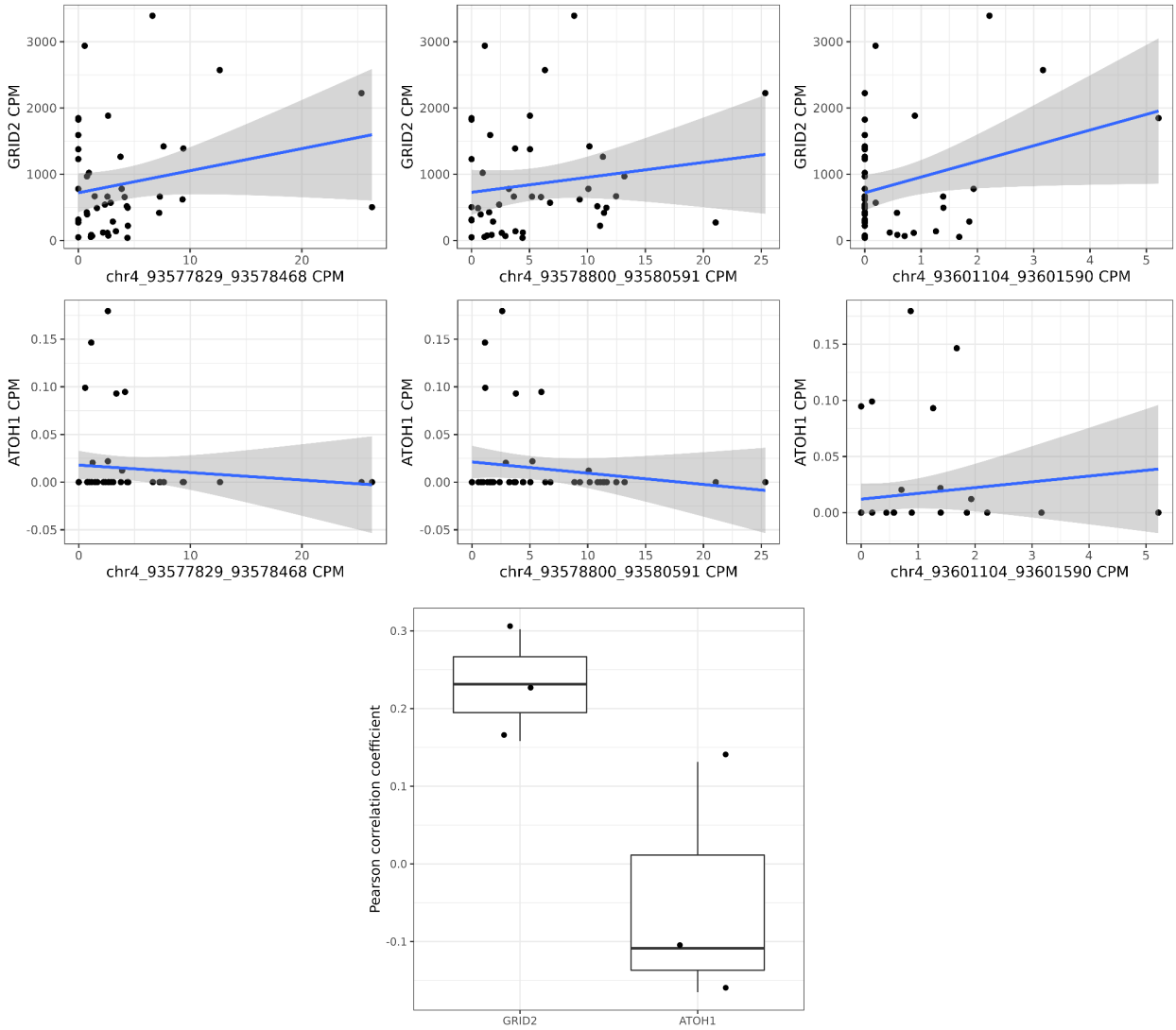

Figure S2. Top panel, each point represents a cell type and each subpanel shows the relationship between gene expression and peak accessibility in the rs17020773/*GRID2* intron locus, which contains two protein-coding genes within 1MB (+/- 500KB) and three accessible chromatin peaks [1]. For each cell type classified in the original publication, counts were summed across all genes and all peaks to generate pseudo-bulk profiles for gene expression and chromatin accessibility respectively, then profiles were normalized for read depth by dividing by the total and multiplying by 10^6 (CPM normalization). Bottom panel, boxplot of each of the correlations shown in the top panels (p = 0.05, two-sided t-test). All 3 regions showed a positive correlation with the expression of *GRID2* whereas only 1 region was positively correlated with *ATOH1*.

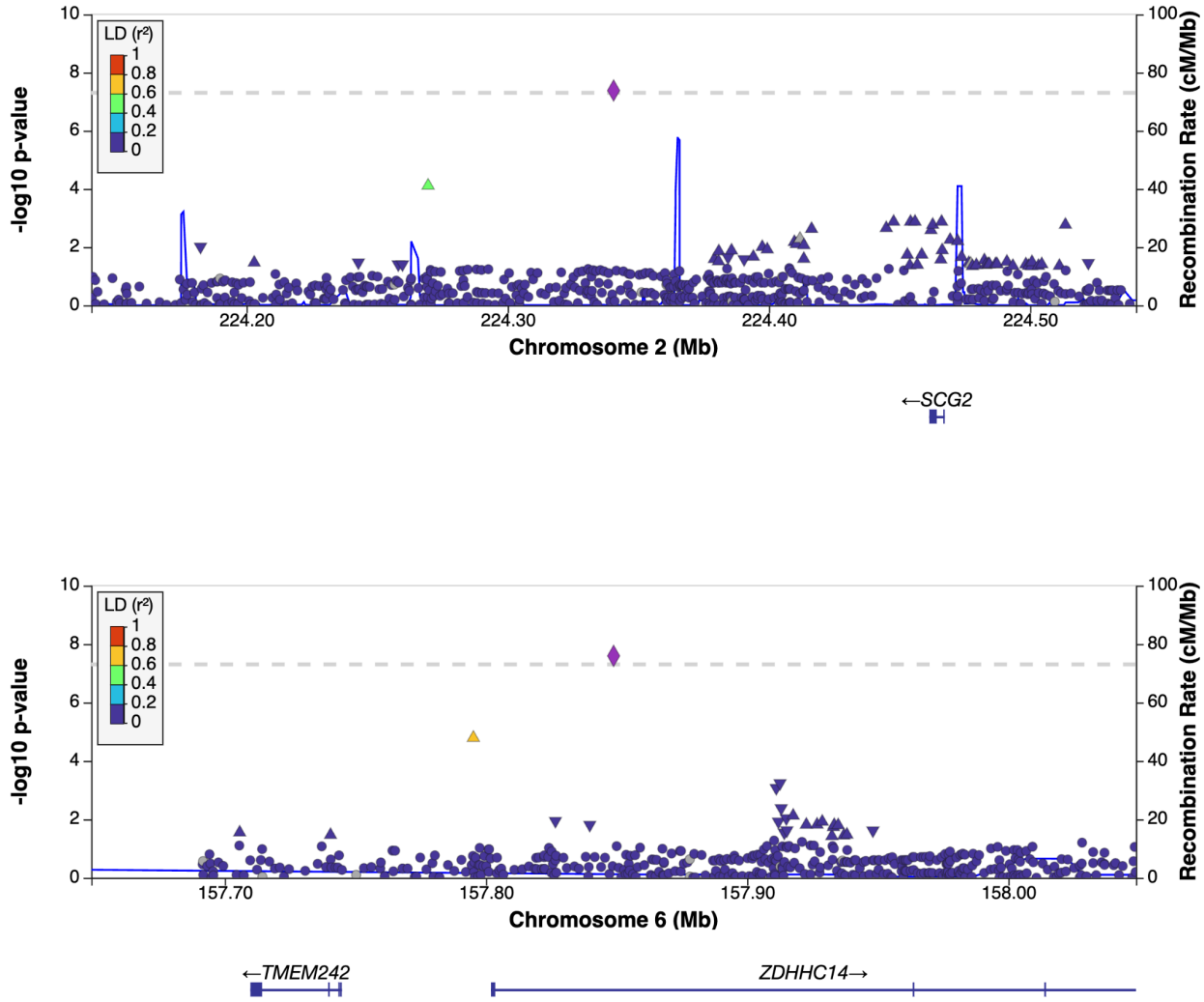

Figure S3. Locus zoom plots for rs115575220 in all patients (top) and for rs191482247 in taxane treated patients (bottom). The colors indicate the strength of linkage disequilibrium (r^2) relative to the index SNP shown as a purple diamond.

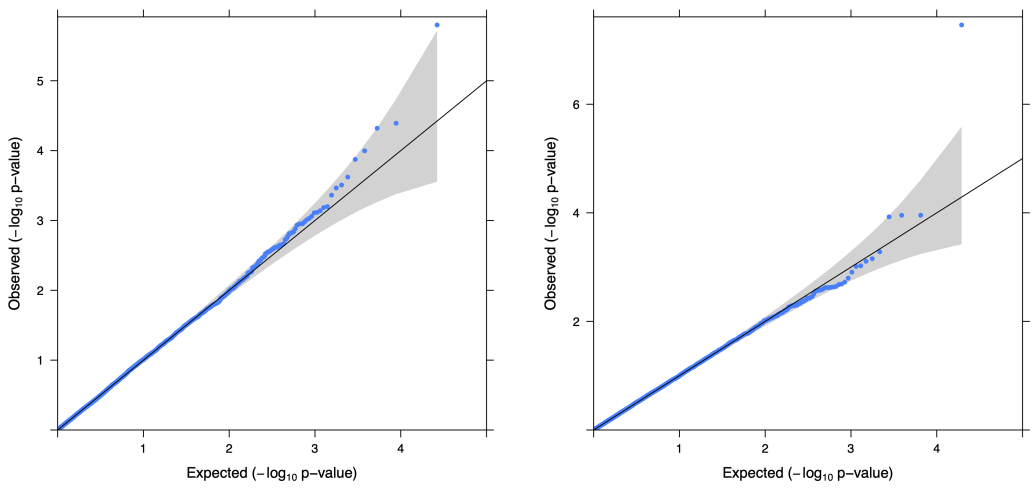

Figure S4. QQ-plot of p-values from a rare variant burden test of time to first peripheral neuropathy for the entire cohort N=4,900 (left) and for taxane treated patients N=2,535 (right). Each point represents a gene. λ_{gc}=1.009 (left) and λ_{gc}=1.017 (right). Gray region designates the 95% confidence interval around the null distribution of p-values.

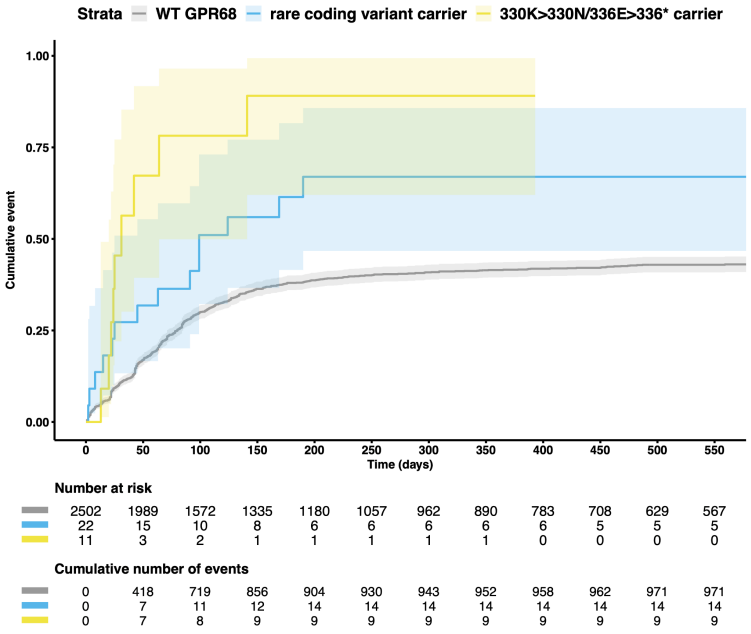

Figure S5. Cumulative incidence plot for PN events in taxane treated patients stratified by rare coding variant burden in *GPR68*.

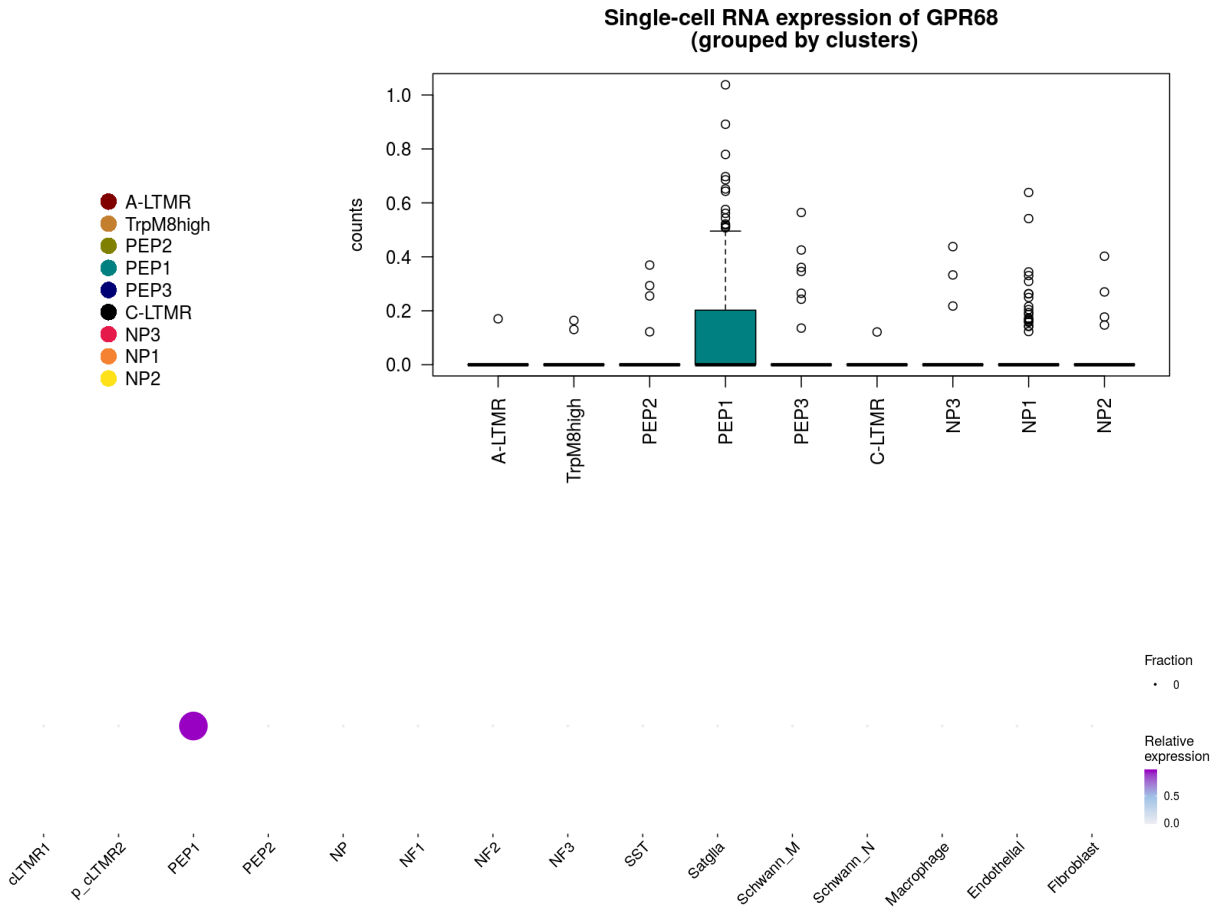

Figure S6. (top) Relative expression patterns *GPR68* in different DRG cell types in macaque (top from https://ernforsgroup.shinyapps.io/macaquedrg/) [2] expressed in normalized in mouse as illustrated by boxplots. (bottom from https://painseq.shinyapps.io/publish/#)[3] indicates a similar expression pattern to *GPR68* in human DRG. PEP1 neurons show relatively high expression of *GRP68* in both organisms illustrated by relative expression dot plot.

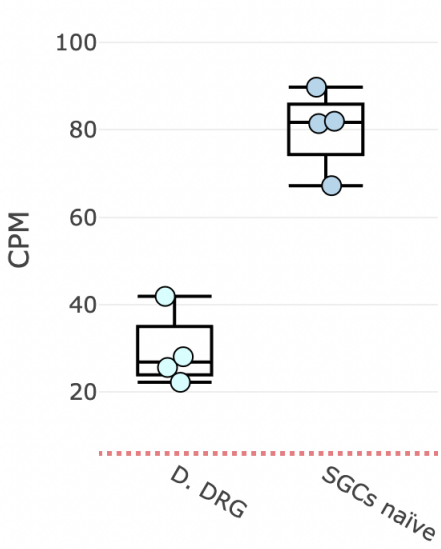

Figure S7. Normalized counts per million expression of *GRID2* in bulk RNA-seq from human DRG (D. DRG) as compared to sorted satellite glial cells (SCGCs) in mice (http://rna-seq-browser.herokuapp.com/)[4].

			Sex		Age			PN Event Grade					
Trial	**Arm**	**Chemo Naive**	**M**	**F**	**≤65**	**>65**	**Diab**	**None**	**1, n**	**%**	**>1,n**	**%**	**N (all)**
ido	Aido	N	25	48	48	25	9	69	2	3	2	3	73
ima050	APCB	Y	0	317	213	104	33	132	140	44	45	14	317
ima050	PCB	Y	0	328	220	108	33	145	130	40	53	16	328
imm151	AB	Y	140	67	130	77	39	194	10	5	3	1	207
imm151	SUN	Y	147	42	132	57	31	176	12	6	1	1	189
imp110	Atezo	Y	59	35	47	47	5	91	1	1	2	2	94
imp110	Chemo	Y	55	24	38	41	12	77	1	1	1	1	79
imp130	ACNabP	Y	110	89	114	85	34	143	35	18	21	11	199
imp130	CNabP	Y	55	46	49	52	18	77	10	10	14	14	101
imp131	ACNabP	Y	125	33	89	69	38	111	31	20	16	10	158
imp131	ACP	Y	131	33	80	84	32	91	42	26	31	19	164
imp131	CNabP	Y	125	32	86	71	34	121	18	11	18	11	157
imp132	ACPem	Y	80	43	79	44	20	114	5	4	4	3	123
imp132	CPem	Y	77	30	67	40	16	102	4	4	1	1	107
imp133	ACE	Y	52	25	51	26	19	71	3	4	3	4	77
imp133	CE	Y	40	32	43	29	13	69	3	4	0	0	72
imp150	ABCP	Y	117	87	122	82	26	109	61	30	34	17	204
imp150	ACP	Y	131	96	140	87	25	132	58	26	37	16	227
imp150	BCP	Y	105	75	111	69	29	107	41	23	32	18	180
impas130	ANabP	Y	1	155	118	38	14	112	16	10	28	18	156
impas130	NabP	Y	1	136	101	36	11	93	26	19	18	13	137
ims170	Acobi	Y	86	56	69	73	17	136	2	1	4	3	142
ims170	Apembro	Y	82	49	70	61	19	129	1	1	1	1	131
imv010	Atezo	N	148	37	88	97	26	183	1	1	1	1	185
imv010	Observ	N	150	37	86	101	31	181	4	2	2	1	187
imv130	AGC	Y	135	33	73	95	35	148	14	8	6	4	168
imv130	Atezo	Y	100	27	52	75	20	124	1	1	2	2	127
imv130	GC	Y	132	53	56	129	40	180	3	2	2	1	185
imv211	Atezo	N	170	49	98	121	29	206	8	4	5	2	219
imv211	Chemo	N*	167	40	80	127	35	160	26	13	21	10	207

Table S1. Frequency and grade of PN events in cancer patients of European ancestry across 14 randomized controlled trials testing immunotherapy and chemotherapy combinations. Chemo naive designates that patients in the trial arm did not receive any prior chemotherapy. N* designates patients that were taxane naive. Diab column indicates the number of patients in the trial arm that had a prior diabetes diagnosis before treatment for the given trial arm. Trial abbreviations are as follows: impXXX = IMpowerXXX, imm151=IMmotion151, imvXX = IMvigorXXX; ims170=IMspire170; imvXXX=IMvigorXXX; impas130=IMpassion130. Treatments in the trial arms are abbreviated as follows: A = atezolizumab, ido = ido inhibitor; Atezo = atezolizumab monotherapy; B = bevacizumab; cobi=cobimetinib; Pembro=pembrolizumab; C = carboplatin or cisplatin ; P = paclitaxel; NabP = nab-paclitaxel; Pem=Pemetrexed; G=Gemcitabine; Observ = designates observation after surgery; Chemo = physicians choice chemotherapy vinflunine, docetaxel, or paclitaxel in IMvigor211; and carboplatin or cisplatin plus pemetrexed or gemcitabine in IMpower110; E = etoposide; SUN = sunitinib. Red rows designate where both a taxane and platinum-based chemotherapy was used. Yellow rows designate use of only platinum-based chemotherapy. Blue rows designate use of only a taxane chemotherapy. Chemotherapy regimens are provided in Tables S2-S3.

Trial	Arm Abbrev.	Taxane Dosing
ima050	APCPB and PCB	Paclitaxel 175 mg/m^2 on Day 1 of each 21-day cycle
imp130	ACNabP, CNabP	Nab-paclitaxel at 100 mg/m^2 on Days 1, 8, and 15 of each 21-day cycle.
imp131	ACNabP, CNabP	Nab-paclitaxel 100 mg/m^2 on Day 1, 8, and 15 of each 21-day cycle
imp150	ABCP, ACP, BCP	Paclitaxel at 200 mg/m^2 on Day 1 of each 21-day cycle
impas130	ANabP, NabP	Nab-Paclitaxel at 100 mg/m^2 on Days 1, 8, and 15 of each 28-day cycle
imv211	Chemo	Docetaxel or paclitaxel 75 mg/m^2 on Day 1 of each 21-day cycle

Table S2 - Taxane Regimens

Trial	Arm Abbrev.	Platinum Chemotherapy Dosing
ima050	APCPB and PCB	˙Carboplatin at AUC of 6 mg/mL min on Day 1 of each 21-day cycle
imp110	Chemo	˙Carboplatin at AUC 6 when given in combination with pemetrexed or at a dose of AUC 5 when given in combination with gemcitabine, every 21 days. ˙Cisplatin at 75 mg/m^2 every 21 days.
imp130	ACNabP, CNabP	˙Carboplatin was administered at AUC 6 mg/mL/min on Day 1 of each 21-day cycle
imp131	ACNabP, ACP, CNabP	˙Carboplatin AUC 6 mg/mL/min on Day 1 of each 21-day cycle
imp132	ACPem, CPem	˙Carboplatin on Day 1 q3w for 4 or 6 cycles (Cycle length=21 days) in induction dosing period with doses calculated using Calvart formula. ˙Cisplatin at 75 mg/m^2 with cycle length=21 days
imp133	ACE, CE	˙Carboplatin intravenous infusion to achieve an initial target AUC of 5 mg/mL/min was administered on Day 1 of each 21-day cycle.
imp150	ABCP, ACP, BCP	˙Carboplatin was administered at AUC 6 mg/mL/min on Day 1 of each 21-day cycle
imv130		˙Carboplatin to AUC of 4.5 mg/mL min by IV infusion on Day 1 of each 21-day cycle. ˙Cisplatin will be administered at a dose of 70 mg/m^2 by IV infusion on Day 1 of each 21-day cycle.

Table S3 - Platinum Chemotherapy Regimens

N=4,900 all patients

Index Variant	Alleles	Effect AF	HR [95% CI]	p	Nearest Gene	Location
rs17020773	T/C	0.03	1.86[1.50-2.31]	$2.03 \cdot 10^{-8}$	*GRID2*	intronic
rs115575220	G/T	0.01	2.44[1.77-3.35]	$4.15 \cdot 10^{-8}$	*SCG2*	intergenic (126kb)
rs191482247	A/G	0.01	2.04[1.52-2.73]	$1.40 \cdot 10^{-6}$	*ZDHHC14*	intronic

N=2,535 taxane treated subcohort

Index Variant	Alleles	Effect AF	HR [95% CI]	p	Nearest Gene	Location
rs17020773	T/C	0.03	1.96[1.56-2.47]	$6.36 \cdot 10^{-9}$	*GRID2*	intronic
rs191482247	A/G	0.01	2.29[1.71-3.06]	$2.54 \cdot 10^{-8}$	*ZDHHC14*	intronic
rs115575220	G/T	0.01	2.43[1.72-3.43]	$4.5 \cdot 10^{-7}$	*SCG2*	intergenic (126kb)

Table S4. Low frequency variants that were associated with risk of PN at $p < 5 \cdot 10^{-8}$ across N=4,900 cancer patients or within the N=2,535 taxane treated cohort. AF = allele frequency. Alleles are designated as: (non-effect)/(affect allele). Hazard ratio (HR) is expressed in dosage of the effect allele.

rsid	Candidate Gene	p (all cohort)	p (taxane)
rs10486003	TAC1	0.82	0.55
rs10771973	FGD4	0.82	0.47
rs2228001	XPC	0.90	0.58
rs2302237	SCN4A	0.94	0.90
rs3114018	ABCG2	0.16	0.19
rs3125923	**GPR177**	**0.03**	**0.05**
rs3213619	ABCB1	0.90	0.75
rs3213619	ABCB1	0.90	0.75
rs3213619	ABCB1	0.90	0.75
rs3213619	ABCB1	0.90	0.75
rs4737264	XKR4	0.63	0.28
rs6438552	GSK3B	0.13	0.05
rs6746030	SCN9A	0.64	0.75
rs7001034	**FZD3**	**0.04**	**0.16**
rs7349683	EPHA5	0.58	0.71
rs74497159	S1PR1	0.87	0.49
rs875858	VAC14	0.89	0.59
rs9501929	TUBB2A	0.12	0.33
rs9937	RRM1	0.55	0.56

Table S5 - Replication of Variants Previously Associated with CIPN.

References

1. Bakken TE, Jorstad NL, Hu Q, Lake BB, Tian W, Kalmbach BE, et al. Comparative cellular analysis of motor cortex in human, marmoset and mouse. Nature. 2021;598:111–9.
2. Kupari J, Usoskin D, Parisien M, Lou D, Hu Y, Fatt M, et al. Single cell transcriptomics of primate sensory neurons identifies cell types associated with chronic pain. Nat Commun. 2021;12:1510.
3. Renthal W, Tochitsky I, Yang L, Cheng Y-C, Li E, Kawaguchi R, et al. Transcriptional Reprogramming of Distinct Peripheral Sensory Neuron Subtypes after Axonal Injury. Neuron. 2020;108:128-144.e9.
4. Liang Z, Hore Z, Harley P, Stanley FU, Michrowska A, Dahiya M, et al. A transcriptional toolbox for exploring peripheral neuroimmune interactions. Pain. 2020;161:2089–106.