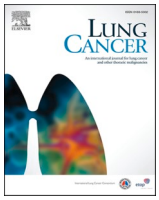
Lung Cancer 181 (2023) 107232

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan



Review

Systemic treatment for neuroendocrine non-small cell lung carcinoma: A cases series and a systematic review of the literature

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ARTICLE INFO

Keywords:
Carcinoid
Large cell neuroendocrine
Somatostatin
Everolimus
Drug therapy

ABSTRACT

Introduction: Neuroendocrine lung cancer constitutes a continuum from carcinoid tumours (CT) to large cell neuroendocrine (LCNEC) and small-cell carcinomas (SCLC). Except for SCLC, there is no consensual agreement on systemic therapy. The aim of this study is to review our clinical experience among patients with CT and LCNEC in the light of a systematic review of the literature.
Methods: A retrospective study of all patients with CT and LCNEC receiving a systemic therapy at Institut Jules Bordet and Erasme Hospital between 01/01/2000–31/12/2020. A systematic review of the literature was performed in Ovid Medline.
Results: 53 patients (21 CT and 32 LCNEC) were included. Despite limited response rates, patients with CT receiving a "carcinoid-like" 1st-line regimen (somatostatin analogues (SSA), everolimus, peptide receptor radionuclide therapy (PRRT)) had a numerically longer survival compared to those receiving other type of regimens (median 51.4 vs 18.6 months, respectively; $p = 0.17$). We observed a similar survival between 1st line "SCLC-like" vs "non-small cell lung cancer (NSCLC)-like" schemes in LCNEC (median 11.2 vs 12.6 months, respectively; $p = 0.46$).
The systematic review identified 23 studies (12 prospective, 15 and 8 for CT and LCNEC respectively). For CT, everolimus and SSA led to prolonged disease control with an acceptable toxicity profile, while higher response rates but lower tolerance were associated with PRRT and chemotherapy regimens including oxaliplatine and dacarbazine. For LCNEC, no difference emerged when comparing "SCLC-like" and "NSCLC-like" regimens considering response rate, progression-free or overall survival.
Conclusions: SSA, everolimus and PRRT present a good therapeutic index for CT, while the role of chemotherapy remains limited to aggressive and rapidly evolving CT. The best type of chemotherapy regimen remains an open question in LCNEC.

1. Introduction

The histological classification of the World Health Organisation (WHO) for neuroendocrine lung tumors was updated in 2021 [1]. These tumours have been separated since 2015 into four different entities including typical carcinoid tumours (CT), atypical CT, large cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC). CT and LCNEC are a relatively uncommon subtype of non-small cell lung cancer (NSCLC), 1–2% and 3%, respectively [2,3]. The histological characterisation of CT and LCNEC remains complex on small biopsy samples, explaining the high reclassification rate in clinical trials [4].

Lung CT have local aggressiveness and a low metastatic potential, differing from LCNEC, with usually a long stability period and survival rates at 5 and 10 years of 60% and 25% [5]. Systemic therapeutic options for CT are somewhat different, including somatostatin analogs (SSA), Peptide Receptor Radionuclide Therapy (PRRT) and targeted therapies (everolimus) while the role of chemotherapy remains debatable. On the opposite, chemotherapy represents the cornerstone for locally advanced and metastatic LCNEC, the debate focusing on the role

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https://doi.org/10.1016/j.lungcan.2023.107232
Received 21 January 2023; Received in revised form 25 April 2023; Accepted 1 May 2023
Available online 10 May 2023

of "SCLC-like" versus "NSCLC-like" regimens.

The aim of this retrospective study is to evaluate the efficacy and toxicity of systemic therapy for the treatment of CT and LCNEC at Institut Jules Bordet and Erasme Hospital, in the light of a systematic review of the literature.

2. Material and methods

2.1. Retrospective study

All patients with CT or LCNEC treated with any type of systemic therapy between 01/01/2000 and 31/12/2020 at Institut Jules Bordet and Erasme Hospital (Brussels, Belgium) were retrospectively reviewed. The study was approved by the Ethical Committees of both institutions (P2021/362 and CE3413). Search for potentially eligible patients was done either through histological diagnostic files at the Erasme pathological department or through the computed charts at Institut Jules Bordet using keywords with the concepts "carcinoid" and "neuroendocrine tumour".

Patients with CT or LCNEC, older than 18 years, with stage IV or recurrent disease, and needing a systemic treatment were included. Patients presenting with SCLC, mixed histology or those only locally treated by surgery or radiotherapy were excluded.

The primary objective was objective response rate (ORR) to 1st-line systemic therapy, according to RECIST 1.1. Secondary objectives were ORR to subsequent therapeutic lines, overall survival (defined as time from date of first systemic treatment until death or last date known to be alive) and toxicity (according to CTCAE 5.0). Disease control rate included any response and stable disease.

The following clinical data were extracted from patients' charts: age, gender, smoking status, comorbidities (chronic renal disease, cardiomyopathy, diabetes, and chronic obstructive pulmonary disease), performance status (PS; according to ECOG scale). When PS was not directly reported, patients considered to be in good general condition were classified as PS 0–1, PS 2 if poorer condition but able to receive a systemic therapy and otherwise PS 3. Tumours' and treatments' characteristics were: histology, TNM classification and stage (8th version) at initial diagnosis, presence of a paraneoplastic functional syndrome (carcinoid or Cushing syndrome), line and type of treatment, toxicity, response, date of death or last date known to be alive.

2.2. Statistical analyses

We used STATISTICA version 13.0.5.17 to perform all statistical analyses. Continuous data were expressed as means and/or medians, categorical data in percentages. Proportions were compared with Fischer exact test. Survival data were assessed by the Kaplan-Meier method and compared by the log-rank test. All significant values were fixed at $p < 0.05$ (bilateral).

2.3. Systematic review

A first literature search was conducted in August 2021 using the Ovid Medline system. An update of the literature was performed in August 2022. Phase II-IV clinical trials and other prospective studies (excluding phase I) were eligible as were retrospective studies including at least 30 patients with NE tumors of the lung (CT, LCNEC) treated with the same systemic therapy regimen. Primary outcome was ORR and secondary outcomes were PFS and OS. Studies evaluating the efficacy of systemic therapy had to provide ORR in the neoadjuvant setting; ORR, PFS and/or OS in the advanced/metastatic setting. If systemic therapy was included in a multimodality approach, ORR to the systemic regimen had to be assessable. This research was performed by a scientific librarian experienced in searching for medical and scientific publications (VD), and by two physicians (TB, MB) expert in the treatment of thoracic neoplasms and trained in evidence-based medicine. The ''PICO'' (population, intervention, comparator, outcome) model for clinical questions was used to identify the concepts included in the questions [6]. The corresponding search criteria of "P" and "I" were translated into MeSH terms, and free-text keywords that were searched for in titles, abstracts, and names of substance (Annex A). Citations were exported from Medline into the reference manager software EndNote to allow the removal of duplicates. All articles were sent to at least two members of the group. They were first selected for their eligibility based on the abstract content and the language, as only publications accessible to the authors (English, French, Dutch, German, Spanish, Italian, and Portuguese) were deemed eligible. The final selection was made after reading the full publication. Selection was independently done by at least two members of the group and discrepancies were consensually resolved. This search was supplemented by screening the references of the selected articles and other literature known by the experts.

3. Results

3.1. Retrospective study

A total of 846 charts were reviewed. According to eligibility criteria, 53 patients (21 with CT and 32 with LCNEC) were eligible (Annex B) and their characteristics are presented in Table 1. In the LCNEC group, no oncogenic driver alteration was found when molecular analysis was done (N = 19). Types of 1st-line therapy are described in Tables 2 and 3.

3.2. Response

Responses to 1st-line systemic therapy are described in Table 2. Four patients with LCNEC were not assessable for response to chemotherapy as they received concomitant radio-chemotherapy with either platinum-etoposide (n = 2, one partial response and one stable disease) or platinum-vinorelbine (n = 2, one complete and one partial response). Median platinum-free survival for stage III patients was 4.5 months (2–18 months). Subsequent therapeutic lines and associated responses

Table 1
Main clinical characteristics of patients with carcinoid tumours or large cell neuroendocrine carcinomas treated at Institut Jules Bordet and Erasme Hospital.

Characteristics	Carcinoid tumours	LCNEC
Number	21	32
Sex (M/F)	11/10	18/14
Age (years (median)/range)	61 (20–75)	61 (38–76)
(Ex-)Smoker (yes)	9	30
Performance status		
0-1	20	31
2	1	1
Number of comorbidities		
0	13	19
≥ 1	8	13
Presence of		
Carcinoid syndrome	4	1
Cushing syndrome	1	0
Histology		
Typical CT	9	0
Atypical CT	6	0
CT NOS	6	0
LCNEC	0	32
Stage at diagnosis (8th TNM)		
I	3	1
II	7	2
III	1	12
IV	10	17
Metastatic sites at diagnosis	N = 10	N = 17
M1a	1	2
M1b	0	3
M1c	9	12
Brain metastases	0	11

LCNEC: large cell neuroendocrine carcinoma; CT: carcinoid tumour; NOS: not otherwise specified.

Table 2
Type of 1st line therapy and responses in carcinoid tumours and large cell neuroendocrine carcinomas.

Therapy	N	CR/PR	SD	PD	ORR/DCR
Carcinoid tumours					
SSA	11	1	7	3	
Everolimus	1	0	1	0	
PRRT	1	0	1	0	
"Carcinoid-like" regimen	**13**	**1**	**9**	**3**	**7.7%/76.9%**
Platinum-etoposide	7	2	1	4	
"SCLC-like" regimen					**28.6%/42.9%**
Platinum-vinorelbine	1	0	1	0	0%/100%
Large cell neuroendocrine carcinomas					
Platinum-etoposide	8	3	1	4	
Platinum-etoposide-ifosfamide	1	0	0	1	
"SCLC-like" regimen	**9**	**3**	**1**	**5**	**33.3%/44.4%**
Platinum-vinorelbine	14	9	1	4	
Platinum-gemcitabine	1	0	0	1	
Platinum-pemetrexed	1	0	0	1	
MIP	2*	0	0	1	
Platinum-pemetrexed-pembrolizumab	1	1	0	0	
	19	**10**	**1**	**7**	**52.6%/57.9%**
"NSCLC-like" regimen					

CR: complete response, PR: partial response; SD: stable disease; PD: progressive disease; SSA: somatostatin analogues (lanreotide or octreotide); PRRT: Peptide Receptor Radionuclide Therapy; MIP: mitomycin-ifosfamide-cisplatinum; ORR: objective response rate; DCR: disease control rate.
* one patient could not be assessed for response.

Table 3
Type of salvage therapy and responses in carcinoid and large cell neuroendocrine tumours.

Therapy	N	CR/PR	SD	PD	ORR/DCR
Carcinoid tumours					
SSA	6	1	3	2	
Everolimus	6*	0	3	2	
PRRT		6	3	0	
	10*				
Temozolomide or CAPTEM		0	2	2	
	4				
"Carcinoid-like" regimen	**26**	**7**	**11**	**6**	**26.9%/69.2%**
Platinum-etoposide	**2**	**0**	**1**	**1**	**0%/50%**
Platinum-vinorelbine	1	0	1	0	0%/100%
Sunitinib	2	1	1	0	50%/100%
Large cell neuroendocrine carcinomas					
Platinum-etoposide	6*	1	2	2	
CAV		1	0	1	
	2				
"SCLC-like" regimen	**8**	**2**	**2**	**3**	**25%/50%**
Platinum-vinorelbine	2	1	1	0	
Pemetrexed	5	1	0	4	
Docetaxel	5	1	1	3	
Ifosfamide-gemcitabine	2	1	0	1	
Immunotherapy[$]	3	1	0	2	
"NSCLC-like" regimen	**17**	**5**	**2**	**10**	**29.4%/41.2%**
Erlotinib	2*	0	0	1	
PRRT		1	0	0	
	1				

CR: complete response, PR: partial response; SD: stable disease; PD: progressive disease; SSA: somatostatin analogues; PRRT: Peptide Receptor Radionuclide Therapy; CAV: Doxorubicin-cyclophosphamide-vincristine; ORR: objective response rate; DCR: disease control rate; CAPTEM: capecitabine-temozolomide; $: 1 atezolizumab, 1 tremelimumab, 1 pembrolizumab.
* one patient in each group could not be assessed for response.

are described in Table 3; no formal statistical comparison was done due to heterogeneity and potential biases, as some patients have received twice the same treatment. LCNEC patients received a median of 1 systemic treatment line (1–4) and CT patients 2 (1–7). In CT, no statistical difference was observed in terms of ORR or disease control rate (DCR) between "carcinoid-like" or "SCLC-like" 1st-line regimens ($p = 0.27$ and $p = 0.17$, respectively). All lines confounded, "carcinoid-like" regimens provided an ORR and a DCR of 22.9% and 74.3%, respectively.

In LCNEC, a trend to higher ORR and DCR favouring 1st line "NSCLC-like" regimens compared to "SCLC-like" schemes was noted, without reaching statistical significance ($p = 0.42$ and $p = 0.45$, respectively).

3.3. Survival

Median overall survival (OS) of patients with CT was 48 months (4.5–124.5 months) from 1st-line systemic therapy. OS of patients treated in 1st-line with a "carcinoid-like" regimens was 51.4 months versus 18.6 months for the others ($p = 0.17$). OS for patients receiving PRRT, whatever the line, was 48.3 months versus 34.5 months for the others ($p = 0.31$). Patients without any comorbidity had an OS of 50.4 months versus 39.9 months for those presenting with at least one co-morbidity ($p = 0.048$). Survival was not influenced by gender ($p = 0.89$) or age ($p = 0.61$).

OS of patients with LCNEC was 11.7 months (2.5–225.1 months) from 1st-line systemic therapy. The type of 1st-line regimen did not impact on survival, with OS of 11.2 months for "SCLC-like" and 12.6 months for "NSCLC-like" regimens ($p = 0.46$). Patients receiving at least a "SCLC-like" regimen during the course of the disease had a similar OS to those who did not ($p = 0.89$). Survival was not impacted by gender ($p = 0.1$), comorbidities ($p = 0.5$) or age ($p = 0.08$). Median follow up of all patients alive at the date of cut-off was 80 months, 64.9 months for patients with LCNEC and 77.2 months for patients with CT.

3.4. Toxicity

Some important toxicities were documented among patients with CT. Among 17 SSA therapies, we observed one grade 3 renal failure and one grade 2 digestive toxicity. Seven everolimus treatments led to two (one grade 3 and one grade 4) nephrotic syndromes and one grade 2 pneumopathy. Only one grade 2 haematological and three grade 2 digestive toxicities were documented among 11 PRRT. One grade 3 haematological toxicity was related to 9 platinum-etoposide therapies. No grade 5 toxicity was documented.

In LCNEC, we separated the toxicities between "SCLC-like" and "NSCLC-like" regimens. Among 19 "SCLC-like", we observed five grade 3 haematological toxicities and one grade 4 febrile neutropenia, three renal failure (two grade 2 and one grade 3), two peripheral neuropathies (grade 2 and 3), one grade 2 hypoacousia. Among the 38 "NSCLC-like", we documented eight grade 2–4 haematological, two grade 2 neuropathy, three grade 2–3 digestive, one grade 4 febrile neutropenia, one grade 2 vasculitis, and one grade 2 immune thyroiditis.

3.5. Systematic review

From 2507 abstracts retrieved with the search equation, 21 articles met the inclusion criteria (Annex C) including one systematic review that was not selected for data presentation. 3 articles that met our inclusion criteria were retrieved afterwards. Among the 23 clinical studies, 12 were prospective and 15 multicentric. Eight publications evaluated patients with LCNEC and the others, patients with carcinoid ($n = 14$) or low grade neuroendocrine tumours ($n = 1$). A summary of the different studies is presented in Tables 4 and 5.

The comparison of therapeutic regimens is difficult because of the highly heterogeneous case-mix, the retrospective nature of many studies, the existence of multiple treatment regimens, and the absence of a central pathological confirmation. Overall, given the heterogeneity of the studies, a quantitative analysis with data aggregation would not be clinically relevant.

Among patients with carcinoid tumours (Table 4), OS and

Table 4
Summary of clinical studies related to carcinoid tumours included in the systematic review.

Reference	Design	N patients	Type of carcinoid (T/A/ND)	Central pathology review	Treatment	Line	ORR	Median OS	Median PFS
Bajetta 2002 [24]	P/U	7	ND	Yes	FDE	1	14.3%	–	–
Bajetta 2014 [25]	P/M	11	ND	No	Everolimus + LAR octreotide	1	9.1%	–	–
Bongiovanni 2017 [26]	R/M	30	T (7)/A (23)	Yes	Somatostatin	1	3.3%	74 m (CI 39-NR) 53% at 5 years	11.1 m (CI 7–15)
Brabander 2017 [27]	P/U	23	NET	ND	Lu-Octreotate	Any	30.4%	52 m (CI 49–55)	20 *m*
Fazio 2013 [28]	P/M	44	ND	No	Everolimus + LAR octréotide LAR octréotide	Any	–	–	13.63 m (CI 5.55–14.29) 5.59 m (CI 2.79–27.76) HR 0.72 (CI 0.31–1.68) p 0.228
Fazio 2018 [29]	P/M	90	ND	No	Everolimus Placebo	Any	1.6%	–	9.2 m (CI 6.8–10.9) 3.6 m (CI 1.9–5.1) HR 0.50 (CI 0.28–0.88)
Ferolla 2017 [30]	P/M	124* 41 42 41	T (39)/A (85)	No	 LAR pasireotide Everolimus Everolimus + pasireotide	Any	 2.4 % 2.4 % 2.4%	–	 8.5 m (CI 5.7-NR) 12.5 m (CI 5.6-NR) 11.8 m (CI 11.1-NR)
Robelin 2019 [5]	R/M	16,224,845,827,296,813,122	T (46)/A (97)/ND (19)	No	 Platinum-etoposide Oxaliplatine Temozolomide + Dacarbazine + Streptozotocine + Everolimus Somatostatine Octreotate	Any	 8.3 % 17.9 % 10.3 % 22.2 % 10.3 % 4.4 % 2.7 % 27.3%	 44 m (CI 33.2-NR) 37.8 m (CI 29.6–45.2) 25 m (CI 14.8–40.2) 26.2 m (CI 17.4–67.7) 49.2 m (CI 35.5–80.9) 28,5m (CI 19.4–43) 75.4 m (CI 53.7–95.7) 30.6 m (CI 27.1-NR)	 7.1 m (CI 3.9–10.8) 9.3 m (CI 7.2–12.7) 4.6 m (CI 3–5.7) 5.8 m (CI 4.6–12)8m (CI 6–18.2) 9m (CI 6.5–9.3) 6.9 m (CI 6.2–8.9) 9.5 m (CI 8.3–19.3)
Sullivan 2017 [31]	R/U	61	T (20)/A (41)	Yes for patients treated before 2004	Somatostatine	Any	0	58.4 m (CI 44.2–102.7)	17.4 m (CI 8.7–26)
Walter 2016 [32]	R/M	45	T (8)/A (24)/ND (10)	Yes	Oxaliplatine (+5FU ou G)	Any	20%	34 m (CI 21–49)	15 m (CI 6–25)
Zidan 2022 [33]	R/M	48	T (5)/A (43)	No	Lu-Octreotate	>1	20%	59 m (CI 50-NR)	23 m (CI 18–28 m)
Lenotti 2021 [34]	R/U	31	T (14)/A (17)	No	Somatostatine	1	6.5%	NR	28.6 m (CI 1.5–41.8)
Chan 2022 [35]	P/M	6	ND (6)	No	Avelumab	Any	0	NR	3.9 *m*
Owen 2022 [36]	P/U	11	T (2)/A (7)/ND (2)	No	Nivolumab + Temozolomide	Any	64%	NR (CI 8.8–NR)	11.1 m (CI 3.0–29.0)
Papaxoinis 2019 [37]	R/U	33	T (10)/A (20)/ND (3)	Yes	CAPTEM	Any	18.2%	30.4 m (CI 23.2–37.6)	9.0 m (CI 3.3–14.7)

T = typical; A = atypical; CAPTEM = capecitabine + temozolomide; ND = not defined; P = prospective; R = retrospective; M = multicentric; ORR = overall response rate; CI = 95% confidence interval; PFS = progression-free survival; NET = neuroendocrine carcinoma; FDE = 5FU, dacarbazine, epirubicin; LAR = long-acting release; G = gemcitabine; NR = not reached; OS = overall survival; U = unicentric;
*8 thymic carcinoïds.

progression-free survival (PFS) times are quite similar, with overlapping confidence intervals most of the time. Everolimus and somatostatin derivatives have a very low response rate but a disease control that can be prolonged, with an acceptable toxicity profile. The highest response rates are observed with PRRT and chemotherapy regimens including oxaliplatin and dacarbazine, but the toxicity profile is less favourable for these chemotherapies than with everolimus and somatostatin. The place of immunotherapies cannot be assessed on the basis of two studies including 6 and 11 patients.

Chemotherapy is the cornerstone treatment for LCNEC, but the

Table 5
Summary of clinical studies related to large cell neuroendocrine carcinomas included in the systematic review.

Reference	Design	N pts	Central pathology review	Treatment	Line	ORR	Median OS	1-year survival	Median PFS
Christopoulos 2017 [38]	P/M	49	No, but face to face training of pathologists	Carboplatin-paclitaxel-everolimus	1	44.9%	9.9 m (CI 6.9–11.7)	–	4.4 m (CI 3.2–6)
Le Treut 2013 [4]	P/M	42	Yes for 40 patients (95%)	Cisplatin-etoposide	1	38.1%	7.7 m (CI 6–9.6)	26.8% (CI 15.7–41.9)	5.2 m (CI 3.1–6.6)
Niho 2013 [39]	P/M	44	Yes	Cisplatin-irinotecan	1	46.7%	12.6 m (CI 9.3–16)	62.1%	5.8 m (CI 3.8–7.8)
Derks 2017 [40]	R/M	128	Yes	NSCLC-t (TXT, G, V) NSCLC-P SCLC	1	–	8.5 m (CI 7–9.9) 5.9 m (CI 5–6.9) p = 0.011 6.7 m (CI 5–8.5) p = 0.012	–	Reference arm 4.1 m (CI 3.8–4.5) p = 0.040 P = 0.147
Dudnik 2021 [17]	R/M	125	No	Monotherapy ICI No ICI	Any	–	12.4 m (CI 10.7–23.4) 6m (CI 4.7–9.4) p = 0.02	57 % 33%	–
Naidoo 2016 [41]	R/U	49	Yes	Platinum-etoposide	1	36.8%	8.3 *m*	–	TTP 4.6 m (CI 3.9–11.1)
Shirasawa 2021 [42]	R/U	70	Yes	No anti-PD1 (n = 57) Anti-PD1 (n = 13)	>1	NR 38.5%	10.9 m [CI 6.7–15.1] 25.2 m [CI 21.3–29.1] HR 0.34 (CI 0.14–0.80; P = 0.01)	–	–
Girard 2021 [18]	P/M	92	No	Nivolumab Nivolumab-ipilimumab	>1	7.3 % 18.2%	–	–	–

P = prospective; R = retrospective; m = multicentric; U = unicentric; ORR = overall response rate; PFS = progression-free survival; CI = 95% confidence interval; TXT = docetaxel; G = gemcitabine; V = vinorelbine; P = pemetrexed; NR = not reported; HR = hazard ratio; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; ICI = immune checkpoint inhibitor; TTP = time to progression; OS = overall survival.

question is about the type of regimen, "SCLC-like" or "NSCLC-like" (Table 5). We compared both schemes according to the three main evaluation criteria, i.e. response rate, PFS and OS (Table 6). The results are similar with confidence intervals on PFS and OS overlapping without clearly favouring one regimen. The five studies considered in Table 6 were all performed in 1st-line. Studies evaluating immunotherapy show an interest in integrating an immune checkpoint inhibitor in the therapeutic plan, but a definitive conclusion cannot be drawn on the basis of one prospective study and two retrospective studies mixing lines of treatment and burdened with bias, such as the number of total lines of treatment proposed to patients in each group. Other small studies have not been integrated into this review but go in the same direction of the interest of immunotherapy alone (>1 line) or in combination with chemotherapy, without being able to conclude on the best chemotherapy regimen to add.

4. Discussion

CT and LCNEC are rare histologies with different prognosis. Therapeutic options for advanced/metastatic diseases are quite different, with SSA and everolimus among the first choice for CT, while chemotherapy remaining the main option for LCNEC. Our clinical experience report shows prolonged survival times with SSA and everolimus in CT, while we cannot distinguish between SCLC-like and NSCLC-like regimens in LCNEC. In the present systematic review, we observed a limited role for cytotoxic chemotherapy in CT and emphasised the role of SSA and PRRT. In the same review, we were not able to demonstrate a difference between SCLC and NSCLC-like regimens in LCNEC in terms of efficacy, while preliminary reports are suggesting a possible interest for immune checkpoint inhibitors.

Table 6
Descriptive comparative analysis of SCLC-like and NSCLC-like chemotherapy regimens in large cell neuroendocrine carcinomas.

	NSCLC-like regimens	SCLC-like regimens
Type	Carboplatin-paclitaxel-everolimus, NSCLC-t, NSCLC-P	Platinum-etoposide, cisplatin-irinotecan
ORR	44.9%	36.8–46.7%
Median PFS	4.1–4.4 months	4.6–5.8 months
Median survival	5.9–9.9 months	6.7–12.6 months

NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; ORR = objective response rate; PFS = progression-free survival.

The first limitation when comparing studies on therapeutic effectiveness is the reproducibility of the histological diagnosis [7]. There is uncertainty about the correct pathological diagnosis on small non-surgical biopsies, which is emphasised by the high rate of reclassification [4,8]. The new histological classification [1] underlined the problem, confirming the distinction between typical and atypical carcinoids but introducing a new NOS (not otherwise specified) entity. Also, LCNEC are heterogeneous tumours [9] as shown by next generation sequencing (NGS); 40% are molecularly close of SCLC (mutations in *TP53* and *RB1* genes), up to 55% are similar to NSCLC (absence of *TP53/RB1* but *STK11, KRAS, KEAP1* mutations), while less than 5% have a molecular profile comparable to carcinoid tumours (*MEN1* mutation). This led to a new classification of LCNEC according to *TP53* and *RB1* status: type I with a genomic profile close to NSCLC and a type II similar to SCLC [10,11].

The clinical impact of this pathological distinction in LCNEC needs yet to be validated, but may probably explain the discrepancies found in the literature regarding the sensitivity of LCNEC to SCLC-like and NSCLC-like regimens. In two recent series [12,13], *RB1* status was informative regarding the therapeutic choice. Patients with wild-type *RB1* had better survival when receiving NSCLC-like chemotherapy (platinum-gemcitabine or taxanes) compared to platinum-etoposide [12]. On the opposite, type II LCNEC presenting co-mutations in *TP53/RB1* genes responded better to platinum-etoposide contrasting with NSCLC-like regimens (response rate 75% versus 20%) and had longer PFS (8.3 vs 2.4 months) [13]. The same authors suggested a possible role of liquid biopsy with a concordance between 85 and 90% with tissue biopsy for assessing *TP53* and *RB1* mutations. In the present systematic review, the information regarding LCNEC subtype was not available and added to the confusion about sensitivity of this rare tumour to chemotherapy.

The assessment of systemic treatment in CT can be complex as they usually grow slowly, and the response rate of metastatic tumors to systemic treatment is generally low; nonetheless, DCR and duration of control can be high. The SSA exemplarily demonstrates this paradigm, having essentially a tumorostatic effect and a major role for the treatment of the carcinoid syndrome. Currently, guidelines are recommending SSA in unresectable slowly progressing CT, with a low proliferation index (Ki67) and a positive somatostatin-based nuclear imaging [14]. The same observation can be done for everolimus with very low response rate but with clinically important PFS [15]. PRRT is a relatively new therapeutic approach with better response rates and a good safety profile. This implies an adequate patient selection based on positive DOTATATE nuclear imaging. At the present time, this technique is available only in dedicated cancer centres. This leads to the question of the more appropriate 1st-line systemic treatment: patients with carcinoid syndrome should be offered SSA. Based on toxicity profiles and disease control duration, everolimus and PRRT are an alternative to SSA for patients with CT without carcinoid symptoms.

Treatment of lung cancer was revolutionised during the last decade by the introduction of targeted therapies in NSCLC with oncogenic driver alterations, and by the discovery of immune checkpoint inhibitors (e.g. anti-PD-(L)1 antibodies). So far, these drugs did not demonstrate any interest in CT, while we have very limited information about the activity of immunotherapy in LCNEC. PD-L1 expression can be low in LCNEC [16], while the predictive value of PD-L1 expression for anti-PD-(L)1 antibodies activity is limited. With this in mind, some series with numerous potential biases suggested that these immunotherapy agents could be of benefit in stage IV LCNEC [17]. A recent prospective study showed a potential interest in combining two ICIs [18]. Extensive biomolecular analysis is now a standard in non-squamous NSCLC, mainly for adenocarcinoma and NOS NSCLC. In LCNEC, oncogenic driver alterations appear to be rare events: a literature review showed 0–4% of *EGFR* and 4–24% of *KRAS* mutations, and 0–2% of *ALK* rearrangements [19]. A few clinical cases reported that EGFR and ALK tyrosine kinase inhibitors could be effective when the target is present [20–23].

When facing advanced/metastatic CT or LCNEC, oncologists remain in doubt about the best systemic therapy to be proposed. The present systematic review emphasises different conclusions: 1) SSA, PRRT and everolimus present the best efficacy in CT, with a low response rate but a long disease control and an interesting toxicity profile; 2) Conventional cytotoxic chemotherapy has a limited role in CT; 3) The best chemotherapy regimen for LCNEC remains to be determined. Genomic profile based on *TP53* and *RB1* mutations may help in subtyping LCNEC and choose between SCLC-like and NSCLC-like regimens.

Clinical trials are in progress to answer those questions, define the place of immunotherapy in this setting, hoping that new therapies and more appropriate initial systemic treatment will ultimately improve overall survival.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Annex A. Search strategy

List of MeSH terms and free-text keywords used to search Ovid Medline database.
Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid Medline® Daily and Ovid Medline® 1946-present.

P criteria	Searched MeSH terms, free-text keywords and phrases
Neuroendocrine tumor	*(Neuroendocrine tumor/ OR Carcinoid Tumor/ OR Neuroendocrine.ti,ab,kw OR Somatostatinoma/ OR Somatostatinoma*.ti,ab,kw OR Carcinoma, Large Cell/ OR Large Cell Carcinoma*.ti,ab,kw OR Carcinoid*.ti,ab,kw)*
	AND
Lung Cancer	(lung neoplasms/ or bronchial neoplasms/ or carcinoma, bronchogenic/ or carcinoma, non-small-cell lung/ or pancoast syndrome/ or lung neoplasm*.ti,ab,kw or lung carcinoma*.ti,ab,kw or lung tumour*.ti,ab,kw or lung tumor*.ti,ab,kw or pulmonary neoplasm*.ti,ab,kw or pulmonary carcinoma*.ti,ab,kw or pulmonary tumour*.ti,ab,kw or pulmonary tumor*.ti,ab,kw or bronchial neoplasm*.ti,ab,kw or bronchial cancer*.ti,ab,kw or bronchial carcinoma*.ti,ab,kw or bronchial tumour*.ti,ab,kw or bronchial tumor*.ti,ab,kw or bronchogenic neoplasm*.ti,ab,kw or bronchogenic cancer*.ti,ab,kw or bronchogenic carcinoma*.ti,ab,kw or bronchogenic tumour*.ti,ab,kw or bronchogenic tumor*.ti,ab,kw or pancoast* syndrome*.ti,ab,kw or pancoast* tumor*.ti,ab,kw or pancoast* tumour*.ti,ab,kw or ((lung.ti,ab,kw or pulmonary.ti,ab,kw) and (cancer*.ti,ab,kw OR neoplasms/)))
I criteria	**Combined with AND**
Chimiotherapy	*(Drug Therapy/ OR Antineoplastic Protocols/ OR Antineoplastic Combined Chemotherapy Protocols/ OR Drug Therapy, Combination/ OR Antineoplastic Combined Chemotherapy Protocols/ OR* exp *Angiogenesis Modulating Agents/ OR Bevacizumab/ OR drug therap*.ti,ab,kw OR antineoplastic protocol*.ti,ab,kw OR chemotherap*.ti,ab,kw OR angiogenesis modulating agent*.ti,ab,kw OR angiogenesis inducing agent*.ti,ab,kw OR angiogenesis inhibitor*.ti,ab,kw OR angiogenesis modulator*.ti,ab,kw OR angiogenesis agent*.ti,ab,kw OR Bevacizumab.ti,ab,kw,nm OR Avastin.ti,ab,kw,nm OR Surufatinib.ti,ab,kw,nm OR Axitinib/ OR Axitinib.ti,ab,kw,nm OR Pazopanib.ti,ab,kw,nm OR Sunitinib/ OR Sunitinib.ti,ab,kw,nm OR Cabozantinib.ti,ab,kw,nm OR Nintedanib.ti,ab,kw,nm OR Regorafenib.ti,ab,kw,nm OR Carfilzomib.ti,ab,kw,nm OR Cisplatin/ OR cisplatin.ti,ab,kw,nm OR* exp *Vinca Alkaloids/ OR vinorelbine.ti,ab,kw,nm OR Vinblastine.ti,ab,kw,nm OR Vindesine.ti,ab,kw,nm OR vincristine.ti,ab,nm OR* exp *Taxoids/ OR Paclitaxel.ti,ab,kw,nm OR taxol.ti,ab,kw,nm OR docetaxel.ti,ab,kw,nm OR pemetrexed.ti,ab,kw,nm OR Pemetrexed/ OR alimta.ti,ab,kw,nm OR etoposide.ti,ab,kw,nm OR etoposide/ OR vp16.ti,ab,kw,nm OR carboplatin.ti,ab,kw,nm OR Carboplatin/ OR* exp *Camptothecin/ OR Camptothecin.ti,ab,kw,nm OR Irinotecan.ti,ab,kw,nm OR Topotecan.ti,ab,kw,nm OR Gemcitabine.ti,ab,nm OR Ifosfamide/ OR ifosfamide.ti,ab,nm OR Adriamycin.ti,ab,nm OR Doxorubicin/ OR Doxorubicin.ti,ab,nm OR Epirubicin/ OR Epirubicin.ti,ab,nm OR epidoxorubicin.ti,ab,nm OR epiadriamycin.ti,ab,nm OR cyclophosphamide.ti,ab,nm OR cyclophosphamide/ OR amrubicin.ti,ab,nm OR Anthracyclines/ OR Anthracyclines.ti,ab,nm OR Teniposide/ OR Teniposide.ti,ab,kw,nm OR Demethyl Epipodophyllotoxin Thenylidine Glucoside.ti,ab,kw,nm OR VM26.ti,ab,kw,nm OR NSC122819.ti,ab,kw,nm OR Oxaliplatin/ OR Oxaliplatin*.ti,ab,kw,nm OR Temozolomide/ OR Temozolomide.ti,ab,kw,nm OR Methazolastone.ti,ab,kw,nm OR Temodal.ti,ab,kw,nm OR Temodar.ti,ab,kw,nm OR TMZ Bioshuttle.ti,ab,kw,nm OR Dacarbazine/ OR Dacarbazine.ti,ab,kw,nm OR Streptozocin/ OR Streptozocin.ti,ab,kw,nm OR 5-FU.ti,ab,kw,nm OR Capecitabine/ OR Capecitabine.ti,ab,kw,nm OR Everolimus/ OR Everolimus.ti,ab,kw,nm OR SDZ RAD.ti,ab,kw,nm OR Afinitor.ti,ab,kw,nm OR Certican.ti,ab,kw,nm OR Eloxatin*.ti,ab,kw,nm OR ACT078.ti,ab,kw,nm OR* exp *Somatostatin/ OR Somatostatin*.ti,ab,kw,nm OR Stilamin.ti,ab,kw,nm OR Somatofalk.ti,ab,kw,nm OR Octreotide/ OR Octreotide.ti,ab,kw,nm OR Lanreotide.ti,ab,kw,nm OR Pasireotide.ti,ab,kw,nm OR Telotristat ethyl.ti,ab,kw,nm OR sandostatin*.ti,ab,kw,nm)*
	OR
	*(*exp *Immunotherapy/ OR immunotherap*.ti,ab OR immunization*.ti,ab OR vaccin*.ti,ab,kw OR Nivolumab.ti,ab,nm,kw OR Opdivo.ti,ab,kw,nm OR Pembrolizumab.ti,ab,kw,nm OR Keytruda.ti,ab,kw,nm OR Atezolizumab.ti,ab,kw,nm OR MPDL3280A.ti,ab,kw,nm OR Durvalumab.ti,ab,kw,nm OR Avelumab.ti,ab,kw,nm OR Ipilimumab/ OR ipilimumab.ti,ab,kw,nm OR yervoy.ti,ab,kw,nm OR tremelimumab.ti,ab,kw,nm OR ticilimumab.ti,ab,kw,nm OR IFN-alpha.ti,ab,kw,nm OR* exp *Interferons/ OR Interferon*.ti,ab,kw,nm OR Spartalizumab.ti,ab,kw,nm OR Cemiplimab.ti,ab,kw,nm)*

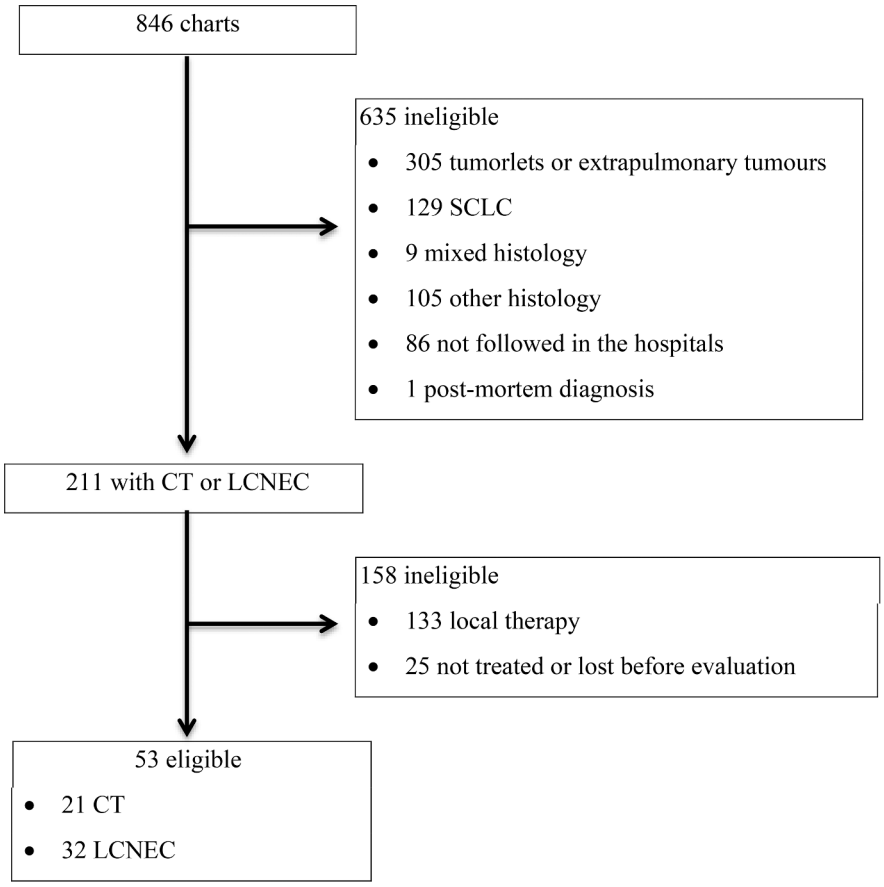
(*continued on next page*)

(*continued*)

P criteria	Searched MeSH terms, free-text keywords and phrases
	OR
Immunotherapy	
PRRT	*(*exp *Receptors, Peptide/tu OR PRRT.ti,ab,kw OR Peptide receptor radionuclide therapy.ti,ab,kw OR Lutetium/tu OR Lutetium.ti,ab,kw,nm OR Luoxodotreotide.ti,ab,kw,nm OR DOTATATE.ti,ab,kw,nm OR Lutathera.ti,ab,kw,nm OR oxodoctreotide.ti,ab,kw,nm OR octreotate.ti,ab,kw,nm)*

term/ = MeSH term (with all the possible subheading combinations).
.ti,ab,nm = terms are searched in the title, the abstract and the name of substance.
* = stands for zero or more characters.

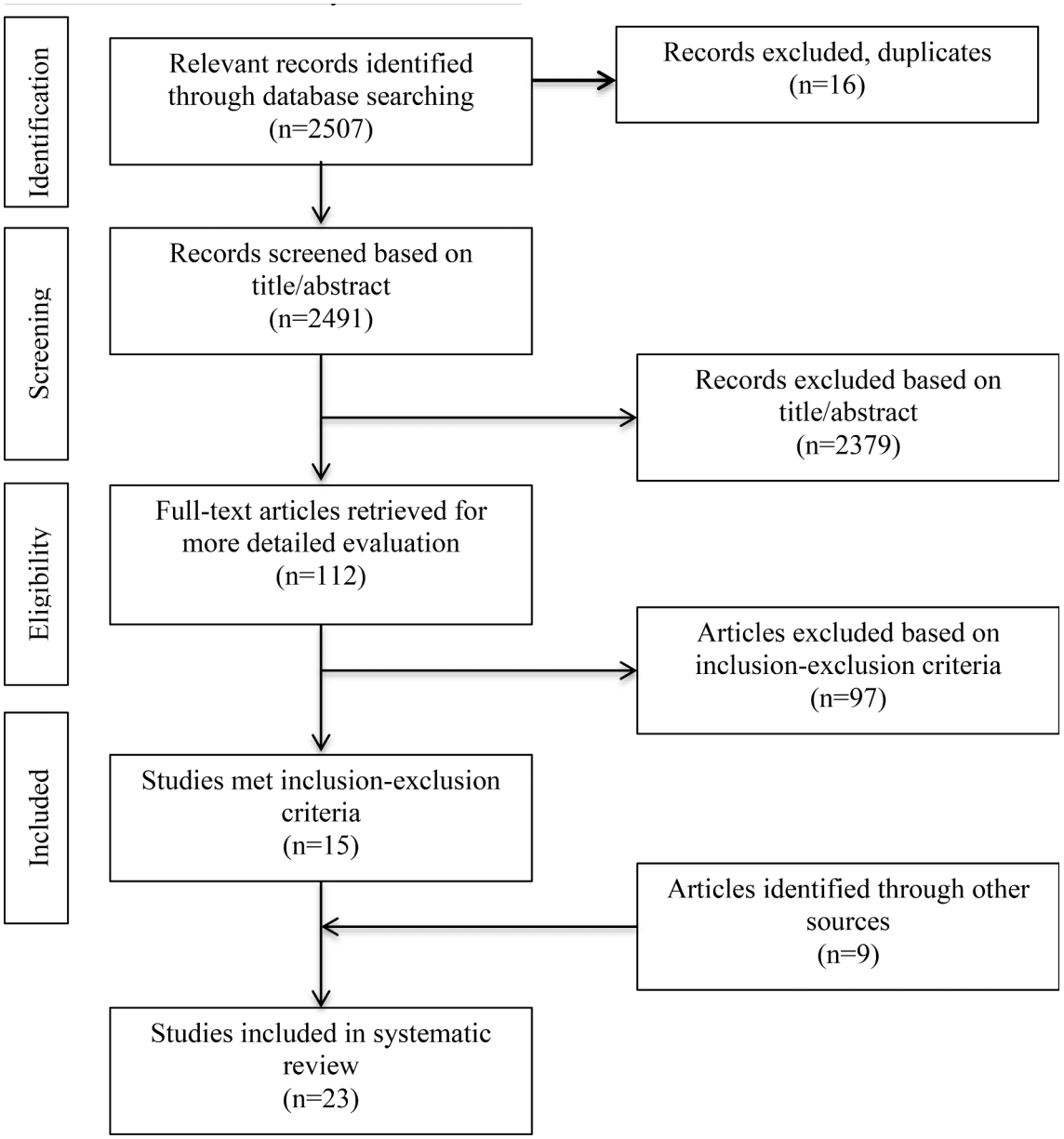
Annex B. Flow chart of patients with CT or LCNEC treated with systemic therapy



CT: carcinoid tumors; LCNEC: large cell neuroendocrine tumors; SCLC: small cell lung carcinomas

CT: carcinoid tumors; LCNEC: large cell neuroendocrine tumors; SCLC: small cell lung carcinomas.

Annex C. Flow chart of the systematic review



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