

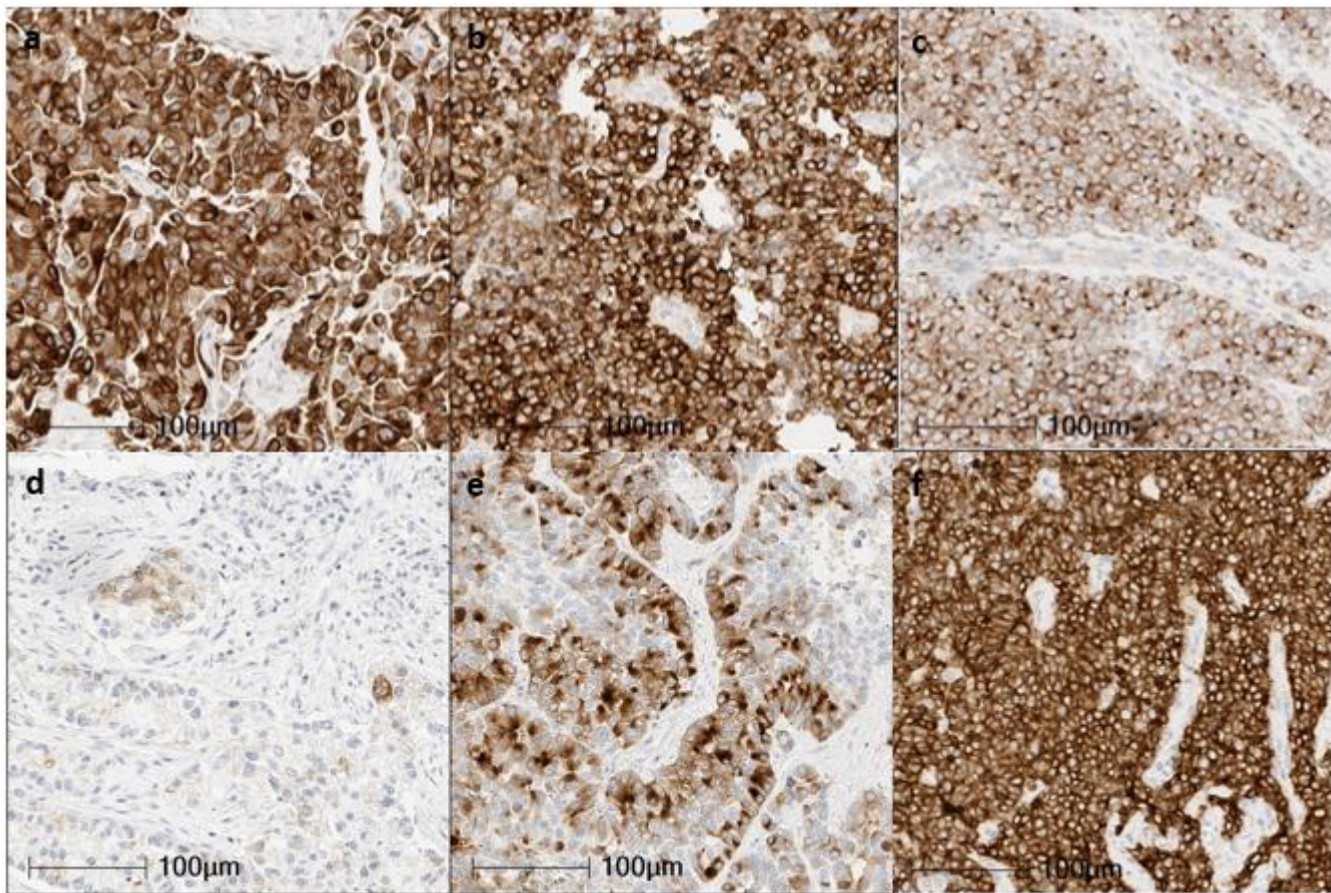
Supplementary Table 1.

Conditions	Status	Name of trial	Drug	Clinical trial
NEPC	ACTIVE, NOT RECRUITING	A Study of AMG 757 in Participants with Neuroendocrine Prostate Cancer (DeL Lpro-300)	Tarlatamab	NCT04702737
SCLC, LCNEC, NEPC, GEP-NEC	RECRUITING	A Study of PT217 in Patients with Advanced Refractory Cancers Expressing DLL3 (the SKYBRIDGE Study)	PT217	NCT05652686
SCLC, and other neoplasms	RECRUITING	A Study to Test Different Doses of BI 764532 in Patients with Small Cell Lung Cancer and Other Neuroendocrine Tumours That Are Positive for DLL3	BI 764532	NCT04429087
SCLC, and other neoplasms	RECRUITING	A Study to Test How Well Different Doses of BI 764532 in Combination with Ezabenlimab Are Tolerated by People with Small Cell Lung Cancer and Other Neuroendocrine Tumours That Are Positive for DLL3	BI 764532, Ezabenlimab	NCT05879978
Neuroendocrine neoplasms - NEC	RECRUITING	DAREON™-7: A Study to Test How Well Different Doses of BI 764532 in Addition to Chemotherapy Are Tolerated by People with Advanced Neuroendocrine Cancers	BI 764532, Carboplatin, Etoposide, Cisplatin	NCT06132113
SCLC, and neuroendocrine neoplasms - NEC	RECRUITING	DAREON™-5: A Study to Test Whether Different Doses of BI 764532 Help People with Small Cell Lung Cancer or Other Neuroendocrine Cancers	BI 764532	NCT05882058
Malignant melanoma, MTC, glioblastoma, LCNEC, NEPC, High grade GEP-NEC, other NEC, and other solid tumors	TERMINATED	Rovalpituzumab Tesirine in Delta-Like Protein 3-Expressing Advanced Solid Tumors	Rovalpituzumab tesirine	NCT02709889

EP-NEN, extrapulmonary neuroendocrine neoplasms; EP-NEC, extra pulmonary neuroendocrine carcinoma; SCLC, small cell lung carcinoma; LCNEC, large cell neuroendocrine carcinoma; GEP-NEC, gastroenteropancreatic neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; MTC, Medullary thyroid carcinoma; NEPC, neuroendocrine prostate cancer;

Clinical trials of DLL3 targeted therapy for patients with EP-NEN and other solid tumors.

Supplementary Figure 1.



DLL3 IHC expression patterns and subcellular location in neuroendocrine neoplasms. Diffuse cytoplasmic expression (a), diffuse membrane expression (b), dot-like expression (c). Patterns of staining of DLL3 on tumor tissue: focal (d), patchy (e), diffuse (f).

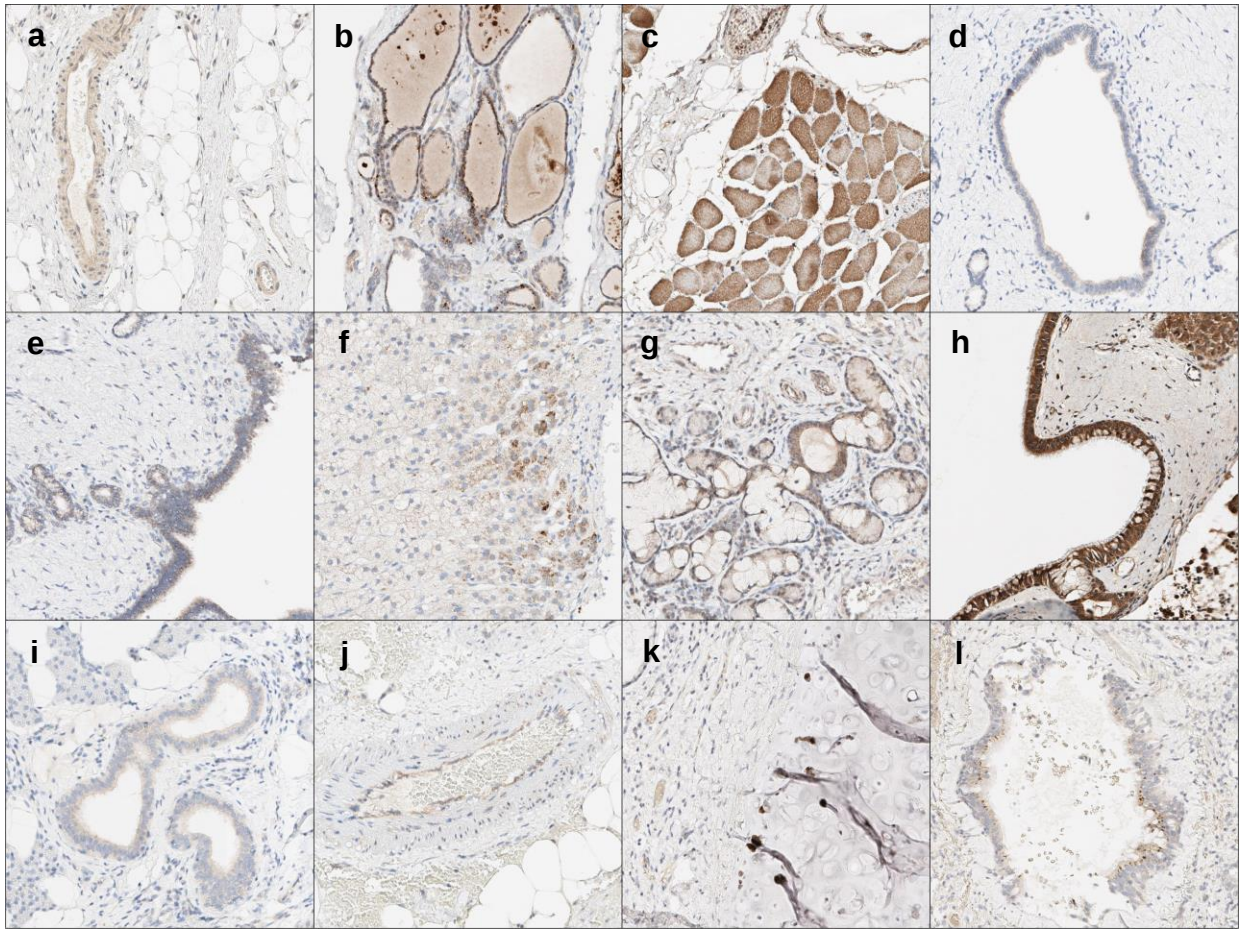
Supplementary table 2.

Tumor	Organ	Presence of adjacent normal tissue/Total samples	Samples with expression in normal tissue/Total samples	Type of cells with DLL3 expression
NEC	Uterine cervix	17/21	2/21	vascular smooth muscle cells
				skeletal muscle cells, adipocytes, glial cells, epithelial cells from respiratory mucosa, vascular smooth muscle cells, follicular cells from thyroid gland, ductal cells of salivary glands.
	H&N	15/19	14/19	
	Skin	16/33	2/33	ductal cells of adjacent salivary gland
	Prostate	6/16	0/16	
				follicular cells from thyroid gland, vascular smooth muscle cells, skeletal muscle cells
	Thyroid gland	42/74	16/74	
	Bladder	0/19	0/19	
NET	Lung	45/45	5/45	bronchiolar epithelial cells, chondrocytes
	Ileum	51/52	23/52	smooth muscle cells epithelial cells from bile ducts, vascular smooth muscle cells, adrenocortical cells from adjacent adrenal gland.
	Pancreas	118/135	20/135	
Sympathetic				epithelial cells from nasal glands, epithelial cells from respiratory mucosa, vascular smooth muscle cells, squamous epithelial cells, ductal cells from salivary glands, adipocytes, endothelial cells
	H&N, Adrenal medulla	60/90	40/90	
Endocrine	Adrenal gland cortex	0/34	0/34	

NEC, neuroendocrine carcinoma; H&N, head and neck; NET, neuroendocrine tumor

DLL3 expression in adjacent non-tumor tissue.

Supplementary Figure 2.



DLL3 IHC expression in tumor-adjacent non-neoplastic tissue. Vascular smooth muscle cells (a), follicular cells from thyroid gland (b), skeletal muscle cells (c), epithelial cells from bile duct (d, e), adrenocortical cells (f), epithelial cells from nasal glands (g), nasal ciliated epithelial cells (h), epithelial cells from ducts of salivary gland (i), endothelial cells (j), chondrocytes (k), bronchial epithelial cells (l).

Supplementary Table 3.

Tumor Type		Total	Positive (≥25%)		High positive (≥75%)	
		N	N	%	N	%
P-NEN						
NEC						
	SCLC	17	13	76%	7	41%
	LCNEC	20	13	65%	9	45%
	Combined histology	8	5	63%	4	50%
	Total	45	31	69%	20	44%
EP-NEN						
NEC						
	Skin	33	28	85%	22	67%
	Prostate	16	11	69%	9	56%
	Uterine cervix	21	14	67%	13	62%
	Bladder	19	12	63%	8	42%
	Head and Neck	19	7	37%	3	16%
	Thyroid	74	15	20%	10	14%
	Total	182	87	48%	65	36%
Epithelial-NET						
	Ileal	52	0	0%	0	0%
	Pancreas	135	5	4%	2	1%
	Total	187	5	3%	2	1%
Non-Epithelial NET						
	Paraganglioma	15	0	0%	0	0%
	Pheochromocytoma	3	0	0%	0	0%
	Extracranial pediatric NB	6	0	0%	0	0%
	Olfactory NB	66	6	9%	5	8%
	Total	90	6	7%	5	6%
Endocrine neoplasms						
	Adrenal	34	2	6%	1	3%
TOTAL		538	131	24%	93	17%

P-NEN, Pulmonary neuroendocrine neoplasm; EP-NEN, Extra pulmonary neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, Neuroendocrine tumor; SCLC, Small cell lung carcinoma; LCNEC, Large cell neuroendocrine carcinoma; NB, neuroblastoma

DLL3 expression categorized based in cutoffs of 25% and 75% expression of DLL3

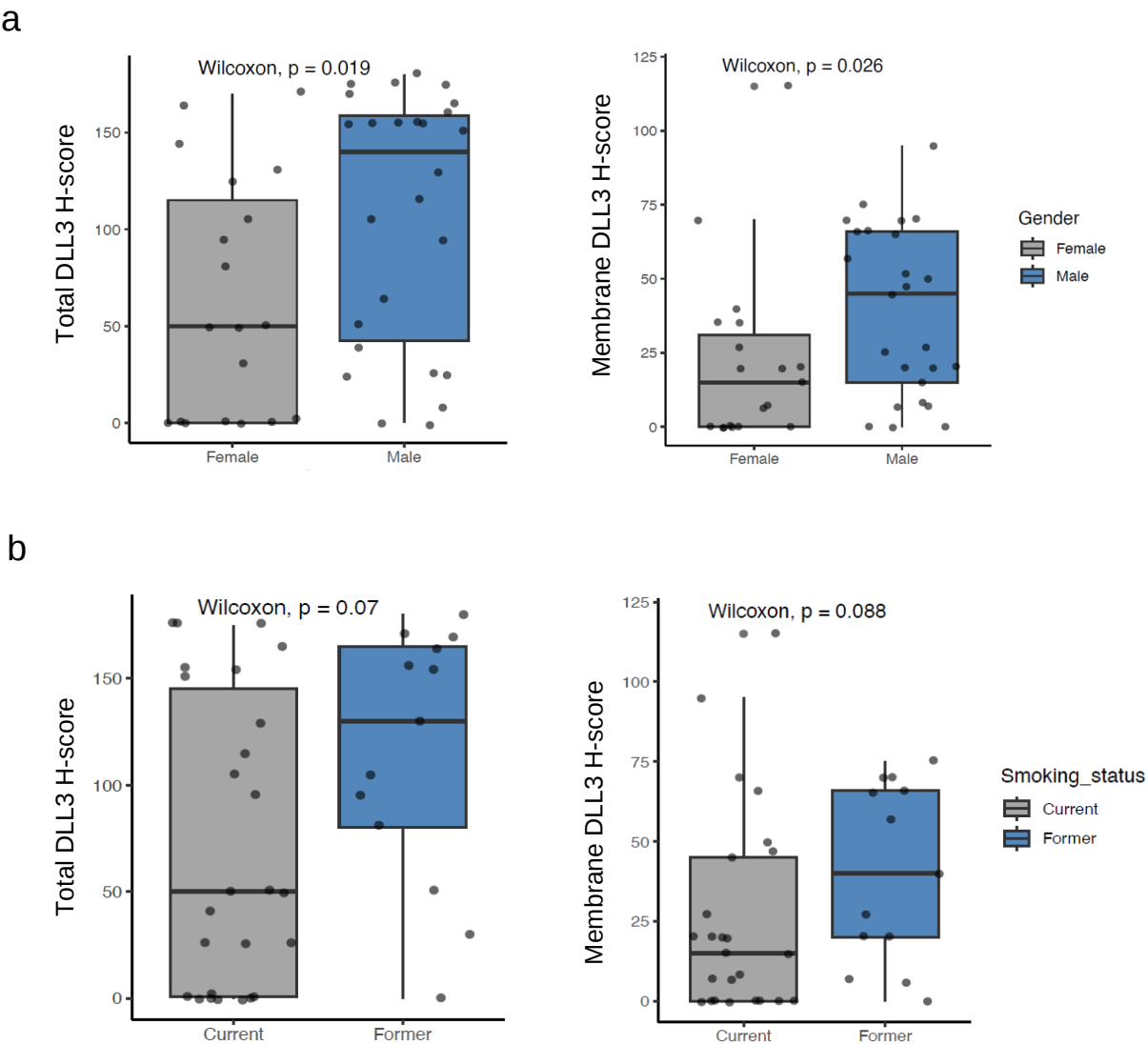
Supplementary Table 4.

Organ site	Sample ID	Combination pattern	DLL3 expression	Total H-score
Lung	SC-08	SCLC/LCNEC	-/-	0
	SC-24	SCLC/LCNEC	+/+	175
	LC-15	SCLC/LCNEC	+/+	170
	SC-21	SCLC/NSCLC	+/-	65
	SC-27	SCLC/NSCLC	-*/-	0
	SC-07	LCNEC/ADC	-/-	0
	LC-10	LCNEC/ADC	+/-	115
	SC-28	SCLC/SCC	+ /NA	155
Uterine cervix	SCNEC-12A5	SCNEC/LCNEC	-/-	0
	SCNEC-12F2	SCNEC/LCNEC	+/+	25
	SCNEC-03	SCNEC/ADC	+/-	6
	SCNEC-06	SCNEC/ADC	-/-	0
	SCNEC-11	SCNEC/ADC	+/-	135
	SCNEC-09	SCNEC/SCC	-/-	0
	SCNEC-02	SCNEC/SCC	+ /+**	140

LCNEC, Large cell neuroendocrine carcinoma; ADC, Adenocarcinoma; SCLC, Small cell lung carcinoma; NSCLC, non-small cell lung carcinoma; SCC, Squamous cell carcinoma; SCNEC, Small cell neuroendocrine carcinoma; NA, No applicable; * Focal expression in <1% of SCLC component; **Poorly differentiated SCC

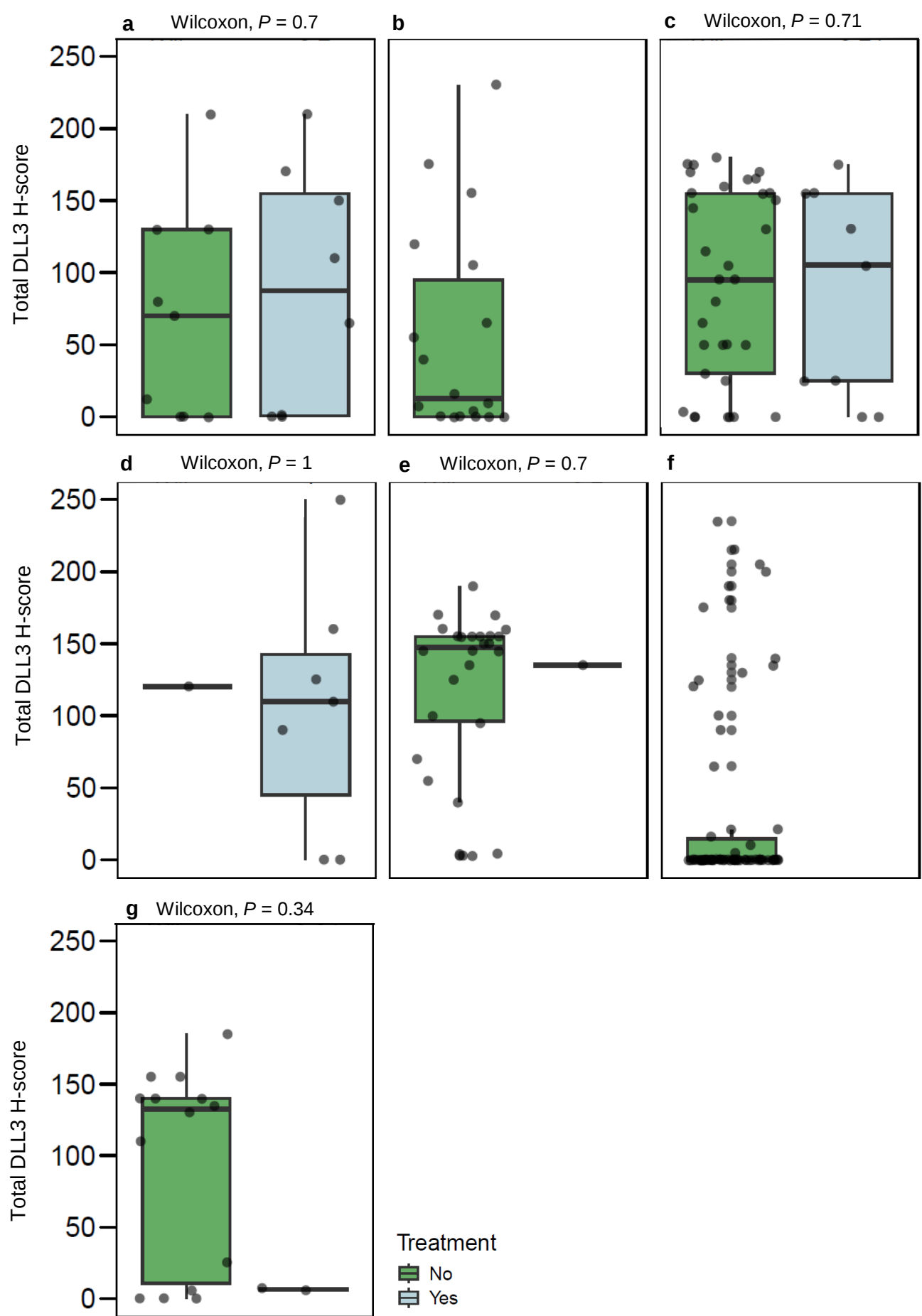
Comparison of DLL3 expression and Total H-score in tumors with combined histology

Supplementary Figure 3.



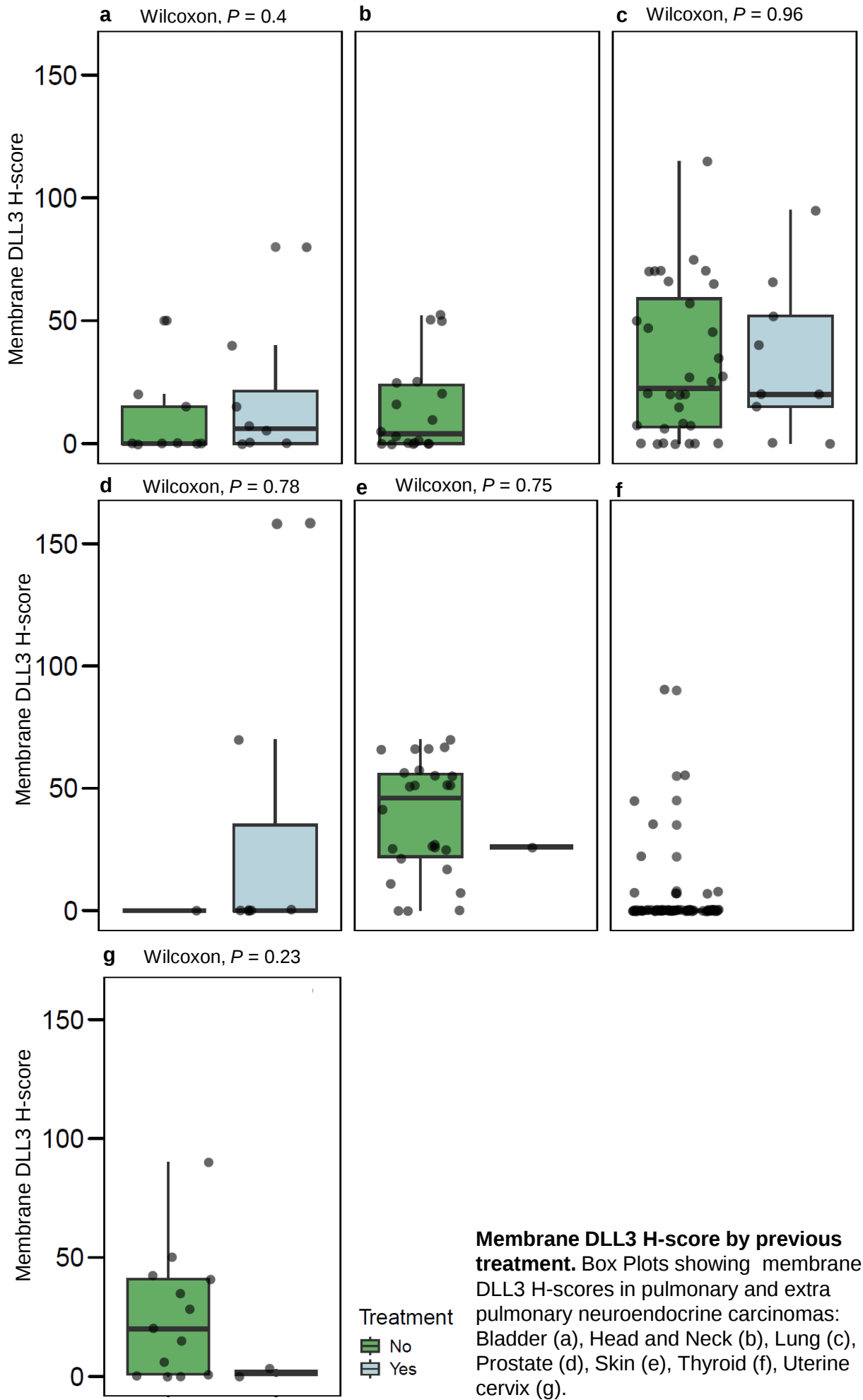
DLL3 expression in Pulmonary neuroendocrine carcinomas. Boxplots showing Total DLL3 H-score by sex (a) and smoking status (b) in pulmonary neuroendocrine carcinomas.

Supplementary Figure 4.

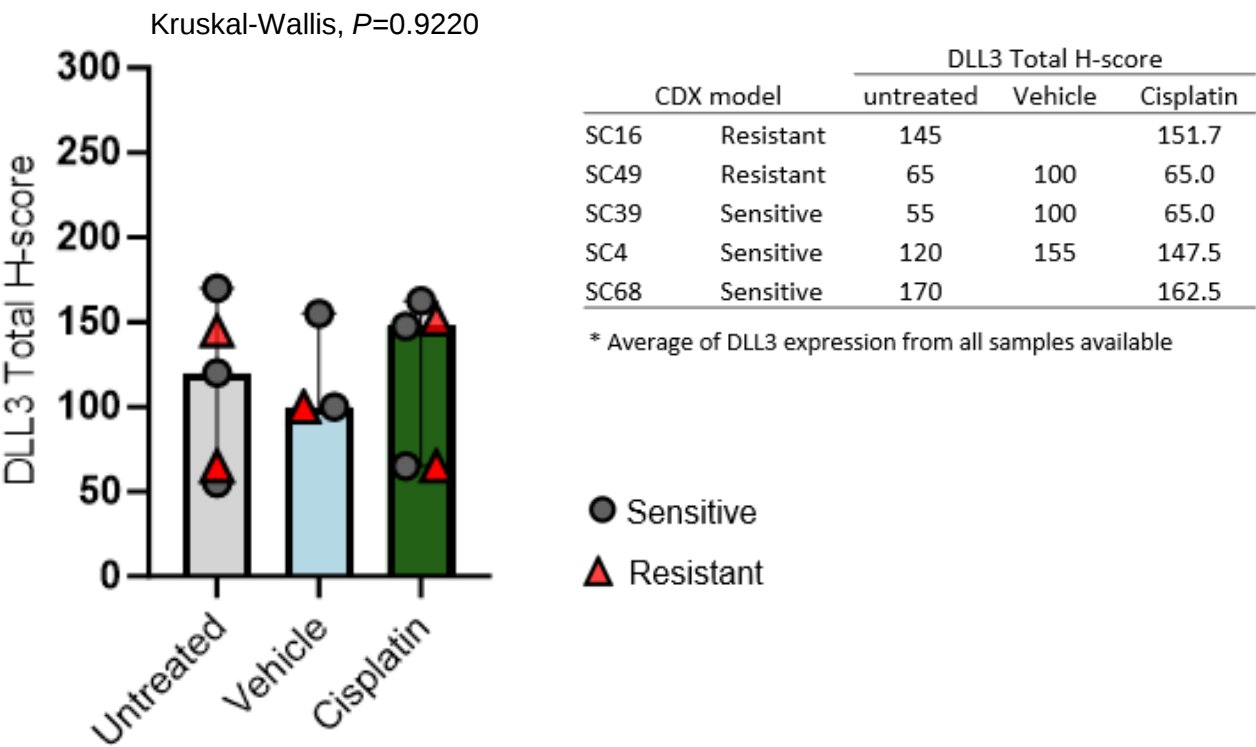


Total DLL3 H-score by previous treatment. Box plots showing total DLL3 H-score in pulmonary and extra pulmonary neuroendocrine carcinomas by previous treatment: Bladder (a), Head and Neck (b), Lung (c), Prostate (d), Skin (e), Thyroid (f), Uterine cervix (g).

Supplementary Figure 5.

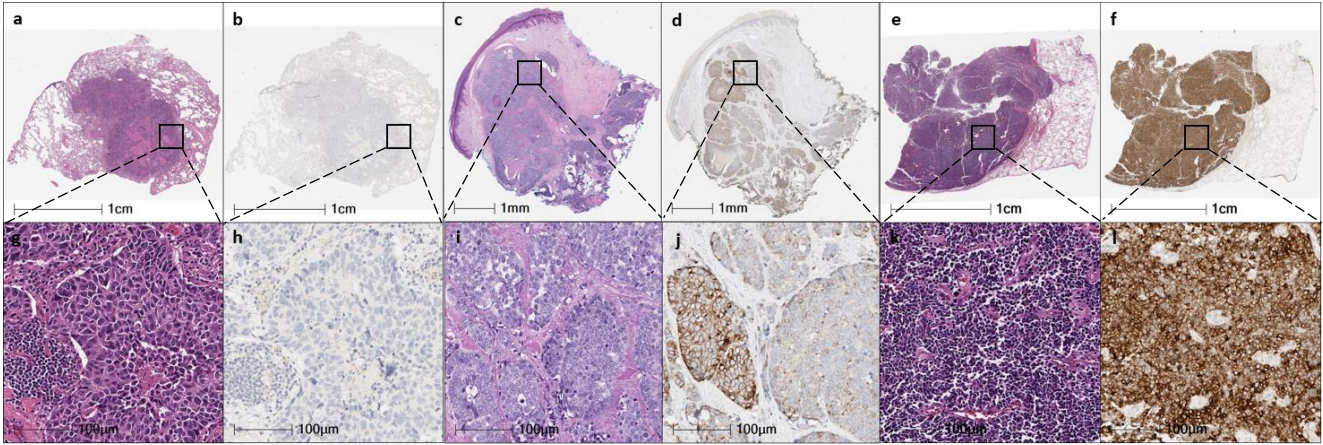


Supplementary Figure 6.



DLL3 Total H-score in Circulating tumor cell (CTC)-derived xenografts (CDXs) Models.
Boxplots showing DLL3 Total H-score in CDXs sensitive- and resistant-models, untreated, vehicle-treated and cisplatin-treated.

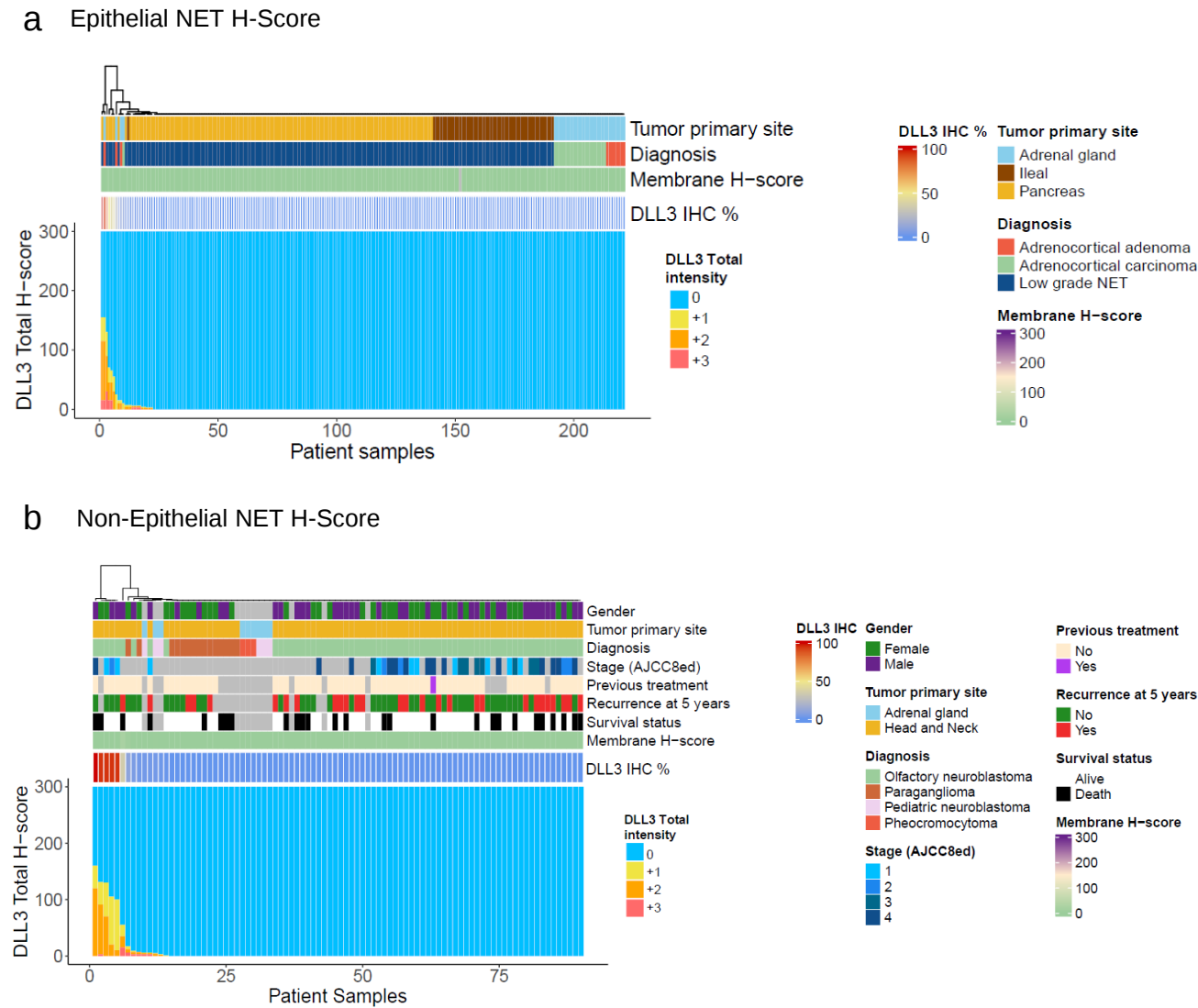
Supplementary Figure 7.



DLL3 IHC expression in Pulmonary and Extrapulmonary neuroendocrine neoplasms.

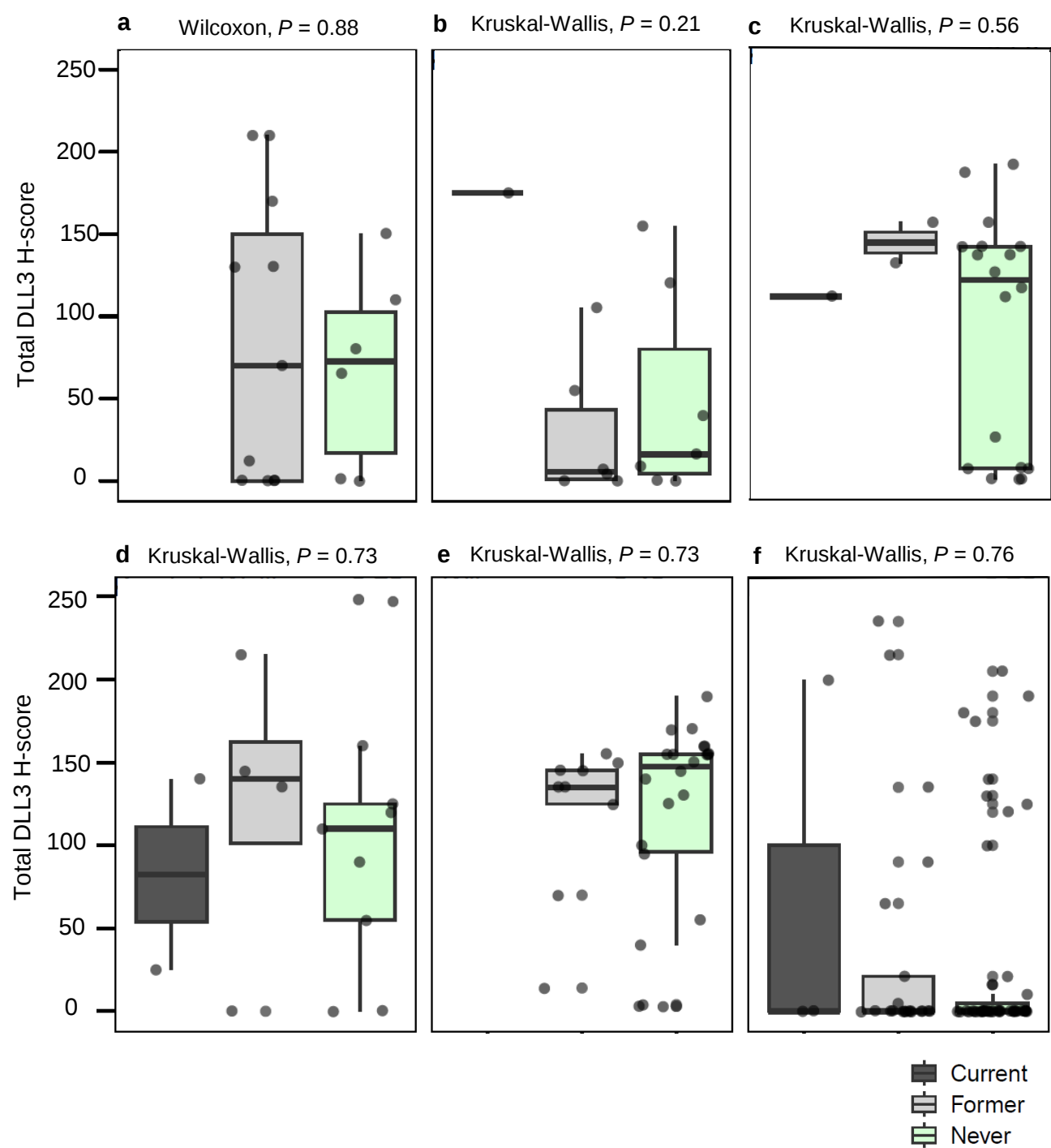
Upper part: Low magnification of tissue samples stained with H&E (**a**, **c**, and **e**) and same samples stained with DLL3 (**b**, **d**, and **f**). Large cell neuroendocrine carcinoma from lung (**a** and **b**), Merkel cell carcinoma (**c** and **d**) and small cell lung carcinoma (**e** and **f**). (**b**) no expression, (**d**) heterogeneous expression, and (**f**) diffuse positive expression (4X). Bottom part: at higher magnification detail of no expression in (**h**), focal expression in (**j**), and diffuse expression in (**l**) (40X).

Supplementary Figure 8.



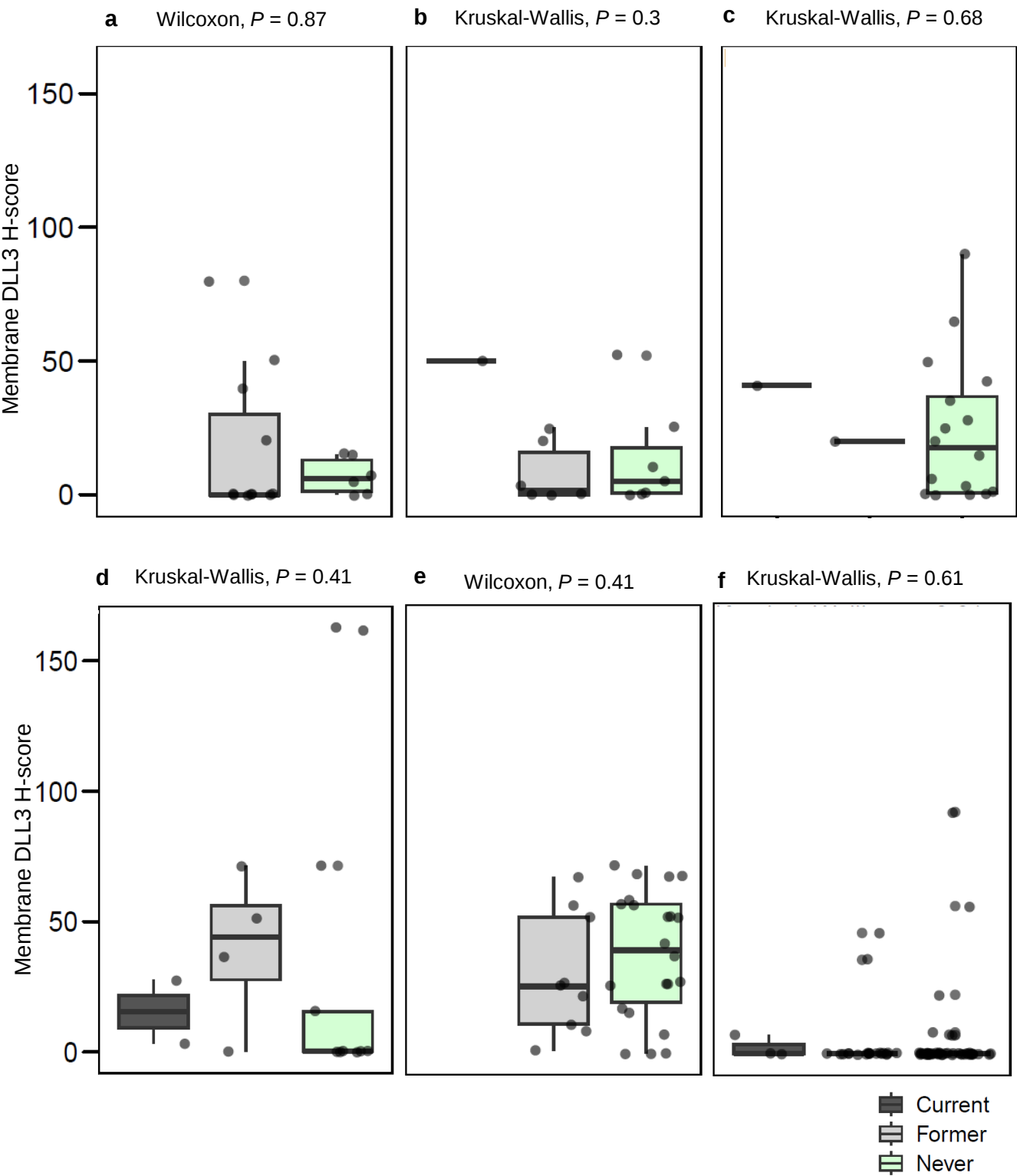
DLL3 in extrapulmonary neuroendocrine neoplasms. Plots showing levels of DLL3 expression in Epithelial neuroendocrine tumors (E-NET) **(a)** and non-epithelial neuroendocrine tumors (NE-NET) **(b)** illustrating the levels of DLL3 Total H-score in neuroendocrine carcinomas by intensity (0, 1+,2+,3+) per sample, DLL3 percentage, and membrane DLL3 H-score, along with clinicopathological information.

Supplementary Figure 9.



Total DLL3 H-score by smoking status in extra pulmonary neuroendocrine carcinomas: Boxplots showing Total DLL3 H-score by organ: Bladder (a), Head and Neck (b), Uterine cervix (c), Prostate (d), Skin (e), Thyroid (f).

Supplementary Figure 10.



Membrane DLL3 H-score by smoking status in extra pulmonary neuroendocrine carcinomas. Boxplots showing Total DLL3 H-score by organ: Bladder (a), Head and Neck (b), Uterine cervix (c), Prostate (d), Skin (e), Thyroid (f).