Overview of originally established diagnoses retrieved from digital summaries and patient chemotherapy treatment

An overview of all patients with metastatic disease treated with first line chemotherapy retrieved from the pathology and cancer registry is presented in table **S1.** Confirmed diagnoses from pathology reports included N=164 large cell neuroendocrine carcinoma (LCNEC), N= 48 neuroendocrine carcinomas (NEC), N=65 non-small cell lung carcinoma with neuroendocrine immunohistochemically differentiation (NSCLC NED) and 'other' compromising cases not differentiating between LCNEC and NSCLC NED (N=7). Patients with NEC were more frequently treated with SCLC-t chemotherapy (54%) compared to LCNEC (43%) and NSCLC NED (13%). NSCLC NED was generally treated with NSCLC-t chemotherapy (71%).

Table S1. overview of possible LCNEC diagnoses and treatment overview of chemotherapy

Chemotherapy Subtype	LCNEC						NEC						NSCLC NED						Other					
	≤2009		≥2010		Total		≤2009		≥2010		Total		≤2009		≥2010		Total		≤2009		≥2010		Total	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
NSCLC-t	45	59	27	31	72	44	13	48	3	14	16	33	35	83	18	55	53	71	2	50	2	67	4	57
SCLC-t	24	31	46	53	70	43	9	33	17	81	26	54	4	10	6	18	10	13	1	25	0	0	1	14
NSCLC-pt	8	10	14	16	22	13	5	19	1	5	6	13	3	7	9	27	12	16	1	25	1	33	2	29

Abbreviations: LCNEC, large cell neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; NSCLC NED, non-small cell lung carcinoma with neuroendocrine immunohistochemically staining; SCLC, small cell lung carcinoma; NSCLC-t, clustered platinum gemcitabine, paclitaxel, docetaxel or vinorelbine chemotherapy; NSCLC-pt, NSCLC platinum-pemetrexed chemotherapy; SCLC-t, SCLC platinum-etoposide chemotherapy.

Additional methods for panel-consensus pathology review

Collectively the reviewers systematically scored all cases (RvS, ET, MdB). WHO 2015 criteria were evaluated for each case including presence of neuroendocrine morphology , estimated mitotic activity in non-crushed fields (≤10, 11-30 or >30 /10 high power field (HPF)), and presence of necrosis (none, 'dot-like' [=as occasionally seen in atypical carcinoids] or abundant [= more extensive than 'dot-like']). CD56 was scored as positive when membrane staining was observed. For chromogranin-A and synaptophysin focal small cytoplasmic dots in an occasional tumor cell observed at 40x microscope objective were sufficient for staining (+). Diffuse complete staining observed at overview (4x or 2.5x objective) was scored as strong positive (+++), and in between staining as (++) for all neuroendocrine markers. Finally, when available, p63/p40/TTF1 and cytokeratin staining were evaluated for positivity.

In small tissue samples ($<2mm^2$), evaluation of mitoses was performed on the maximal number of assessable high power fields. Counting mitoses was not possible in some cases (Thunnissen et al. JTO 2016, DOI 10.1016/j.jtho.2016.12.004). When available, the MIB1 (Ki-67) staining was scored (<25%, >25%). Either >10 mitosis/10 HPF, abundant tumor necrosis or a Ki-67 staining of more than 25% of tumor cells was sufficient to score for high-grade tumor disease (Rindi et al. 2014 ERC, DOI 10.1530/ERC-13-0246).

All diagnoses established by panel consensus as LCNEC required staining for at least one neuroendocrine marker and were analyzed for OS and PFS **(Figure 2-4, table S2)**. Occasionally LCNEC was diagnosed despite the absence of neuroendocrine morphology (N=19) or evidence of high-grade disease (N=1) as this could not be observed; mainly because of a limited availability of vital tumor tissue (**table S2**). Therefore, we additionally analyzed OS and PFS in panel-consensus classified LCNEC for which all required World Health Organization (WHO) 2015 criteria were evaluable (**Figure S4-6, table S2**).

Table S2. Overview of panel consensus diagnosis, scoring of WHO criteria and original diagnosis.		
Panel-Consensus diagnosis	WHO 2015 criteria	Original diagnosis
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	DD LCNEC vs NSCLC NED
LCNEC	Yes	NEC
LCNEC	Yes	NEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC

LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	NSCLC NED
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	NEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
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LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	NEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC

LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NEC
LCNEC	Yes	LCNEC
LCNEC	Yes	NSCLC NED
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	Yes	LCNEC
LCNEC	No	LCNEC
LCNEC	No	LCNEC
LCNEC	No	NSCLC NED
LCNEC	No	LCNEC
LCNEC	No	LCNEC
LCNEC	No	DD LCNEC vs NSCLC NED
LCNEC	No	LCNEC
LCNEC	No	LCNEC
LCNEC	No	NSCLC NED
LCNEC	No	LCNEC
LCNEC	No	NSCLC NED
LCNEC	No	LCNEC
LCNEC	No	LCNEC
LCNEC	No	NEC
LCNEC	No	NSCLC NED
LCNEC	No	LCNEC
LCNEC	No	LCNEC
LCNEC	No	LCNEC
LCNEC	No	LCNEC
LCNEC	No	LCNEC

Abbreviations: LCNEC, large cell neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; NSCLC NED, non-small cell lung carcinoma with neuroendocrine immunohistochemically staining;DD differential diagnosis.