Lung Cancer 134 (2019) 121–126

Contents lists available at ScienceDirect

Lung Cancer

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

Maintenance with lanreotide in small-cell lung cancer expressing somatostatine receptors: A multicenter, randomized, phase 3 trial☆

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ARTICLE INFO

Keywords:
Small-cell lung cancer
Lanreotide
Somatostatine analogue
Maintenance

ABSTRACT

Objectives: Considering the frequent expression of somatostatine receptors, we designed the G04.2011 trial to investigate the efficacy of the somatostatine analogue lanreotide in maintenance for SCLC patients after response to standard treatment.

Materials and Methods: A multicenter, randomized, phase 3 trial was conducted in SCLC expressing somatostatine receptors at baseline Octreoscan, responding after platinum-based chemotherapy with/without radiotherapy. Patients were randomized 1:1 to receive maintenance lanreotide 120 mg subcutaneously every 28 days, up to 1 year or progression *versus* observation. Randomization was stratified according to stage (limited/extended, LD/ED). The primary end-point was progression-free survival (PFS). Secondary endpoints were overall survival (OS) and safety.

Results: Seventy-one patients were randomly assigned (39 to lanreotide, 32 to observation) in 9 Italian institutions. Median PFS was 3.6 (95% CI 3.2–3.9) with lanreotide *versus* 2.3 months (95% CI 1.7–2.9) with observation (HR 1.51, 95% CI 0.90–2.50; $P = 0.11$). Stage was an independent predictor for PFS (HR 3.14, 95%

☆ Abstract accepted as oral presentation at IASLC 18th World Conference on Lung Cancer 2017. Presenter: Sara Pilotto. MA.01 SCLC: Research Perspectives. Lanreotide Maintenance in SCLC Expressing Somatostatine Receptors: Efficacy Results of Multicenter Randomized G04.2011 Trial. Tokyo (Japan) 15–18 October 2017.

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https://doi.org/10.1016/j.lungcan.2019.06.011
Received 29 April 2019; Received in revised form 6 June 2019; Accepted 11 June 2019

CI 1.77–5.57; $P < 0.0001$). Median PFS was 7.0 (95% CI < 1-13.5) with lanreotide *versus* 3.8 months (95% CI < 1-8.6) with observation in LD ($P = 0.21$), and 3.0 (95% CI 2.2–3.8) *versus* 2.2 (95% 1.7–2.7) in ED ($P = 0.19$). Median OS was 9.5 (95% CI 4.8–14.3) with lanreotide *versus* 4.7 months (95% CI < 1-16.6) with observation ($P = 0.47$). Treatment-related adverse events occurred in 28% of patients with lanreotide (grade 3 in two patients).

Conclusion: Although survival outcomes were not significantly prolonged with lanreotide as a maintenance in SCLC expressing somatostatin receptors after response to standard treatment, lanreotide showed a slight PFS benefit in LD SCLC deserving further investigations.

1. Introduction

Small-cell lung cancer (SCLC) represents an aggressive disease, which is intrinsically predisposed to a fast and early metastatization [1]. This peculiar natural history drives the dismal outcome of SCLC patients, whose prognosis has remained unchanged in the last three decades. Consequently, most patients survive less than 1 year after the diagnosis, with a 5-year overall survival rate around 5–6% [2].

This scenario is likely to be mainly due to the lack of significant therapeutical improvements in the context of a disease where chemotherapy has since a long time reached a plateau of efficacy. In particular, the high response rate achieved with the standard upfront treatment (platinum-etoposide chemotherapy with or without radiotherapy) is counteracted by the elevated rates of relapse, with a usually short period of disease remission or stability, and the limited efficacy of currently available second-line options [3]. Considering this, the maintenance or consolidation therapy represents an appealing strategy in SCLC. Nevertheless, a systematic review and meta-analysis including twenty-one randomized clinical trials employing mainly chemotherapy, but also interferons and other biological agents as maintenance therapy, reported no statistical advantage in overall survival [4]. The same conclusion was achieved for targeted therapies as maintenance in patients affected by limited and extensive-stage SCLC [5]. In this regard, a recent phase 3 trial evaluating the association of bevacizumab to cisplatin-etoposide regimen followed by maintenance bevacizumab *versus* chemotherapy alone failed to demonstrate a significant improvement in terms of overall survival, although a significant progression-free survival advantage and an acceptable toxicity profile were reported [6].

It is widely acknowledged that SCLC cells harbor a neuroendocrine phenotype and express somatostatine receptors in a relevant percentage of cases (around 40%) [7]. Early preclinical and clinical data demonstrated a potential antiproliferative effect of somatostatine analogues in SCLC, related to a series of direct and indirect mechanisms. Blockade of mitogenic growth factor signals (as MAPK/ERK pathway), induction of apoptosis and restoration of functional gap junctions represent candidate direct antitumor actions of somatostatine analogues and are dependent on to the subtype of somatostatin receptor to which they bind. In addition, a series of indirect mechanisms have been identified, such as suppression of angiogenesis and synthesis/secretion of growth factors, as well as modulation of the immune system [8]. Nevertheless, clinical experiences are still few and not conclusive. The largest study so far, although limited by a complex 3-arms design including a not-standard chemotherapy schedule, suggested that long acting somatostatine analogues might exert a positive influence on patients' outcome [9]. In order to address this issue, we designed and conducted a randomised, phase 3 trial exploring the efficacy of somatostatine analogue lanreotide as a maintenance strategy for SCLC expressing somatostatine receptors after response to standard upfront treatment.

2. Material and methods

2.1. Patient selection

Patients were eligible for enrolment if they met the following criteria: age 18 years or older; cytologically or histologically confirmed diagnosis of SCLC limited disease (LD, defined as T1-4, N1-3, M0 according to TNM system 7th edition for lung cancer) or extended disease (ED, defined as each T, each N, M1 according to TNM system 7th edition for lung cancer) [10] before the start of initial chemotherapy; partial or complete tumour response after standard initial chemotherapy (with or without radiotherapy) concluded within 60 days; somatostatin receptor positivity at disease diagnosis, thus before the start of initial chemotherapy (considering the lack of validated cut-off in SCLC, any intensity of radioactivity uptake was considered as Octreoscan positivity); an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; an estimated life expectancy of 3 months or more; adequate organ function. Complete response (CR) and partial response (PR) were defined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Responses were assessed by the local investigators and confirmation of response was not required. Key exclusion criteria were stable or progressive disease after standard initial chemotherapy (with or without radiotherapy); more than 60 days from the end of standard initial treatment; any active concomitant malignancy; any mental disorder and/or somatic comorbidities of clinical concern. All patients provided written informed consent before being enrolled in the study. The study protocol was approved by the institutional ethics review boards of the participating institutions. The study was conducted in accordance with good clinical practice and the ethics principles of the Declaration of Helsinki.

2.2. Study design

The G04.2011 trial is a multicenter, randomised, open-label, phase 3 trial that recruited patients from 9 institutions in Italy. After standard initial treatment, eligible patients were randomly assigned (1:1 ratio) to receive maintenance treatment with lanreotide (120 mg by subcutaneous injection every 28 days) until disease progression, unacceptable toxicity, decision of the patient or physician or for maximum 12 months of treatment or observation until disease progression. The choice of this experimental drug and dose is related to the fact that, when the G04.2011 protocol was designed, preliminary data were available supporting the potential activity of high-dose somatostatin analogues both in term of symptoms management and disease control [11,12]. Moreover, the CLARINET trial was ongoing testing the antitumor efficacy of the same lanreotide dose (120 mg/28 days) *versus* placebo for metastatic gastroenteropancreatic grade 1/2 neuroendocrine tumours [13].

Randomization was centrally performed using a computer-generated allocation sequence managed by an external contract research organization. Investigators did not have access to the allocation sequence and the contract research organization staff notified investigators at each site of the allocation result with a follow-up fax. The random assignment incorporated initial disease stage (limited disease *versus* extended disease) as a stratification factor. Patients and investigators were not masked to treatment allocation. Total-body CT scans were performed throughout the study, bimonthly during the first 12 months, and then trimonthly. Patients were followed until death, study withdrawal, loss to follow-up or study closure. Progression was determined by the local investigator using RECIST criteria version 1.1.

Safety was assessed through monitoring of adverse events, injection-site reactions, vital signs and laboratory assessments. The standard definition and the severity of adverse events was described according to the NCI Common Terminology Criteria for Adverse Events version 4.0. This study is registered with the European Union drug regulating authorities Clinical Trials (EudraCT) database, number 2011-005730-20.

2.3. End points and sample size

On the assumption of a 1-year progression-free survival of 40% in the experimental arm *versus* 15% in the observation arm (HR 2.07), we estimated 47 events (progression or death) to be necessary to provide at least 80% power for detecting a significant difference between groups with a one-tailed α-error of 5%. In order to achieve these events and considering an attrition rate of 5%, we calculated a final sample size of 76 patients. The primary endpoint of progression-free survival after randomization was analysed with a log-rank test, stratified by disease stage (limited disease *versus* extended disease). Secondary endpoints for the study were overall survival and safety. Further details about endpoints are described in Supplementary material. Progression-free survival was estimated with data from the intention-to-treat population (all randomised patients) by the Kaplan-Meier method and hazard ratio (HR) was generated with a Cox regression model. The secondary endpoint 2-year overall survival was estimated by the Kaplan-Meier method and analysed with the long-rank test with data from the intention-to-treat population. Adverse events were compared between the two arms considering the safety analysis population. All the statistical analyses were performed with IBM SPSS Statistics v. 21.

3. Results

From May 30, 2012 to April 15, 2016, 71 patients were enrolled from 9 Italian institutions (Supplementary Table 1) and randomly assigned (39 to lanreotide and 32 to observation; Fig. 1). Due to slow enrollment, the target sample size was not reached. Participants' demographic and clinicopathological characteristics, including age, sex, stage at diagnosis and response to initial treatment, were balanced between the two groups (Table 1). Notably, 36% of the patients in the experimental arm and 44% of the patients in the observation arm were affected by a SCLC limited disease. All the patients underwent platinum-etoposide chemotherapy as initial treatment. Median time from diagnosis and end of first-line to inclusion was 5.7 months (3–160) and 30 days (0–119), respectively.

With a median follow-up of 9.4 months and 62 events, progression-free survival did not significantly differ between the two groups (log-rank $P = 0.11$, $P = 0.07$ when stratified by disease stage, Fig. 2A). Median progression-free survival was 3.6 months (95% CI 3.2–3.9) in the lanreotide group *versus* 2.3 months (95% CI 1.7–2.9) in the observation group with a 1-year progression-free survival of 10.3% *versus* 7.3%, respectively (HR 1.51 [95% CI 0.90–2.50], Fig. 2A). After 34 events, median overall survival was 9.5 months (95% CI 4.8–14.3) in the lanreotide group *versus* 4.7 months (95% CI < 1-16.6) in the observation group with a 1-year overall survival of 40.8% *versus* 41.4%, respectively (HR 1.30 [95% CI 0.64–2.65]; log-rank $P = 0.47$; Fig. 2B).

Table 1
Participants' demographic and clinicopathological characteristics.

	Lanreotide (N = 39)	Observation (N = 32)
Gender		
Male	26 (67%)	25 (78%)
Female	13 (33%)	7 (22%)
Age, years	65 (37-81)	67 (44–82)
Diagnosis		
Histological	30 (77%)	25 (78%)
Cytological	9 (23%)	7 (22%)
ECOG performance status		
0	21 (54%)	19 (59%)
1	16 (41%)	13 (41%)
2	2 (5%)	0
Stage		
Limited disease	14 (36%)	14 (44%)
Extensive disease	25 (64%)	18 (56%)
Best tumor response to upfront therapy		
CR	1 (3%)	2 (6%)
PR	38 (97%)	30 (94%)
Regimen of initial chemotherapy		
Carboplatin plus etoposide	21 (54%)	15 (47%)
Cisplatin plus etoposide	18 (46%)	17 (53%)
Radiotherapy		
Thoracic	16 (41%)	11 (34%)
CNS (PCI/curative)	23 (59%)	21 (66%)
Time from diagnosis to study inclusion (months)	5.6 (3-12)	5.8 (3–160)
Time from end of 1st line to study inclusion (days)	29 (0-119)	30 (0–108)

ECOG, Eastern Cooperative Oncology Group; CR, complete response; PR, partial response; CNS, central nervous system; PCI, prophylactic cranial irradiation.

At the Cox-proportional multivariable modelling, the stage (extended disease *versus* limited disease) was an independent predictor for progression-free survival (HR 3.14 [95% CI 1.77–5.57]; $P < 0.0001$; Table 2) an overall survival (HR 4.76 [95% CI 1.81–15.53]; $P < 0.0001$; Supplementary Table 2). A trend towards interaction according to stage was found ($P = 0.055$ according to Breslow [Generalized Wilcoxon]; $P = 0.68$ according to Tarone-Ware). Median progression-free survival for experimental arm and observation arm was 7.0 [95% CI < 1-13.5] and 3.8 months [95% CI < 1-8.6] in limited disease patients ($P = 0.21$; Fig. 3A), and 3.0 (95% CI 2.2–3.8) and 2.2 (95% 1.7–2.7) in extended disease patients ($P = 0.19$; Fig. 3B).

The median number of lanreotide doses was 4 (1–12) and treatment duration was 83 days (1–392). The most common adverse events are reported in Supplementary Table 3. Treatment-related adverse events were reported in 28% of patients in the experimental arm. Among

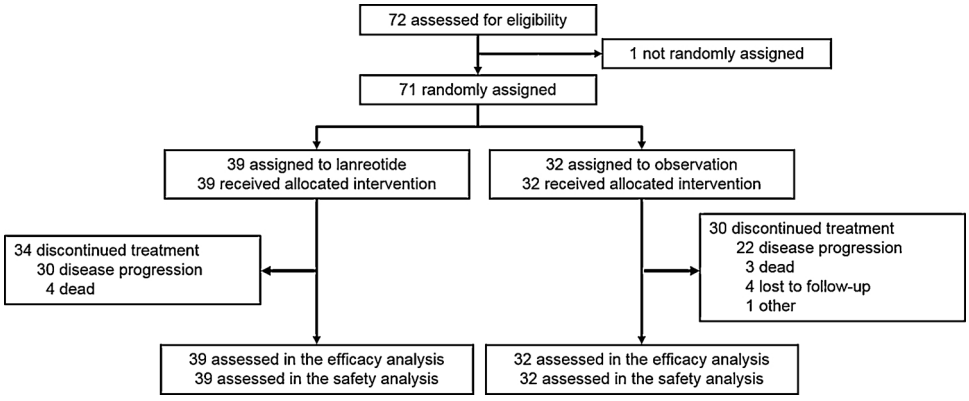

Fig. 1. Trial profile.

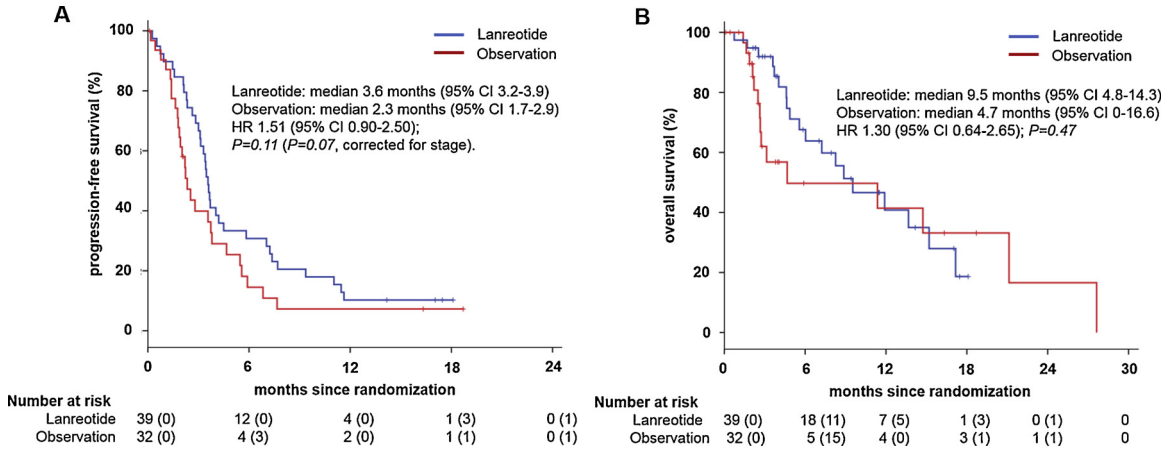

Fig. 2. Progression-free survival (A) and overall survival (B) in the intention-to-treat population.

Table 2
Univariate and multivariable analysis for progression-free survival.

Variables	Progression-free Survival	
	Univariate analysis	Multivariable analysis
Gender	1.51 (0.86–2.64)	–
[male *versus* female]	*P = 0.15*	
Age	1.52 (0.92–2.51)	–
[> 65 *versus* ≤65 years]	*P = 0.10*	
Stage	2.76 (1.58–4.80)	3.14 (1.77–5.57)
[ED *versus* LD]	*P < 0.0001*	*P < 0.0001*
ECOG PS	2.20 (1.30–3.72)	–
[1-2 *versus* 0]	*P = 0.003*	
Time from diagnosis to study inclusion (months) [< 6 ms *versus* ≥6 ms]	1.36 (0.81–2.29) *P = 0.24*	–
Time from end of 1 st line to study inclusion (days) [< 30 days *versus* ≥30 days]	1.60 (0.95–2.69) *P = 0.07*	–
Arm	1.50 (0.91–2.50)	1.64 (0.98–2.75)
[B *versus* A]	*P = 0.12*	*P = 0.06*

ED, extended disease; LD, limited disease; ECOG, Eastern Cooperative Oncology Group; ms, months.

them, a grade 3 abdominal pain and electrolyte disorder were observed in one patient without leading to treatment discontinuation. No treatment-related deaths were reported. Second-line chemotherapy was given to 21 (54%) patients in the lanreotide arm and 17 (53%) patients in the observation group (Supplementary Table 4).

4. Discussion

The G04.2011 trial represents the first phase 3, randomized trial exploring the efficacy of the somatostatine analogue lanreotide as a maintenance strategy for extended and limited disease SCLC, expressing somatostatin receptors, after response to standard upfront treatment. The results of this study suggested that the primary endpoint progression-free survival did not significantly differ in patients who received lanreotide compared with observation. We observed a not statistically significant effect of lanreotide in patients affected by limited disease SCLC with a 3.2 months improvement in median progression-free survival, although the small sample size does not allow drawing any conclusions. The disease stage was a stratification factor and a subgroup analysis based on this variable was prespecified in the protocol.

A recent analysis identified somatostatin receptor 2 overexpression in 48% of a cohort of 96 primary tumors from patients affected by SCLC, with a significant association with poor clinical outcome. *In vitro* and *in vivo* experiments suggested that somatostatin receptor 2 expression might contribute to tumor aggressiveness through activation of downstream signaling pathways, and therefore its downregulation might lead to enhance apoptosis and dramatically inhibit tumor growth [14]. Another set of preclinical experiments suggested that, depending on the drug, treatment with somatostatin analogues before or after chemotherapy might increase apoptosis in SCLC cells [15].

To date, only a limited number of clinical analyses evaluated the role of somatostatin analogues in SCLC patients. Among them, the largest study enrolled 130 untreated patients affected by SCLC overexpressing somatostatin receptors [9]. Although limited by a relevant

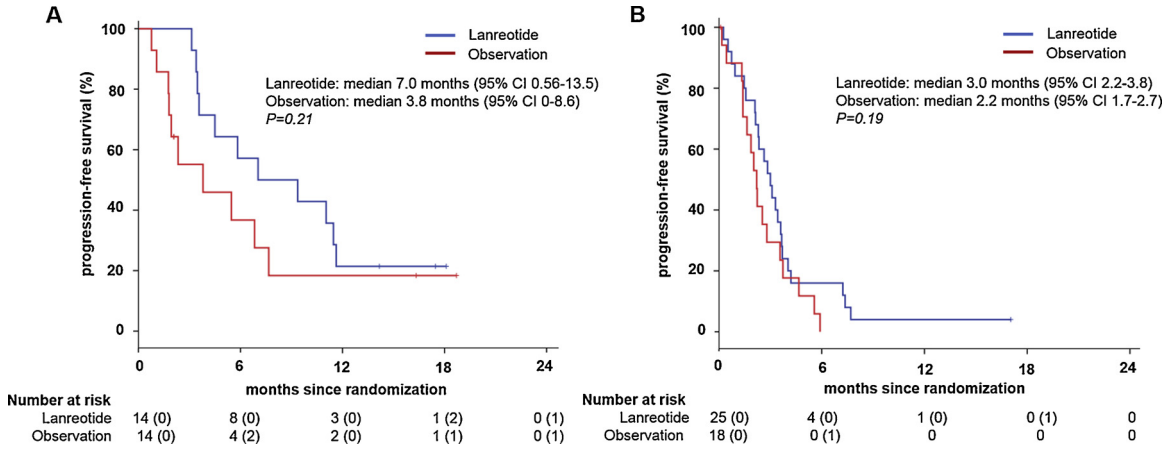

Fig. 3. Progression-free survival according to disease stage: limited disease (A) and extended disease (B).

heterogeneity in term of type of treatment included, the authors reported a potential benefit from the combination of long acting somatostatin analogues with antineoplastic agents, particularly in patients with limited disease, as we observed in our trial.

In addition to the use of somatostatine analogues, peptide radioreceptor radionuclide therapy (PRRT) in somatostatin receptors overexpressing SCLC was evaluated. The available data did not show any efficacy of PRRT in extended disease small-cell lung cancer [16,17]. Moreover, taking into account the not negligible hematological toxicity of radionuclide therapy, the safety profile further contribute to support the use of somatostatin analogues as the most appropriate approach to target somatostatin receptors overexpressing SCLC.

Among the innovative approaches currently under investigation in order to improve the outcome of SCLC patients, immunotherapy represents a solid perspective. Although a low amount of tumor infiltrating lymphocytes and an overall modest programmed death-ligand 1 expression, the high non-synonymous mutation rate, the correlation with smoking history, as well as the frequent presence of immune-triggered paraneoplastic phenomena provide a strong rationale for the design and conduction of immunotherapy studies in SCLC [18]. The addition of atezolizumab to platinum-etoposide recently demonstrated to significantly improve overall survival and progression-free survival compared to chemotherapy alone in the first-line treatment of extensive-stage SCLC [19]. Nevertheless, to date this represents the only positive and potentially practice-changing trial with immunotherapeutic agents in both first-line setting and relapsed SCLC [20–24]. As a maintenance strategy, pembrolizumab reported only a modest efficacy in the context of a single-arm phase 2 study [23]. Similarly, the randomized phase 2 IMPULSE trial in patients affected by extended-disease SCLC with complete or partial response after induction chemotherapy, failed to demonstrate a significant overall survival improvement deriving from the toll-like receptor 9-agonist lefitolimod as an immunotherapeutic maintenance [24]. Moreover, a major concern is represented by the severe immune mediated toxicity reported after radiation with checkpoint inhibitors, particularly in combination [25]. By contrary, in the G04.2011 study the safety analysis confirmed the tolerability profile of lanreotide. There were no clinically meaningful differences between lanreotide and observation for any adverse events and only two cases of grade 3 adverse events were observed.

Interpretation of the results of the G04.2011 trial has limitations related to the lack of a placebo-controlled comparison arm and the limited number of patients. Moreover, patient selection might represent a factor potentially contributing to the progression-free survival benefit observed in limited compared with extended disease. In this regard, considering the high overall response rate expected during initial chemotherapy for SCLC (around 55–60%) and the limited number of disease stability (around 10–15%) [26], in order to exclude those patients rapidly progressing after chemotherapy, we decided to include in the G04.2011 trial only patients responding to initial chemotherapy. Despite we might have selected a favorable prognostic subgroup of patients, considering the generally dismal prognosis of SCLC, these inclusion criteria are unlikely influencing the results validity and reliability. Although the findings of our trial need confirmation, available experimental data support the potential antiproliferative effect of somatostatine analogues in oncological patients, including those affected by SCLC, through a series of direct and indirect antitumor mechanisms [8]. Moreover, the favorable toxicity profile demonstrated in daily clinical practice has provided increasing value to somatostatine analogues in cancer treatment.

5. Conclusions

Survival outcomes were not significantly prolonged with lanreotide as a maintenance in SCLC expressing somatostatin receptors after response to standard upfront treatment, although lanreotide showed some benefit in terms of progression-free survival in the predefined subgroup of patients affected by a limited disease. Considering the biological rationale and the favorable risk-benefit ratio, future investigations may include somatostatine analogues, particularly in this subgroup of SCLC patients.

Author contributions

E.B. had full access to all the study data and takes responsibility for the content of the manuscript, including integrity and accuracy of data analysis. A.S., S.P., L.G., D.G. and E.B. were involved in the study design, writing of the protocol and running of the trial. A.S., S.P., D.G., F.G., G.F., G.R., L.B., A.B., M.P., E.R., A.C., A.F., E.R., C.G., P.P., A.F., L.G., G.T., M.M. and E.B. participated in data collection and enrolment of patients. D.G. was responsible for the statistical analysis. A.S., S.P., D.G. and E.B. had full access to all the study data, participated in data analysis and interpretation of the results, wrote the initial draft of the manuscript and had the final responsibility for the decision to submit for publication. All authors participated in drafting, reviewing, and approval of the final manuscript.

Funding

This work was supported by Medical Oncology, Azienda Ospedaliera Universitaria Integrata Verona (Italy). The trial was partially supported by an unrestricted grant and free lanreotide supply by Ipsen. The drug manufacturer was not involved in the trial design, data collection, data analysis, data interpretation or preparation of the manuscript. A.S., S.P., D.G. and E.B. had full access to all the study data, wrote the initial draft of the manuscript and had the final responsibility for the decision to submit for publication. All the authors were involved in writing the manuscript and approved the final version for submission.

Declaration of Competing Interest

A.S. reports personal fees from Astra Zeneca, Roche, BMS, Boeringher, MSD, Pfizer, outside the submitted work; S.P. reports personal fees from Astra Zeneca, Roche, BMS, Boeringher, grants from Astra Zeneca, outside the submitted work; D.Ga. reports personal fees from Roche, BMS, MSD, Boeringher, MSD, outside the submitted work; E.Ri. reports personal fees from Astra Zeneca and non-financial support from Roche, outside the submitted work; C.G. reports personal fees from Astra Zeneca, Roche, BMS, Boeringher, MSD, outside the submitted work; M.M. reports personal fees from Pfizer, EUSA Pharma and Astra Zeneca, outside the submitted work; G.T. reports personal fees from Novartis, Celgene, Merck, outside the submitted work; E.B. reports personal fees from Astra Zeneca, MSD, Roche, BMS, Novartis, grants from Astra Zeneca and Roche, outside the submitted work. All remaining authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.06.011.

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