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Original Research

Lurbinectedin in patients with pretreated neuroendocrine tumours: Results from a phase II basket study

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Abstract ***Background:*** Patients with neuroendocrine tumours (NETs) need alternative therapies after failure of first-line therapy.

Patients and methods: This phase II trial evaluated lurbinectedin, a selective inhibitor of oncogenic transcription, at 3.2 mg/m^2 as a 1-h intravenous infusion every 3 weeks in 32 NETs patients treated in the second- or third-line setting. The primary efficacy endpoint was overall response rate (ORR) according to RECIST v1.1 assessed by the investigators. Secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety.

Results: Two of 31 evaluable patients had confirmed partial responses (ORR = 6.5%; 95%CI, 0.8–21.4%). Median DoR was 4.7 months (95% CI, 4.0–5.4 months), median PFS was 1.4 months (95% CI, 1.2–3.0 months) and median OS was 7.4 months (95% CI, 3.4–16.2 months). Lurbinectedin showed an acceptable, predictable and manageable safety profile. The most common grade 3/4 toxicity was neutropenia (40.6%; grade 4, 12.4%; febrile

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neutropenia, 3.1%).
Conclusions: Considering the exploratory aim of this trial that evaluated a heterogeneous population of NETs patients, and the signs of antitumour activity observed (two confirmed partial responses and seven long disease stabilisations), further development of lurbinectedin is warranted in a more selected NETs population.
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1. Introduction

Neuroendocrine tumours (NETs) are a heterogeneous family of tumours that originate from the diffuse neuroendocrine system. They are rare neoplasms, but their incidence has increased over the last decades, reaching 6.98 new cases/100,000 population/year in the USA in 2017 [1]. NETs are classified based on tumour differentiation and proliferation rate. Approximately 80% are well-differentiated NETs, which usually present a low proliferation rate (Ki-67 index <20%), and are classified as G1 or G2 NETs. However, a small subset may have a proliferation index ≥20% (G3 NETs) and are more aggressive. NETs can be also classified as functioning (~20%) or non-functioning depending on their capacity to produce hormones, peptides and neurotransmitters.

Surgery is the only curative approach for NETs. However, surgical excision is not always possible because 50–60% of patients have metastatic disease at diagnosis. Treatment with somatostatin analogues is the mainstay of systemic therapy for low-grade NETs [2]. Effectiveness of peptide-receptor radionuclide therapy for patients positive for somatostatin receptors has been proven [3]. Chemotherapy is the standard of care for aggressive, poorly differentiated NETs, but its use is limited to those of pancreatic origin or rapidly progressive extra-pancreatic NETs that have failed other more effective therapies [4,5]. Response rates with everolimus, temozolomide, or topotecan as second-line monotherapy were 0% [6–8]. The only approved targeted agents for advanced progressive NETs are sunitinib for those of pancreatic origin [9,10], and everolimus for lung, gastrointestinal and pancreatic tumours [11,12]. Nevertheless, despite recent therapeutic achievements, systemic treatments remain limited, and a consensus on the optimal sequence in patients with advanced disease is still lacking [13].

Lurbinectedin is a selective inhibitor of oncogenic transcription that binds preferentially to guanines located in the GC-rich regulatory areas of DNA gene promoters [14,15]. Prevention of the binding of transcription factors to their recognition sequences leads to inhibition of oncogenic transcription and tumour cell apoptosis [16]. Lurbinectedin also affects the tumour microenvironment landscape by inhibiting activated transcription in tumour-associated macrophages [17].

Nine cohorts of patients each with different tumour types were treated with lurbinectedin in an open-label, phase II basket study. Results in the small cell cancer (SCLC) cohort were published previously [18] and led to the approval of lurbinectedin in SCLC with disease progression on/or after platinum-based chemotherapy, first in the USA [19] and later in Canada, Australia, Singapore and the Arab Emirates. This report focuses on the outcomes in the NETs cohort. A previous phase I study showed three partial responses in a small cohort of eight patients with NETs treated with lurbinectedin combined with doxorubicin [20] and was the basis for the evaluation of antitumour activity of lurbinectedin as a single agent.

2. Patients and methods

Thirty-two patients with NETs were treated at 17 investigational sites in Belgium, France, Spain, Sweden and the USA. The study protocol was approved by the Independent Local Ethics Committee of each centre. The study was conducted according to the Declaration of Helsinki, Good Clinical Practice guidelines and local regulations for clinical trials. Signed informed consent was obtained from all patients prior to any procedure.

2.1. Eligibility criteria

Eligibility criteria included patients ≥18 years old with grade 2 and 3 pathologically proven NET diagnosis according to the WHO classification; pretreated with one or two prior chemotherapy-containing lines, and no more than three prior hormone or biological therapy lines; measurable disease as per the Response Criteria in Solid Tumors (RECIST) v.1.1 [21]; Eastern Cooperative Oncology Group performance status ≤2; and adequate major organ function. Patients were excluded if they had: previously received lurbinectedin or trabectedin; prior or concurrent malignant disease unless in complete remission for more than 5 years; known central nervous

system involvement; concomitant unstable or serious medical condition or impending need for radiotherapy.

2.2. Treatment

All patients were treated with lurbinectedin 3.2 mg/m^2 administered as a 1-h intravenous (i.v.) infusion every 3 weeks (q3wk). All patients received antiemetic prophylaxis. Primary granulocyte colony-stimulating factors (G-CSFs) prophylaxis was not allowed.

2.3. Efficacy assessment

The primary objective of this study was to assess the antitumour activity of lurbinectedin in terms of overall response rate (ORR) assessed by the investigators. Radiological tumour evaluation was performed every 6 weeks (two cycles) until Cycle 6, and every 9 weeks (three cycles) thereafter. Objective response was to be confirmed at least 4 weeks later. Secondary efficacy endpoints included disease control rate (objective response or stable disease), duration of response (DoR), progression-free survival (PFS) and overall survival (OS).

2.4. Safety assessment

Safety was evaluated in all patients who received at least one lurbinectedin infusion by assessment of adverse events (AEs), clinical laboratory test results, physical examinations and vital signs. Laboratory tests were done weekly during Cycles 1 and 2, and on Day 1 of subsequent cycles. AEs were recorded and coded with the Medical Dictionary for Regulatory Activities (MedDRA), v.21.0. AEs and laboratory values were graded according to the National Cancer Institute-Common Toxicity Criteria for Adverse Events (NCI-CTCAE), v. 4.0. All patients with lurbinectedin-related AEs were followed until recovery.

2.5. Statistical methods

Up to 25 patients were to be recruited to test the null hypothesis that 1% or less patients get a response ($p \leq 0.01$) versus the alternative hypothesis that 10% or more patients get a response ($p \geq 0.10$). The variance of the standardised test was based on the null hypothesis. The type I error (alpha) associated with this one-sided test is 0.025, and the type II error (beta) is 0.2; hence, statistical power is 80%. With these assumptions, if the number of patients who achieve a confirmed response is ≥ 2, then this would allow the rejection of the null hypothesis.

Descriptive statistics were used. Non-continuous variables are described in frequency tables using counts and percentages. Continuous variables are described by median, minimum and maximum. Binomial exact estimates and its 95% confidence interval (CI) were calculated for the evaluation of the main endpoint (ORR). The Kaplan–Meier method was used to analyse DoR, PFS and OS. SAS software was used to generate statistical outputs.

3. Results

3.1. Patient characteristics

Thirty-two patients were treated with lurbinectedin between 13 November 2015 and 16 November 2020. Initially, 15 patients were to be included in a first stage. If one confirmed response occurred in the first 15 evaluable patients, recruitment had to continue up to 25 evaluable patients. If ≥ 2 confirmed responses occurred in the first 15 evaluable patients with NETs, the cohort would have enough power and therefore recruitment could be stopped. One of the first 15 patients had confirmed partial response (PR) to lurbinectedin treatment and, therefore, recruitment continued. A total of 32 patients were included into this cohort. Seven additional patients were recruited while the assessment of ORR data was ongoing.

Most patients were male (62.5%), with ECOG PS 0–1 (96.9%), median age of 63 years (range, 23–77 years; 40.6% were ≥65 years old) and with metastatic disease at diagnosis (59.4%) (Table 1). Twenty patients (62.5%) had gastroenteropancreatic NETs. Twenty-three patients (71.9%) had non-functioning NETs. KI-67 > 10% was observed in 59.4% of patients. The median number of sites involved at baseline was 3 (range, 1–7), with 59.4% of patients having ≥3 disease sites. Liver (71.9%), lymph nodes (68.8%), lung (46.9%) and bone (31.3%) were the most common disease sites. Bulky disease was observed in 40.6% of patients. The median time from disease diagnosis to study entry was 13.3 months (range, 3.0–93.2 months). Eleven patients (34.4%) had previously undergone surgery (curative resection in eight patients). Prior radiotherapy had been administered to seven patients (21.9%). The patients had received a median of one prior line of chemotherapy (range, 0–2 lines). The most common prior agents were etoposide (71.9%) and platinum compounds: carboplatin (43.8%) and cisplatin (34.4%). Response to last prior therapy was 15.6%.

3.2. Treatment

A total of 178 cycles were administered to the 32 treated patients. The median number of cycles per patient was 2 (range, 1–36 cycles), with 28.1% of patients having received ≥4 cycles. The median relative dose intensity was 100.0% (range, 53.2–123.8%). Overall, 3.4% of cycles had dose delay due to treatment-related AEs in four patients (14.3%), grade 3/4 neutropenia being the most common cause. Dose was reduced due to treatment-related AEs in 2.1% of cycles in three patients (10.7%) because of grade 4

Table 1
Baseline characteristics (n = 32).

	n	%
Gender		
Male	20	62.5
Female	12	37.5
Age: median (range), years	63 (23–77)	
Race		
White	24	75.0
Other[a]	7	21.9
American Indian or Alaska native	1	3.1
ECOG PS status		
0-1	31	96.9
2	1	3.1
Albumin: median (range), g/dL	4.0 (3.1–4.6)	
Stage at diagnosis		
Early	5	15.6
Locally advanced	8	25.0
Metastatic	19	59.4
NET type		
Gastroenteropancreatic[b]	20	62.5
Lung[c]	3	9.4
Merkel	2	6.3
Other/unknown	5	15.5
Adrenal[d]	2	6.3
NET subtype		
Functioning neuroendocrine tumours	9	28.1
Non-functioning neuroendocrine tumours	23	71.9
KI-67/MIB-1		
<10%	5	15.6
>10%	19	59.4
Not done/unknown	8	25.0
No. of sites at baseline: median (range)	3 (1–7)	
≥3 sites	19	59.4
Most common sites of disease at baseline[e]		
Liver	23	71.9
Lymph nodes	22	68.8
Lung	15	46.9
Bone	10	31.3
Bulky disease (one lesion > 50 mm)	13	40.6
Prior therapy		
Surgery	11	34.4
Radiotherapy	7	21.9
No. of prior lines of chemotherapy: median (range)	1 (0–2)[f]	
Most common prior agents for advanced disease		
Etoposide	23	71.9
Carboplatin	14	43.8
Cisplatin	11	34.4
Everolimus	8	25.0
Best response to last therapy		
PR	5	15.6
SD	14	43.8
PD	11	34.4
Unknown/not available	2	6.3

Data shown are n (%) of patients except for median (range).
Abbreviations: CR, complete response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NET, neuroendocrine tumours; PD, disease progression; PR, partial response; SD, stable disease.
[a] Patients recruited in France and Belgium had not race available because of specific ethical requirements in these countries.
[b] Gastrointestinal (site of origin not specified) (n = 7), pancreas (n = 6), gastroenteropancreatic neuroendocrine tumour (site of origin not specified) (n = 4), oesophageal (n = 1), colon/rectal (n = 1) and rectal (n = 1).
[c] Large cell neuroendocrine tumour (n = 2) and not specified (n = 1).
[d] Pheochromocytoma (n = 1) and tumour type not specified (n = 1).
[e] Other less common sites included pancreas, peritoneum and pleura (n = 3 each).
[f] One patient did not receive prior chemotherapy; this was a protocol deviation.

neutropenia (n = 2) and both grade 3 neutropenia and grade 3 respiratory tract infection (n = 1).

3.3. Efficacy

One patient was not evaluable for efficacy because of patient refusal prior to the first tumour assessment. Two of the 31 evaluable patients had confirmed PR. Therefore, ORR according to RECIST v.1.1 was 6.5% (95% CI, 0.8–21.4%) (Table 2).

One patient with PR was a 23-year-old male diagnosed with metastatic gastroenteropancreatic NET (sites of disease: lung/liver/lymph nodes/mediastinal lymph nodes and bone-pelvic). The NET tumour was non-functioning, and Ki-67 was >10%. He did not receive surgery and was previously treated with one line of cisplatin/etoposide with PR as best response. Three target lesions were observed in pelvis and right lobe of liver (sum of 153 mm at baseline). Lesions decreased to 103 mm (PR, reduction of 33%). He was treated with 15 cycles of lurbinectedin. The reason for treatment discontinuation was disease progression, and the following subsequent therapies were administered: folic acid-5-fluorouracil, oxaliplatin, PDR (investigational anti PD-L1), LCL-161 (investigational antagonist of inhibitors of apoptosis proteins) and FOLFIRI. He had died at last follow-up of 22.6 months.

The other patient with PR was a 64-year-old male diagnosed with neuroendocrine carcinoma. Metastases were reported in lung/liver/lymph nodes/pleura/bone (multiple nodular osteoblastic lesions of the spine, mostly at dorsal level, and pelvis) and pancreas. The NET tumour was functioning (F-NET: Cushing syndrome),

Table 2
Lurbinectedin treatment in patients with neuroendocrine tumours: efficacy results (n = 31 evaluable patients).

RECIST responses (n, %)	
PR	2 (6.5%)
SD[a]	9 (29.0%)
PD	18 (58.1%)
NE	2 (6.5%)
ORR, % (95% CI)	6.5% (0.8–21.4%)
Clinical benefit rate[b] (95% CI)	29.0% (14.2–48.0%)
Disease control rate[c] (95% CI)	35.5% (19.2–54.6%)
Duration of Response (DoR)	
Median, months (95% CI)	4.7 (4.0–5.4)
Progression-free survival (PFS)	
Median, months (95% CI)	1.4 (1.2–3.0)
PFS at 6 months, % (95% CI)	16.7% (3.3–30.0%)
Overall survival (OS)	
Median, months 95% CI)	7.4 (3.4–16.2)
OS at 12 months, % (95% CI)	38.2% (20.5–55.9%)

Abbreviations: CI, confidence interval; DoR, duration of response; NE, not evaluable; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a] SD ≥ 4 months in seven patients (22.6%).
[b] Clinical benefit rate = PR + SD ≥ 4 months.
[c] Disease control rate = PR + SD.

Table 3
Characteristics of patients with neuroendocrine tumours and clinical benefit (partial response or stable disease ≥4 months) with lurbinectedin.

Baseline characteristics							Lurbinectedin treatment characteristics				
Age (years)/ Gender /ECOG PS	Primary tumour	Location sites	Ki-67	No. of prior lines	Last therapy /Best response	TTP last therapy (months)	Cycles received	Best response	DoR (months)	PFS (months)	OS (months)
23/Male/1	Gastrointestinal	Pelvis/liver	>10%	1[b]	Cisplatin /Etoposide/PR	6.8	15	PR	5.4	10.3	22.6
64/Male/1	Other[e]	Liver, bone and pancreas	>10%	1[b]	Carboplatin /Etoposide/PR	5.9	8	PR	4.0	5.3	11.3
54/Female/0	Pancreas	Liver	>10%	2[b]	Sunitinib/PR	13.1	9	SD ≥ 4	–	6.1	31.3[a]
61/Male/1	Pancreas	Liver	<10%	4	Everolimus/PR	24.0	28	SD ≥ 4	–	18.7	35.8[a]
36/Female/1	Mediastinum	Bone, mediastinum and lymph node	<10%	1[b]	Carboplatin /Etoposide/PD	2.5	7	SD ≥ 4	–	4.1	5.5
77/Female/1	Pancreas	Pancreas	<10%	3	Capecitabine /SD	2.1	8	SD ≥ 4	–	4.1	38.8[a]
57/Female/1	Adrenal	Lung and skin	NA	1	BAY 1217389[c] /SD	1.7	8	SD ≥ 4	–	5.9	19.2
73/Female/2	Other[d]	Lung and liver	>10%	2	Sunitinib/SD	7.5	14	SD ≥ 4	–	10.8	11.5
56/Male/0	Lung	Lymph node, lung and liver	>10%	1[b]	Carboplatin /Etoposide/PD	2.1	36	SD ≥ 4	–	24.7	25.8[a]

DoR, duration of response; ECOG, Eastern Cooperative Oncology group; NA, not available; OS, overall survival; PD, disease progression; PFS, progression-free survival; PR, partial response, PS, performance status; SD; stable disease; TTP, time to progression.

[a] Ongoing.
[b] Cisplatin or carboplatin/etoposide as first-line.
[c] Investigational drug.
[d] Well differentiated neuroendocrine tumour.
[e] High grade neuroendocrine tumour.

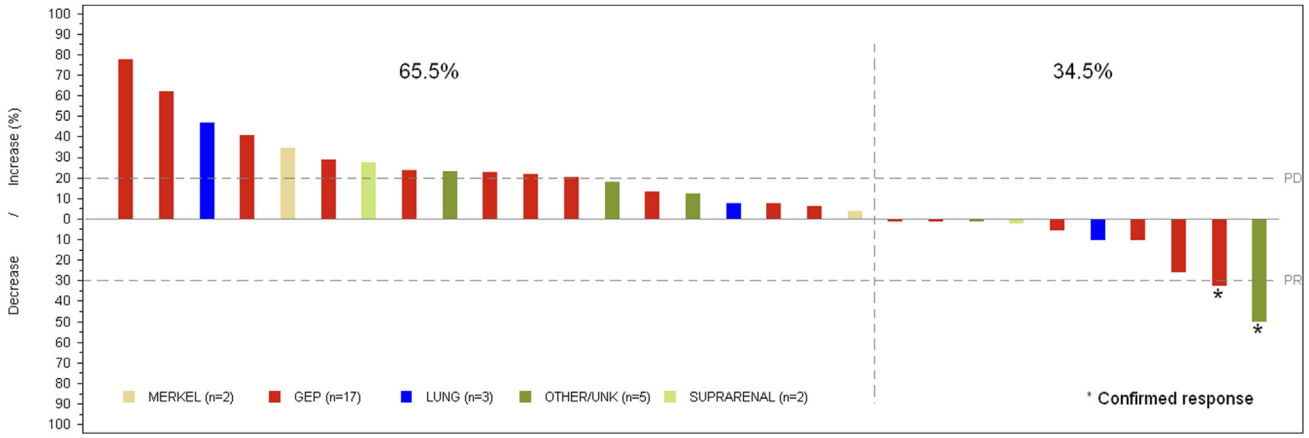

Fig. 1. Waterfall plot showing maximum variation of target lesions size in patients with neuroendocrine tumours. Abbreviations: GEP, gastroenteropancreatic; PD, disease progression; PR, partial response; UNK, unknown.

Table 4
Most common laboratory abnormalities and treatment-related adverse events (≥10% of patients or grade ≥3) in patients with neuroendocrine tumours treated with lurbinectedin (n = 32 patients).

	NCI-CTCAE grade									
	Grade 1-2		Grade 3		Grade 4		Grade 5		Total	
	n	%	n	%	n	%	n	%	n	%
Haematological abnormalities (regardless of relationship)										
Anaemia	23	71.9	7	21.9	–	–	–	–	30	93.8
Leukopenia	15	46.9	3	9.4	4	12.5	–	–	22	68.8
Neutropenia	5	15.6	8	25.0	5	15.6	–	–	18	56.3
Thrombocytopenia	14	43.8	1	3.1	2	6.3	–	–	17	53.1
Biochemical abnormalities (regardless of relationship) [a]										
Creatinine increased[b]	28	90.3	–	–	–	–	–	–	28	90.3
ALT increased	12	38.7	2	6.5	–	–	–	–	14	45.2
GGT increased	9	29.0	6	19.4	4	12.9	–	–	19	61.3
AST increased	15	48.4	–	–	–	–	–	–	15	48.4
ALP increased	17	54.8	1	3.2	–	–	–	–	18	58.1
Total bilirubin increased	4	12.9	1	3.2[c]	–	–	–	–	5	16.1
Treatment-related adverse events										
Nausea	17	53.1	–	–	–	–	–	–	17	53.1
Fatigue	16	50.0	–	–	–	–	–	–	16	50.0
Constipation	6	18.8	–	–	–	–	–	–	6	18.8
Vomiting	5	15.6	1	3.1	–	–	–	–	6	18.8
Diarrhoea	4	12.5	–	–	–	–	–	–	4	12.5
Febrile neutropenia	–	–	–	–	1	3.1	–	–	1	3.1
Lung infection	–	–	–	–	–	–	1	3.1	1	3.1
Pneumonia	–	–	–	–	–	–	1	3.1	1	3.1
Colitis	–	–	–	–	1	3.1	–	–	1	3.1
Respiratory tract infection	–	–	1	3.1	–	–	–	–	1	3.1

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyltransferase; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events v.4.

[a] Based on 31 patients with laboratory data available.

[b] Version 4.0 of NCI-CTCAE grades creatinine increases from baseline, even if creatinine values remain normal.

[c] One patient had during Cycle 1 grade 3 biliary tract obstruction related to the disease under study and a biliary stent was placed.

and Ki-67 was >10%. He did not receive surgery or radiotherapy and was pretreated with one line of cisplatin/etoposide with PR as best response. Two target lesions were observed in lung and pancreas (sum of 32 mm at baseline). PR was observed (16 mm, reduction of 50%). One month later, new lesions appeared on lung (pleural effusion) and liver (peri-hepatic effusion) that together with the worsening of Cushing syndrome led to the diagnostic of clinical deterioration and PD. He was treated with eight cycles of lurbinectedin. As further therapy, he received irinotecan and bilateral adrenalectomy. He was alive at last follow-up of 11.3 months.

Stable disease (SD) was observed in nine patients (29.0%), with seven of them (22.6%) reaching SD ≥ 4

months. Therefore, nine patients showed clinical benefit (two PRs and seven SD ≥ 4 months). Clinical benefit rate and disease control rate in the population of 31 evaluable patients were 29.0% (95% CI, 14.2–48.0%) and 35.5% (95% CI, 19.2–54.6%), respectively. Table 3 shows the characteristics of the nine patients with clinical benefit.

Gastroenteropancreatic was the most frequent NET type enrolled (20 of 32 patients; 62.5%), and in this population was observed more frequently reduction in the size of target tumour lesions (Fig. 1).

Median DoR was 4.7 months (95% CI, 4.0–5.4 months), and median PFS was 1.4 months (95% CI, 1.2–3.0 months). Time to progression with last therapy versus PFS with lurbinectedin is shown for the nine patients with clinical benefit in Supplementary Figure S-1.

With a median follow-up of 32.2 months and a censoring rate of 25.8%, median OS was 7.4 months (95% CI, 3.4–16.2 months). OS in the two patients with PR was 22.6 and 11.3 months, respectively.

3.4. Safety

All 32 treated patients were evaluable for safety (Table 4). Treatment-related grade 3/4 AEs were febrile neutropenia, colitis and respiratory tract infection (3.1% each). Laboratory abnormalities regardless of relationship were haematological disorders including anaemia (21.9%), leukopenia (21.9%), neutropenia (40.6%; grade 4, 12.5%), and thrombocytopenia (9.4%; grade 4, 6.3%) and increased liver function tests, including increased ALT (6.5%), ALP (3.2%) and GGT (32.3%). Eight patients (25.0%) received G-CSF as secondary prophylaxis or therapeutic for neutropenia. Since 72% of patients had liver metastases at baseline, abnormal liver function tests may be due to underlying disease (some of them were already present at baseline) rather than to lurbinectedin treatment. Of note, no Hy's law cases [22] were observed.

Most patients (84.4%) discontinued treatment due to disease progression. Two patients discontinued lurbinectedin therapy due to treatment-related AEs (grade 4 colitis and grade 4 pneumonia after two and one cycle) (Table 4). These two patients died later due to treatment-related AEs: grade 5 lung infection and grade 5 pneumonia.

4. Discussion

This cohort of a basket study included 32 patients with advanced NETs, mainly gastroenteropancreatic tumours (62.5%). Thirty-one patients were evaluable for the primary endpoint (ORR). Two of the 31 evaluable patients had confirmed PR. Therefore, ORR according to RECIST v.1.1 was 6.5% (95%CI, 0.8–21.4%). These two patients with PR had Ki-67 > 10% and were treated with lurbinectedin as second-line therapy after having received carboplatin/etoposide. Interestingly, an ORR of 60% has been demonstrated with lurbinectedin in platinum-sensitive SCLC [23].

Median PFS with lurbinectedin as second- or third-line in this heterogeneous population of patients with NETs was 1.4 months, and median OS was 7.4 months. A systematic review and meta-analysis of second-line treatment for patients with advanced extrapulmonary poorly differentiated neuroendocrine carcinoma, which included monotherapy but also combinations, showed median (range) PFS of 2.5 (1.2–6.0) months and median (range) OS of 7.6 (3.2–22) months [24]. However, the ORR was 0% for single-agent everolimus, temozolomide or topotecan as second-line therapies [6–8]. An epidemiological comparative study of lung and extrapulmonary poorly differentiated neuroendocrine carcinomas (NEC) using the Surveillance, Epidemiology, and End Results (SEER) database analysis of 162,983 cases showed median survival of lung NEC of 7.6 months, gastrointestinal NEC 7.5 months and unknown NEC 2.5 months [25].

An established second-line chemotherapy regimen does not currently exist for gastroenteropancreatic NETs [26]. Sorbye *et al.* [27] observed 51% disease stabilisation in 100 patients who received second-line therapy in the NORDIC NEC study. This suggests that many patients with gastroenteropancreatic NETs would benefit from subsequent lines of chemotherapy. Gastroenteropancreatic NETs were the most frequent tumour type included in the current phase II study (20 of 32 patients; 62.5%), and reduction in the size of target tumour lesions with lurbinectedin was more frequently observed in this population.

Lurbinectedin administered at 3.2 mg/m^2 as a 1-h i.v. q3wk infusion in NETs patients treated in the second- or in the third-line demonstrates a predictable and manageable safety profile, with the main toxicity being reversible myelosuppression. The safety profile reported for lurbinectedin in patients with NETs agrees with that observed in patients with other solid tumours such as ovarian [28,29], breast [30] or SCLC [18].

In conclusion, this phase II study showed signs of clinical benefit in patients with NETs treated with lurbinectedin as a single agent. Considering the exploratory aim of this basket trial, a very heterogeneous NET population was enrolled in this cohort (e.g., in terms of primary tumour location; KI-67 cut-off, number and type of prior lines of treatment). Further development of lurbinectedin in NETs could be warranted as monotherapy or combination therapy although it should be performed in a selected NET population. Further pharmacogenomic and molecular analysis may help to define the NET population that could obtain benefit from lurbinectedin therapy. For instance, large cell neuroendocrine carcinoma or higher grade 3 NETs, where the Ki-67 is in the range 30–55% might better mirror the SCLC population, where lurbinectedin has shown activity. In accordance, the ongoing EMERGE-201 trial (NCT05126433) has included a cohort of large cell neuroendocrine carcinoma patients to be treated with lurbinectedin as a single agent. Other

ongoing phase I/II study (NCT02611024) is evaluating lurbinectedin in combination with irinotecan and includes a gastroenteropancreatic NETs cohort. Finally, an ongoing phase I/II trial seeks to study the efficacy of berzosertib, an ATR kinase inhibitor, in combination with lurbinectedin for SCLC and high-grade neuroendocrine cancers (NCT04802174).

Access to data

Individual participant data are not publicly available since this requirement was not anticipated in the study protocol considering that this trial started patient enrolment in 2015. Clinical trial summary results were placed in the European Clinical Trials Database (EudraCT; https://eudract.ema.europa.eu; study 2014-003773-42) and ClinicalTrials.gov (Identifier: NCT01970540).

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Author contributions

Federico Longo-Muñoz: Investigation, Resources, Writing – review and editing. **Daniel Castellano:** Investigation, Resources, Writing – review & editing. **Jerome Alexandre:** Investigation, Resources, Writing – review and editing. **Sant. P. Chawla:** Investigation, Resources, Writing - review and editing. **Cristian Fernandez:** Conceptualisation, Methodology, Writing - original draft, Writing – review and editing, Supervision. **Carmen Kahatt:** Conceptualisation, Methodology, Writing – review and editing, Supervision. **Vicente Alfaro:** Methodology, Writing – original draft, Writing – review and editing. **Mariano Siguero:** Methodology, Formal analysis, Writing – review and editing. **Ali Zeaiter:** Methodology, Writing – review and editing, Supervision. **Victor Moreno:** Investigation, Resources, Writing – review and editing. **Enrique Sanz-García:** Investigation, Resources, Writing – review and editing. **Ahmad Awada:** Investigation, Resources, Writing – review and editing. **Ana Santaballa:** Investigation, Resources, Writing – review and editing. **Vivek Subbiah**: Conceptualisation, Investigation, Resources, Writing – original draft, Writing – review and editing.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: **Cristian Fernández**, **Carmen Kahatt**, **Vicente Alfaro**, **Mariano Siguero** and **Ali Zeaiter** are permanent employees of PharmaMar. **Victor Moreno** reports consulting fees from Roche, Bayer, BMS, Janssen and Basilea. **Vivek Subbiah** reports grants from Pharmamar, Eli Lilly/LOXO Oncology, Blueprint Medicines Corporation, Turning Point Therapeutics, Boston Pharmaceuticals; and grants from Helsinn Pharmaceuticals during the conduct of the study; in addition, **Vivek Subbiah** reports a grant and advisory board/consultant position with Eli Lilly/Loxo Oncology during the conduct of the study; research grants from Roche/Genentech, Bayer, GlaxoSmithKline, Nanocarrier, Vegenics, Celgene, Northwest Biotherapeutics, Berghealth, Incyte, Fujifilm, D3, Pfizer, Multivir, Amgen, Abbvie, Alfa-sigma, Agensys, Boston Biomedical, Idera Pharma, Inhibrx, Exelixis, Blueprint Medicines, Altum, Dragonfly Therapeutics, Takeda, National Comprehensive Cancer Network, NCI-CTEP, University of Texas MD Anderson Cancer Center, Turning Point Therapeutics, Boston Pharmaceuticals, Novartis, Pharmamar, Medimmune; an advisory board/consultant position with Helsinn, Incyte, QED Pharma, Daiichi-Sankyo, Signant Health, Novartis, Janssen, Relay Therapeutics, Roche, Medimmune; travel funds from Pharmamar, Incyte, ASCO, ESMO; other support from Medscape; all outside the submitted work. No disclosures were reported by the other authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.06.024.

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