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Statins Support the Antitumor Activity of Somatostatin Analogues in Advanced Bronchopulmonary Neuroendocrine Tumors: A Clinical and In Vitro Study

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Abstract

Background/Objectives: Metabolic alterations, including dyslipidemia, may influence tumor biology and treatment outcomes in neuroendocrine tumors. However, the clinical relevance of dyslipidemia and lipid-lowering therapy in bronchopulmonary neuroendocrine tumors (BP-NETs) treated with somatostatin analogues (SSAs) remains poorly defined. This translational proof-of-concept study evaluated progression-free survival (PFS) in patients with advanced BP-NETs receiving SSAs according to dyslipidemia and statin therapy and explored the effects of statin-SSA combination treatment in vitro. Methods: We retrospectively analyzed 24 patients with advanced well-differentiated BP-NETs treated with SSAs as first-line therapy. Fourteen patients (58.3%) had dyslipidemia, and 11 of them were receiving statins. In parallel, NCI-H727 cells were treated with atorvastatin (10 μM), lanreotide (5 or 10 μM), or their combination for 48–72 h. Cell viability, proliferation, cell death, apoptosis, DNA damage, and ATP production were assessed. Results: Median PFS was 22.5 months overall. A trend toward longer PFS was observed in non-dyslipidemic vs. dyslipidemic patients (70 vs. 36 months, $p = 0.08$). Among dyslipidemic patients, statin therapy was associated with a non-significant trend toward longer PFS compared with no statin therapy (36 vs. 18 months, $p = 0.30$). In vitro, combined atorvastatin–lanreotide treatment reduced cell viability and proliferation, increased cell death, enhanced cleaved caspase-3 and p-γH2AX expression, and reduced ATP production. Conclusions: These findings support the potential relevance of lipid metabolism modulation as an adjunct strategy in advanced BP-NETs while highlighting the need for larger prospective studies and dedicated biochemical investigation of the underlying lipid-related pathways.

Keywords: bronchopulmonary neuroendocrine tumors; statin; SSAs; NCI-H727; dyslipidemia

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1. Introduction

Neuroendocrine tumors (NETs) are heterogeneous, well-differentiated, generally slow-growing epithelial neoplasms that predominantly arise in the gastroenteropancreatic (GEP) and bronchopulmonary (BP) systems. BP NETs include typical carcinoids (mitotic index < 2 per 2 mm^2 and absence of necrosis), atypical carcinoids (mitotic index of 2–10 per 2 mm^2 with possible necrosis), and high mitotic/Ki-67 variants (morphologically similar to atypical carcinoids but characterized by a mitotic index > 10 per 2 mm^2 and/or Ki-67 > 30%) [1]. Overall, the incidence of NETs is increasing, and diagnosis frequently occurs at a metastatic stage, which is associated with a worse prognosis [2]. NETs commonly express somatostatin receptors (SSTRs), a feature exploited for both diagnostic and therapeutic purposes. Surgery represents the standard first-line treatment for localized disease [3], whereas therapeutic options for advanced NETs remain limited and include somatostatin analogues (SSAs) (Octreotide, Lanreotide), peptide receptor radionuclide therapy (PRRT with ˆ177Lu-DOTATATE), everolimus, and chemotherapy [4–8]. Despite these options, validated molecular biomarkers and personalized therapeutic strategies are still lacking, particularly in BP-NETs. The biological complexity of NETs underscores the need to identify novel prognostic factors and therapeutic targets [9,10]. SSAs, such as octreotide LAR and lanreotide, are widely used in the management of NETs and exert their effects primarily through activation of somatostatin receptor subtype 2 (SSTR2), resulting in inhibition of proliferative and angiogenic signaling pathways. There is growing interest in lipid metabolism and metabolic alterations, including metabolic syndrome, obesity, and dyslipidemia, which have already been implicated in the development and progression of several solid tumors [11–13]. Lipid metabolism supplies energy substrates and structural phospholipids essential for tumor growth; accordingly, dyslipidemia, characterized by elevated cholesterol and triglyceride levels, may promote angiogenesis, metastatic dissemination, and resistance to anticancer therapies [14–17]. Observational studies suggest that dyslipidemia is more prevalent in patients with NETs and has been associated with a worse prognosis [18,19]. In this context, increasing attention has been directed toward statins, cholesterol-lowering agents that inhibit 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase, thereby impairing cholesterol biosynthesis and protein prenylation. Beyond their lipid-lowering activity, statins exert pleiotropic effects, including inhibition of cell proliferation and migration, induction of apoptosis, and modulation of key oncogenic signaling pathways such as PI3K/AKT/mTOR and ERK. Accordingly, several studies have investigated their potential role as anticancer agents [20–24].

A retrospective multicenter study including 393 patients with GEP- and BP-NETs reported that dyslipidemia tended to be associated with shorter progression-free survival (PFS); however, among dyslipidemic patients, statins use was associated with a significant improvement in PFS (108 months vs. 26 months in untreated patients), suggesting a possible antitumor role for statins in NETs [25]. Consistent with these observations, recent studies have explored statins as potential adjuvant agents in antineoplastic therapy across different cancer models [21]. Numerous preclinical studies have demonstrated the antiproliferative and pro-apoptotic effects of statins, which act on key cellular processes including the cell cycle, lipid metabolism, migration, and intracellular signaling in various tumors, such as breast, prostate, lung, liver, and adrenal NET cell lines [26–31]. In parallel, in vitro studies on NET models have investigated combination strategies involving somatostatin analogues (SSAs) and inhibitors of signaling pathways, including PI3K and mTOR [32]. Pretreatment with these inhibitors enhanced the efficacy of SSAs, in part through reinduction of somatostatin receptor expression [33]. Additionally, crosstalk between TGF-β signaling and the SST/SSTR pathway has been reported, affecting differentiation, receptor expression, and microRNA regulation and suggesting a complex regulatory network [34].

Taken together, these biological findings, together with emerging clinical evidence, support the hypothesis that modulation of lipid metabolism via statins may represent a promising strategy in NETs. However, despite the increasing interest in this field, data specifically addressing BP-NETs are still scarce, and the biological interaction between statins and SSAs has not been explored in depth in this setting.

The present study was designed as a translational proof-of-concept investigation integrating clinical and experimental evidence. Specifically, the primary objective was to assess the impact of dyslipidemia and statin therapy on progression-free survival (PFS) in patients with advanced BP-NETs treated with SSAs. As a secondary exploratory objective, we evaluated in vitro whether atorvastatin could enhance the biological effects of lanreotide in a BP-NET cell model.

2. Materials and Methods

2.1. Clinical Study

Data from outpatients with well-differentiated (G1–G3) BP-NETs referred to the ENETS center of excellence Sant'Andrea University Hospital of Rome, from January 2010 to November 2025, were retrospectively collected. Inclusion criteria were: (1) histological diagnosis of well differentiated (G1–G3) BP-NET; (2) age $\geq$ 18 years; (3) advanced disease treated with SSAs as first-line therapy; (4) follow-up time $\geq$ 12 months from the histological diagnosis; (5) available lipid profile at NET diagnosis. Exclusion criteria were (1) NETs of non-respiratory origin; (2) neuroendocrine carcinoma; (3) age < 18 years; (4) treatment with therapies other than SSAs; (5) follow-up < 12 months; and (6) unavailable data. All patients provided written informed consent to data collection; clinicopathological data were retrospectively collected through review of clinical records. For each patient, demographic and clinicopathological data were recorded, including age, sex, tumor histology, Ki-67 index, disease stage, SSA treatment, carcinoid syndrome, and lipid profile status.

Dyslipidemia was defined by the presence of elevated serum LDL cholesterol and/or triglyceride levels on routine laboratory testing, assessed by standard commercial kits, or by a history of or ongoing treatment with lipid-lowering medications. No predefined time points for lipid measurements were established, with the exception of baseline assessment. Tumor radiologic assessment was performed using contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) at diagnosis and during follow-up, including post-surgical and systemic treatment phases. Given the retrospective design of the study, imaging time points were not predefined. The main clinical outcome was progression-free survival (PFS), defined as the interval from initiation of SSA therapy to radiological progression according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or last follow-up [35]. Overall survival was not analyzed because of the limited number of death events. Data regarding lipid-lowering therapies, with main focus on statins, but also ezetimibe, bile acid sequestrants, fibrates, or supplements (omega-3 fatty acids, fermented red rice) and their dosages were also collected. Given the retrospective design and the limited sample size, no multivariable adjustment model was performed; therefore, the clinical analysis should be interpreted as exploratory and hypothesis-generating.

The study was approved by the Sapienza University Ethic Committee (Reference number 6648/2022) and conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent to data collection.

2.2. In Vitro Study

2.2.1. Cell Cultures and Treatments

The human Lung NET cell line of typical carcinoid NCI-H727, which was purchased from the American Type Culture Collection (ATCC), was cultured in RPMI-1640 culture medium (Sigma Aldrich) supplemented with 10% heat-inactivated fetal bovine serum (FBS) (Invitrogen), 100 µg/mL streptomycin, and 100 U/mL penicillin (Gibco, Grand Island, NY, USA) and incubated at 37 °C, 5% CO_2 in a sterile biosafety hood environment, and medium was changed every 48-h. Approximately 78.000 cells/cm^2 were plated and treated after 24 h. NCI-H727 cells were exposed to atorvastatin (10 µM), lanreotide (5 µM or 10 µM), or their combination for 48 or 72 h, depending on the experiment. Drug concentrations were selected on the basis of published evidence [36] and internal preliminary experiments designed to explore dose-dependent effects.

Atorvastatin Calcium (SML3030, Sigma Aldrich, St. Louis, MO, USA) is a hydrophobic substance, which is dissolved in organic solvents such as Dimethyl sulfoxide (DMSO). DMSO (Sigma Aldrich) has a lower final concentration (less than 0.1% in RPMI medium); thus, we used it as an atorvastatin solvent. Lanreotide Acetate (SML0132, Sigma Aldrich) is a hydrophobic substance that is dissolved in organic solvents such as Dimethyl sulfoxide (DMSO). DMSO (Sigma Aldrich) has a lower final concentration (less than 0.1% in RPMI medium); thus, we used it as a lanreotide solvent.

2.2.2. Viability Assay

We utilized the MTT colorimetric protocol to assay the mitochondrial respiration rate of viable cells with and without treatment. The MTT(3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) (Sigma Aldrich) was dissolved in PBS at a final concentration of 0.5 mg/mL. After two-day-incubation, we removed the medium, and 100 µL MTT reagents were added to each well and left for three hrs at 37 °C in a CO_2 incubator. After removing the MTT reagent, the colored Formazan product was dissolved in 150 µL DMSO, and plates were agitated for 20 min at room temperature for fully dissolving the MTT product. We measured the optical density (OD) of products at a maximum absorbance wavelength of 560 nm with a micro-plate reader (GloMax, Promega Corporation Madison, WI, USA). Results are presented as the log2 fold change of the mean optical density (O.D.) relative to the control.

2.2.3. Proliferation Assay

Cell proliferation was assessed using the EdU incorporation assay and Ki-67 immunofluorescence (IF). EdU, a thymidine nucleoside analog, is incorporated into newly synthesized DNA during cell proliferation and is detected as green nuclear staining. Cells were cultured and treated as previously described for 48 h and incubated with 10 µM EdU for the last 24 h. Cells were fixed with 4% paraformaldehyde, and EdU incorporation was detected using the Click-iT™ Plus EdU Imaging Kit (Invitrogen, #C10337, Carlsbad, CA, USA) according to the manufacturer's instructions. Ki-67 immunofluorescence staining was subsequently performed by blocking cells with 3% BSA in PBS for 30 min, followed by incubation with the anti-Ki-67 antibody (DAKO, #M7240, Glostrup, Denmark) at 1:100 dilution, overnight at 4 °C and then with the appropriate fluorescent secondary antibody (Alexa Fluor™ 594, #A-11005, Invitrogen). Nuclei were counterstained with 1X Hoechst33342 solution (Invitrogen) for 10 min, followed by three washes. Images were acquired using Zeiss Axiovert 200M (Carl Zeiss, Jena, Germany) with a 20X air objective and analyzed with ImageJ version 1.54g software (National Institutes of Health, Bethesda, MD, USA).

2.2.4. Cytotoxicity Assay

NCI-H727 cells were cultured in ibidi chambers at 7.8×10^4 cells/cm^2 and treated as previously described for 48 h. After treatment, the cells were twice washed with PBS and stained with 2 μM Calcein AM and 4 μM EthD-1 (LIVE/DEAD viability/Cytotoxicity kit, # L3224, Invitrogen), diluted in PBS for 20 min at 37 °C. The fluorescence was examined according to the manufacturer's instructions.

2.2.5. Western Blot

Total protein extracts from cells were obtained in RIPA buffer (150 mM NaCl, 50 μM Tris-HCl pH 8.0, 1% NP40, 0.5% Sodium deoxycholate, 0.1% SDS) containing fresh proteases and phosphatases inhibitors cocktail and 0.005 M Na3VO4 and 0.05 M NaF. Cell lysates were centrifuged at 16.200× g for 30′, and the supernatants were separated by SDS-PAGE and blotted into the nitrocellulose membrane. Membranes were blocked with 5% BSA and incubated with primary and secondary antibodies at the appropriate dilutions. Primary Abs were as follows: Cleaved Caspase-3 (Asp175) Antibody #9661, Invitrogen; Phospho-Histone H2A.X (Ser139) (20E3) #9718, Invitrogen; Vinculin #sc-73614 Santa Cruz. Immunoreactive bands were visualized using WesternBright ECL HRP substrate.

2.2.6. Seahorse Metabolic Assay

Bioenergetic changes following treatment of the NCI-H727 cell line were evaluated using the Seahorse XF 96 Cell Culture Microplate analyzer (Agilent Technologies, Santa Clara, CA, USA), which allows real-time analysis of oxygen consumption rates (OCR) and extracellular acidification rates (ECAR) in living cells. The assay quantifies total ATP production and distinguishes mitochondrial and glycolytic contributions. The cells were plated at a density of 3.5×10^4 per well. Following 48 h of treatment, the wells were washed with XF BASE culture medium (Seahorse Biosciences, North Billerica, MA, USA) supplemented with 2 mM L-glutamine, 11 mM glucose, and 1.2 mM pyruvate for Atp Rate Assay tests, adjusted to pH 7.35, and then incubated for 30 min at 37 °C in a CO2-free incubator before reading. The XF Atp Rate kits were purchased from Seahorse Biosciences and used according to the manufacturer's instructions. OCR and ECAR were measured after sequential injection of oligomycin (2.5 μM) and a mixture of antimycin A (14 μM) and rotenone (14 μM) (all reagents from Merck KGaA, Darmstadt, Germany). All values were normalized with respect to viability. The data were analyzed using dedicated software (XF Wave version 2.6.4, Agilent Technologies, CA, USA).

2.3. Statistical Analysis

Clinical and in vitro data were analyzed separately according to the nature of the variables and study design. Regarding the clinical study, descriptive statistics were summarized using the median for continuous variables and frequencies for categorical variables. Patients were classified according to the presence or absence of dyslipidemia and further stratified based on ongoing pharmacological treatment with statins. Comparisons between groups (dyslipidemic vs. non-dyslipidemic and statin-treated vs. untreated patients) were performed using the χ^2 test or Fisher's exact test, as appropriate, for categorical variables. Clinical outcome was assessed in terms of PFS, defined as the interval from initiation of SSA therapy to disease progression, evaluated according to routine clinical practice at the time of diagnosis, or to the last follow-up visit, death from any cause, or loss to follow-up. Survival analyses were conducted using the Kaplan–Meier method, and differences between groups were assessed using the log-rank test. Median survival estimates were reported with a 95% confidence interval. Due to the limited sample size, multivariable analyses were not performed; therefore, results should be interpreted as exploratory and hypothesis-generating.

Regarding the in vitro study, results were expressed as mean ± standard deviation of at least three independent biological replicates. Group comparisons were performed using unpaired t-test or non-parametric tests, as appropriate according to data distribution. For both portions of the study, results were considered significant at $p < 0.05$. Graphs and statistical analyses were performed using Microsoft Excel (Microsoft, Redmond, WA, USA), GraphPad Prism 6 (GraphPad Software, San Diego, CA, USA), Image J version 1.54g (NIH, Bethesda, MD, USA), and IBM SPSS Statistics (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Clinical Investigation

3.1.1. Patients' Characteristics

We analyzed data from a total of 131 patients; among these, 30 patients (22.9%) were treated with somatostatin analogues (SSAs). Six patients were subsequently excluded due to insufficient data or too short follow-up time (Figure 1).

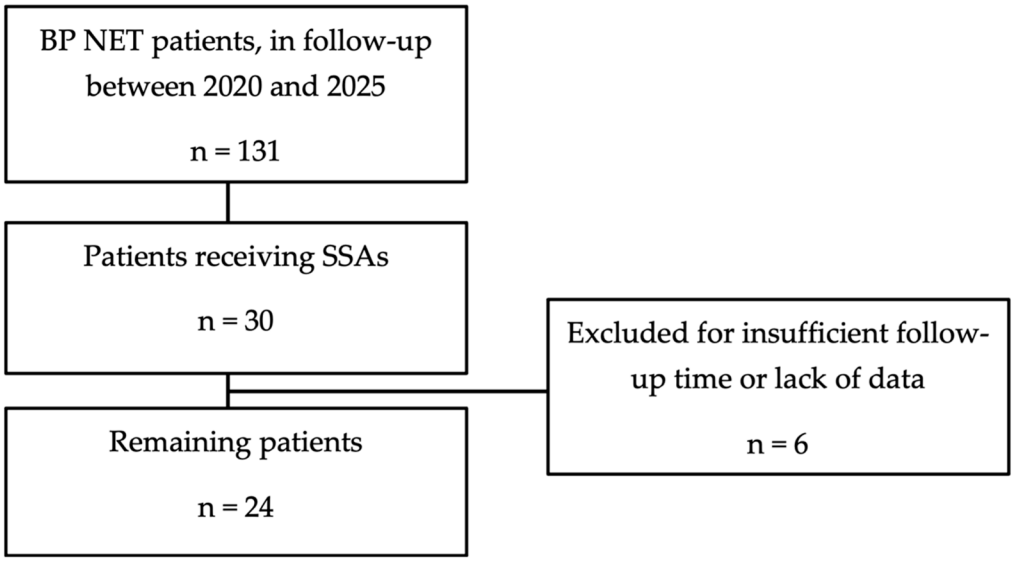


Figure 1. Flow-chart for patients' selection. Overall, 131 patients with BP-NETs were screened, 30 received somatostatin analogues (SSAs), and 24 met the inclusion criteria for the final analysis.

Among the 24 patients considered for the study, 14 (58.3%) were dyslipidemic, and 10 (41.7%) had normal lipid profile. Baseline clinicopathological characteristics are summarized in Table 1. Eleven of the fourteen dyslipidemic patients were receiving statin therapy: one patient was treated with simvastatin, six with atorvastatin, and four with rosuvastatin. In addition, two dyslipidemic patients were receiving ezetimibe, two were taking dietary supplements, and one was receiving both; these treatments were not mutually exclusive with statin therapy. One dyslipidemic patient was not receiving any lipid-lowering treatment.

Women accounted for 70.8% of the study population (7 in the non-dyslipidemic group and 10 in the dyslipidemic group), whereas men represented 29.2% (three and four patients, respectively). The mean age was 66.3 ± 11.28 years in non-dyslipidemic patients and 73.7 ± 7.47 years in dyslipidemic patients ($p > 0.05$). Three patients were affected by clinical or biochemical carcinoid syndrome. The disease was loco-regional in 41.7% cases, whereas distant metastases were present in 58.3%; no significant difference in disease extent was observed between the two subgroups of dyslipidemic and non-dyslipidemic patients ($p = 0.124$). The majority of patients showed low to intermediate proliferative activity, with Ki-67 index ≤ 3% in 7/21 patients (mean value 1.71%, 95% CI: 1.02–2.41) and between

4% and 20% in 13/21 patients (mean value 9.62%, 95% CI: 6.43–12.80). Only one patient showed a Ki-67 index ≥ 21%. Data on Ki-67 index were not available in three patients. Distant metastases were present in 58.3% of cases (Table 1). No major baseline imbalance emerged between dyslipidemic and non-dyslipidemic groups with respect to sex, histology, or stage, although the limited sample size precluded robust subgroup comparisons.

Table 1. Patients' characteristics according to dyslipidemia. Patients were then stratified according to lipid status into non-dyslipidemic and dyslipidemic groups; dyslipidemic patients were further categorized according to ongoing statin therapy. BP-NETs, bronchopulmonary neuroendocrine tumors; SSAs, somatostatin analogues.

Patients' Characteristics	Total (n = 24)	Non-Dyslipidemic (n = 10)	Dyslipidemic (n = 14)	*p*-Value	Dyslipidemic Without Statins (n = 3)	Dyslipidemic with Statins (n = 11)	*p*-Value
Sex, No. (%)							
Male	7 (29.2%)	3	4	1.00	1	3	0.837
Female	17 (70.8%)	7	10		2	8	
Histology, No. (%)							
Typical	13 (54.2%)	5	8	0.917	2	6	0.727
Atypical	7 (29.2%)	3	4		1	3	
NOS	4 (16.7%)	2	2		0	2	
Tumor stage, No. (%) *							
Loco-regional	10 (41.7%)	6	4	0.124	1	8	0.207
Distant metastases	14 (58.3%)	4	10		2	3	
Ki67, No. (%)							
≤3%	7 (29.2%)	4	3	0.556	*	3	
4–20%	13 (54.1%)	6	7		*	7	
≥21%	1 (4%)	0	1		1	0	
Somatostatin analogue, No. (%)							
Octreotide LAR	8 (33.3%)	3	5	0.770	0	5	0.145
Lanreotide	16 (66.6%)	7	9		3	6	

* Data unavailable.

3.1.2. Clinical Outcome

Among the 24 patients treated with SSAs, the median PFS (mPFS) was 22.5 months (95% CI: 18.3–34.0).

The mPFS showed a trend toward longer duration in patients without dyslipidemia compared with those with dyslipidemia (70 months, 95% CI: 3.8–136.1 vs. 36 months, 95% CI: 15.4–56.5, $p = 0.08$) (Figure 2).

A similar trend was observed between patients receiving statin therapy and those without statins (mPFS 36 months, 95% CI 19.7–52.3 vs. 18 months, 95% CI 0.0–42.0, $p = 0.30$), (Figure 2). Although these differences did not reach statistical significance, likely because of the limited sample size, the observed trends were consistent with the hypothesis that dyslipidemia may be associated with a less favorable disease course, whereas statin exposure may have a protective effect in this setting.

3.2. In Vitro Investigations

3.2.1. Combined Lanreotide–Atorvastatin Treatment Reduces NCI-H727 Cell Viability

The effects of combined lanreotide and atorvastatin treatment (hereafter referred to as ato and lan) on cell viability were assessed using the MTT assay. NCI-H727 cells were treated with ato (0 or 10 μM), lan (0, 5, or 10 μM), or their combination. After 48 and 72 h, all treatments, both single agents and combinations, significantly reduced cell viability compared with the control (Figure 3a,b, Supplementary Table S1). However, the combination of ato and lan decreased cell viability more strongly than lan alone. At 48 h, ato + lan5 and ato + lan10 induced a 0.7 and 0.6 log2 fold reduction in cell viability, respectively, compared to lan alone ($p = 0.014$ and $p = 0.043$). This effect was even more evident at 72 h, with reductions of 2.2 and 1.7 log2 fold, respectively ($p = 0.019$ and $p = 0.034$). Detailed

quantitative values for each treatment condition are reported in Supplementary Table S1. Overall, these findings indicate that the combination of atorvastatin and lanreotide reduces cell viability in a dose- and time-dependent manner. To further investigate the mechanisms underlying this effect, subsequent analyses focused on cell proliferation, cell death, and cellular metabolic activity.

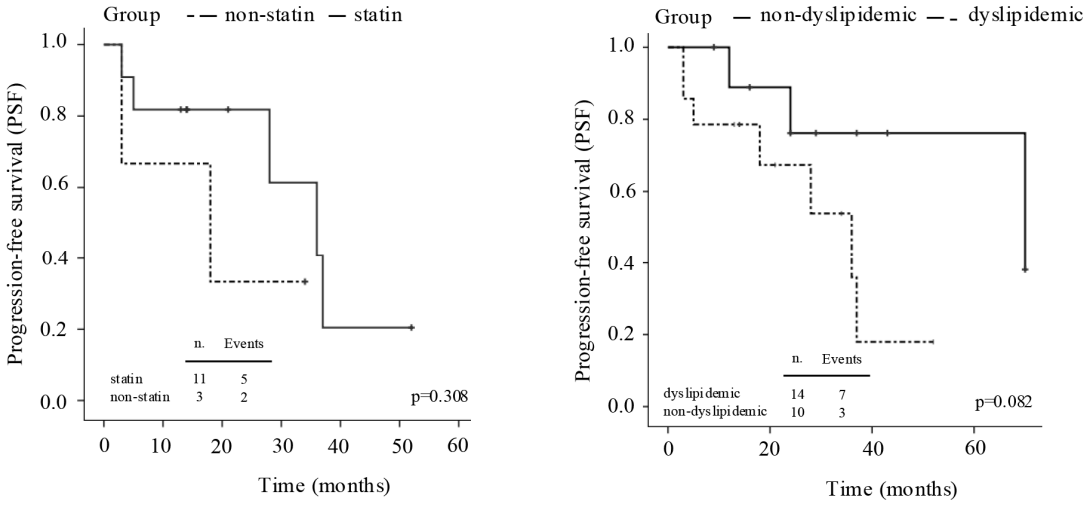


Figure 2. Kaplan–Meier analysis of progression-free survival (PFS) in patients with advanced BP-NETs treated with SSAs. (**a**) PFS according to the presence or absence of dyslipidemia. (**b**) PFS in dyslipidemic patients according to statin therapy (statin-treated vs. not statin-treated). Median PFS values, 95% confidence intervals, and *p* values are reported in the main text. PFS was calculated from the start of SSA treatment to radiological progression or last follow-up. BP-NETs, bronchopulmonary neuroendocrine tumors; SSAs, somatostatin analogues.

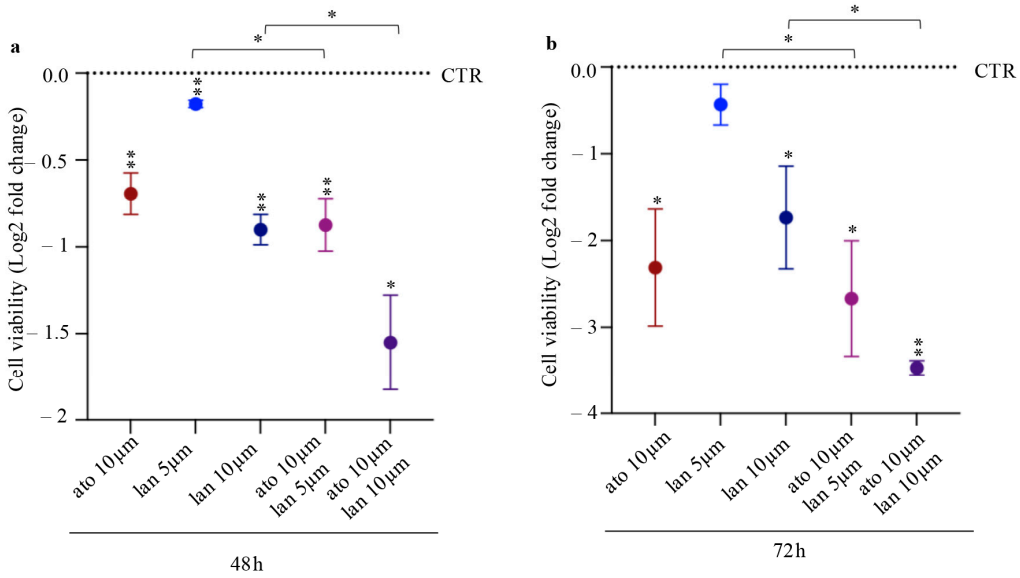


Figure 3. Combined lanreotide–atorvastatin treatment reduces NCI-H727 cell viability. NCI-H727 cells were treated with atorvastatin (ATO, 10 µM), lanreotide (LAN, 5 or 10 µM), or their combination for 48 h (**a**) and 72 h (**b**), and cell viability was assessed by MTT assay. Results are expressed as log2 fold change relative to vehicle-treated control (DMSO, horizontal dashed line = 0). Data are presented as mean ± SD of three independent biological replicates. Statistical significance is indicated in the graphs (* $0.01 < p < 0.05$; ** $p < 0.01$).

3.2.2. Combined Lanreotide–Atorvastatin Treatment Reduces NCI-H727 Cell Proliferation

NCI-H727 cell proliferation was evaluated using Ki-67 immunofluorescence (IF) and EdU incorporation assay. While Ki-67 staining did not show major differences after 48 h (Figure 4a; Supplementary Figure S1), EdU incorporation revealed a significant reduction in S-phase entry in cells treated with the combination compared with lan alone and with controls. Specifically, EdU-positive cells were reduced by approximately 35% with ato + lan 5 μM (p = 0.002) and by 24% with ato + lan 10 μM (p < 0.001), compared with SSA alone (Figure 4a,b). By contrast, lan alone was associated with a relative increase in EdU incorporation, suggesting a possible compensatory proliferative response under single-agent exposure. These findings indicate that the combination treatment more effectively suppresses proliferative activity than SSA treatment alone (Figure 4a,b).

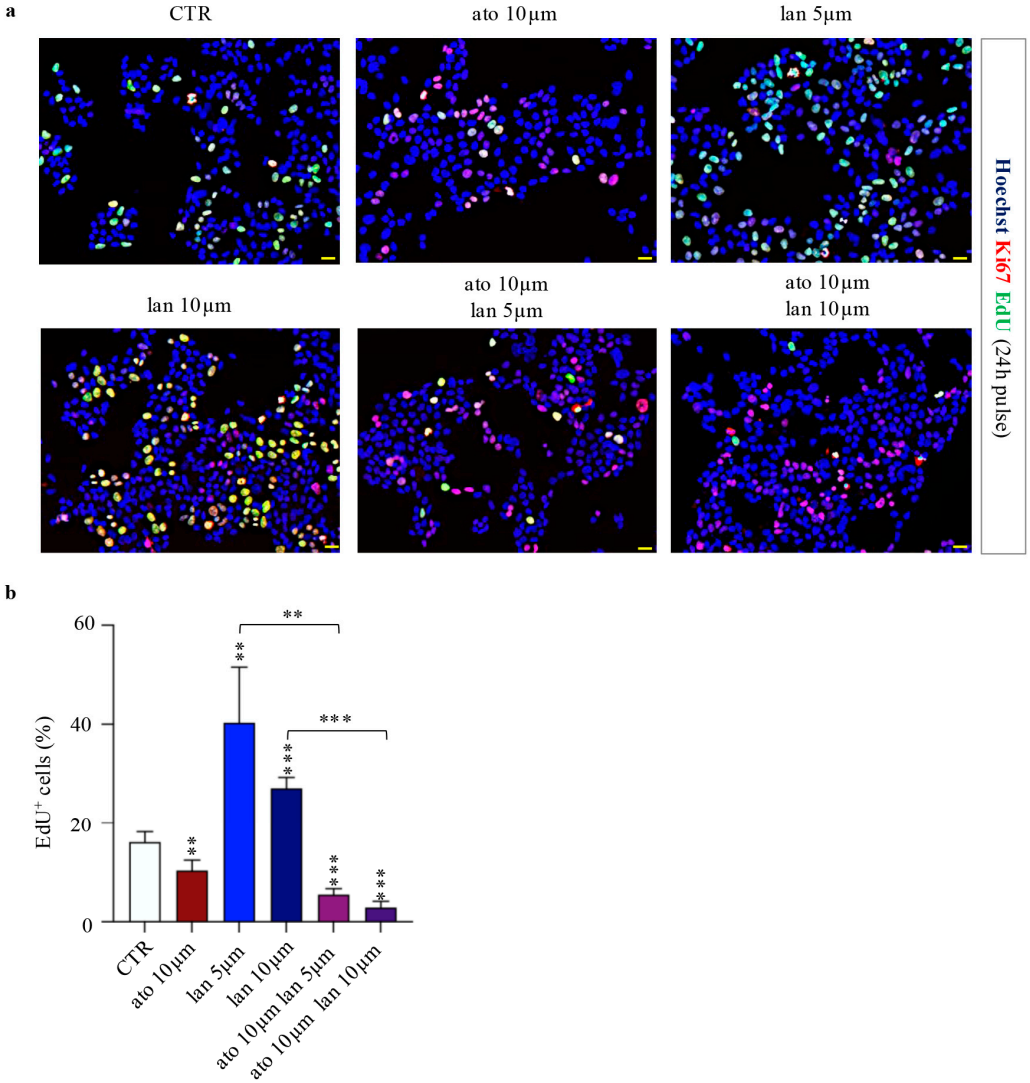


Figure 4. Combined lanreotide–atorvastatin treatment reduces NCI-H727 cell proliferation. (**a**) Representative immunofluorescence images of NCI-H727 cells treated for 48 h with atorvastatin (ATO, 10 μM), lanreotide (LAN, 5 or 10 μM), or their combination. Ki-67 is shown in red, EdU incorporation in green, and nuclei are counterstained with Hoechst in blue. EdU was added during the last 24 h of treatment. Scale bar: 20 μm. (**b**) Quantification of EdU-positive cells, expressed as percentage of total cells. Data are presented as mean ± SD of independent experimental replicates. Statistical significance is indicated in the graphs (** p < 0.01; *** p < 0.001).

3.2.3. Combined Lanreotide–Atorvastatin Treatment Increases NCI-H727 Cell Death, Apoptosis, and DNA Damage

To investigate cytotoxicity in NCI-H727 cells, LIVE/DEAD staining was performed after 48 h of treatment. The combination of lan and ato produced a dose-dependent increase in dead cells, exceeding the effect of either single treatment. In particular, compared with a single SSA treatment, the combination induced an approximately 2-fold increase in dead cells with ato + lan 5 µM ($p = 0.047$) and approximately 10-fold increase with ato + lan 10 µM ($p = 0.0002$) (Figure 5a,b). Western blot analysis further showed increased cleaved caspase-3 expression in combination-treated cells, supporting activation of apoptotic pathways. In parallel, phospho-γH2AX levels were increased, suggesting treatment-associated DNA damage or cellular stress. Overall, these results indicate that combined lan-ato exposure enhances cell death and apoptosis more effectively than either treatment alone (Figure 5c).

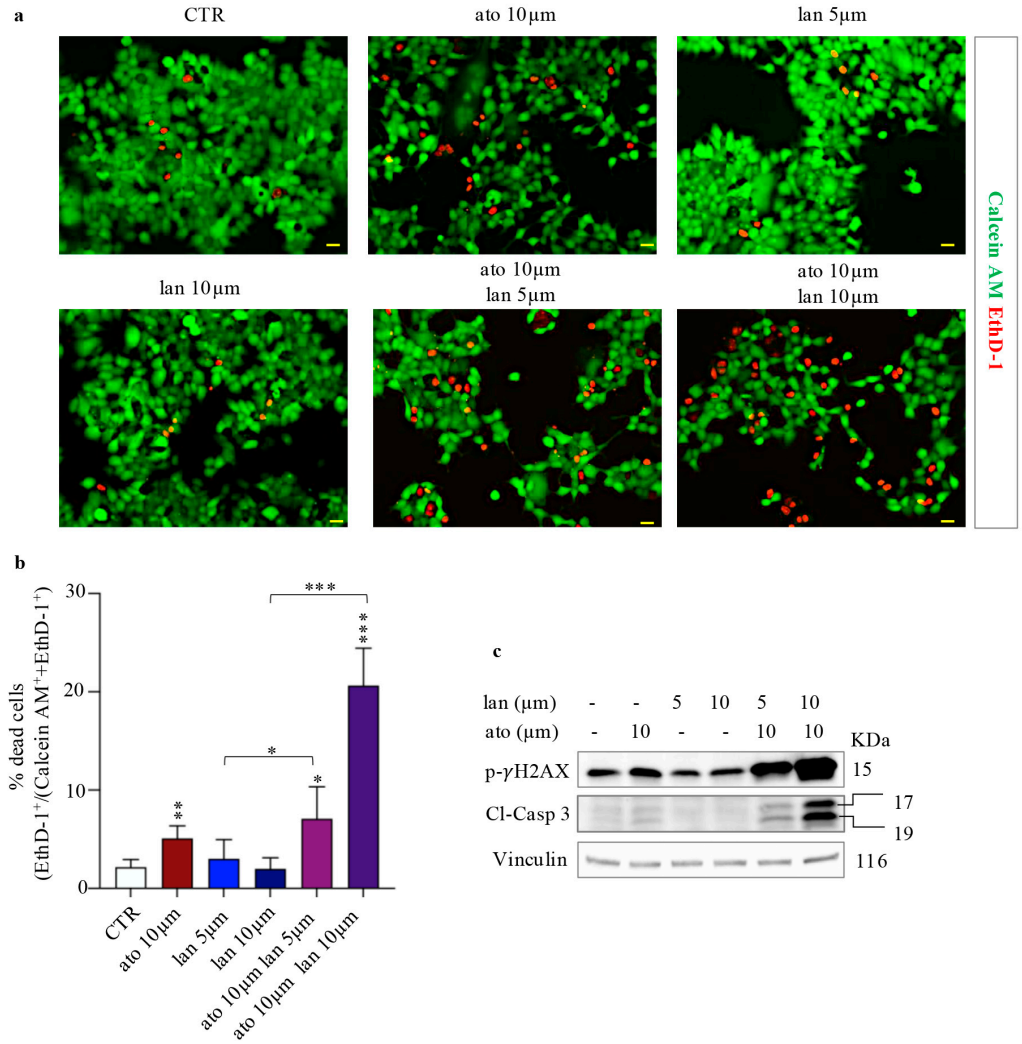


Figure 5. Combined lanreotide–atorvastatin treatment increases NCI-H727 cell death, apoptosis, and DNA damage. (**a**) Representative LIVE/DEAD fluorescence images of NCI-H727 cells treated for 48 h with atorvastatin (ATO, 10 µM), lanreotide (LAN, 5 or 10 µM), or their combination. Live cells are stained with Calcein AM (green), whereas dead cells are stained with EthD-1 (red). Scale bar: 20 µm. (**b**) Quantification of dead cells, expressed as the percentage of EthD-1-positive cells over total cells. Data are presented as mean ± SD of independent experimental replicates. Statistical significance is indicated in the graphs (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). (**c**) Western blot analysis of cleaved Caspase-3 and p-γH2AX in NCI-H727 cells treated under the same conditions; Vinculin was used as loading control.

3.2.4. Combined Lanreotide–Atorvastatin Treatment Impairs NCI-H727 ATP Production

Cellular ATP production in NCI-H727 cells was evaluated by Seahorse analysis after 48 h of treatment. After incubation, an ATP rate measurement test was performed to quantify ATP production per unit time, distinguishing between the contributions of oxidative phosphorylation and glycolysis. Ato significantly reduced total ATP production compared with control (1660.8 ± 99.9 vs. 1137.2 ± 315.1 pmol/min; $p < 0.001$) (Figure 6a), mainly through a reduction in mitochondrial ATP production (1163.6 ± 41.5 vs. 744.9 ± 220.5 pmol/min; $p < 0.001$) (Figure 6d). In contrast, lan (5 µM) increased total ATP production (1998.5 ± 250.7 pmol/min; $p < 0.001$) (Figure 6a), mainly due to enhanced mitochondrial respiration ($p < 0.001$) (Figure 6d). The combination of ato (10 µM) and lan (5 µM) reduced total ATP production to 938.2 ± 341.1 pmol/min ($p < 0.001$) (Figure 6a), with mitochondrial ATP decreasing to 461.6 ± 241.8 pmol/min ($p < 0.001$) (Figure 6d), consistent with a marked impairment of cellular bioenergetics. Lan (10 µM) did not affect ATP production, and its combination with ato (10 µM) prevented reliable analysis due to extensive cell death. Taken together, these results suggest that impairment of mitochondrial energy metabolism may contribute to the biological effects of ato, particularly when combined with lan.

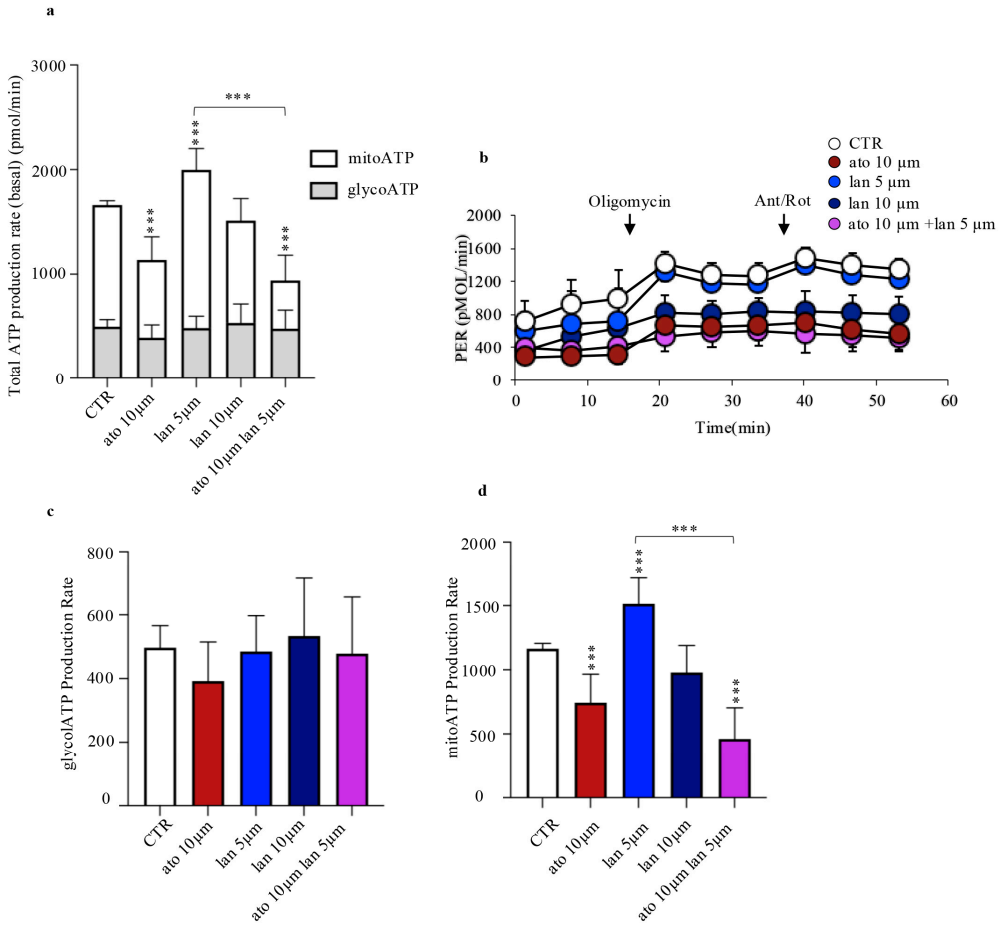


Figure 6. Combined lanreotide–atorvastatin treatment impairs NCI-H727 ATP production. Cells were treated for 48 h with atorvastatin (ATO, 10 µM), lanreotide (LAN, 5 or 10 µM), or their combination, and ATP production was evaluated by Seahorse XF ATP Rate Assay. (**a**) Total ATP production rate, calculated as the sum of mitochondrial and glycolytic ATP production. (**b**) Representative Seahorse assay profile recorded during instrumental acquisition. (**c**) Mitochondrial ATP production rate. (**d**) Glycolytic ATP production rate. All values were normalized to cell viability and are expressed as mean ± SD of three independent biological replicates. Statistical significance is indicated in the graphs (*** $p < 0.001$).

4. Discussion

NETs represent a heterogeneous group of malignancies rapidly increasing in incidence. Although the majority of NETs arise from the gastroenteropancreatic tract, the incidence of bronchopulmonary NETs has also been steadily increasing [2]. The contribution of potential risk factors to NET development, including familial predisposition, smoking, and metabolic disorders, remains a matter of ongoing debate [37].

The treatment of localized NETs is primarily surgical, whereas systemic therapies are usually required in more advanced disease stages. In this context, SSAs play a central role, representing the most widely used therapeutic option for gastroenteropancreatic NETs and, more recently, for the control of tumor growth in BP-NETs expressing somatostatin receptors [38].

Systematic reviews have shown that SSAs not only control hormone-related symptoms in NET patients but also exert antiproliferative activity, slowing tumor growth and stabilizing disease in a subset of patients. In a phase II clinical study, lanreotide demonstrated tumor size stabilization and reduction of biochemical markers in patients with carcinoid tumors, supporting its antitumor potential beyond symptom control [39,40]. Mechanistically, SSAs are known to bind to somatostatin receptors (particularly SSTR2 and SSTR5) and inhibit downstream proliferative pathways such as cyclic AMP, MAPK, and insulin-like growth factor signaling, thereby reducing cell proliferation and promoting apoptosis [39].

Emerging clinical evidence also supports a potential role for statins in NET progression. A recent observational cohort study of patients with gastroenteropancreatic and BP-NETs found that statin use was associated with improved PFS compared to non-users, suggesting an antiproliferative effect of statins in NET patients [25]. These findings are consistent with the growing recognition of dyslipidemia as a relevant factor in oncology, maybe comparable in clinical impact to diabetes mellitus [41,42].

This translational proof-of-concept study combined retrospective clinical observations with in vitro experiments to explore the potential relevance of dyslipidemia and statin therapy in advanced BP-NETs treated with SSAs. Overall, our results are in line with the multicenter study by Faggiano et al. 2025 [25] and further extend these observations by focusing specifically on BP-NETs treated with SSAs as first-line therapy. In particular, our findings suggest that dyslipidemia may be associated with a less favorable disease course, while statin exposure may support the antitumor activity of SSAs. In the clinical cohort, dyslipidemic patients showed a shorter median PFS than non-dyslipidemic patients, and dyslipidemic patients receiving statins showed a numerically longer PFS than those not receiving statins, despite comparable baseline clinicopathological characteristics, including sex distribution and histological subtypes. Although these differences did not reach statistical significance, they are directionally consistent with recent clinical evidence suggesting that lipid metabolism may influence NET behavior and treatment outcome. Given the small sample size and retrospective nature of the study, these data should be interpreted cautiously; however, they provide a rationale for further investigation in larger prospective cohorts. While combinations of SSAs with targeted therapies such as mTOR inhibitors and antiangiogenic agents have been explored in clinical settings with encouraging disease control and acceptable safety profiles, studies focusing on SSA-statin combinations are lacking [22].

Although clinical evidence suggests that SSAs are an effective treatment for NETs, preclinical studies show highly variable results [43–45]. Indeed, in our study, we observed a reduction of cell viability in vitro, accompanied by a controversial effect on cell proliferation, as reported in the literature, as well as on cell death and metabolism [44]. We hypothesize that the observed in vitro single-agent effect may reflect a compensatory survival response of tumor cells. Such adaptive responses have been described in previous studies, indicating

that tumor cells can activate compensatory mechanisms when exposed to conditions of strong cellular stress [46]. However, we also found that concomitant treatment with atorvastatin offers biological support for this clinical signal. In NCI-H727 cells, the combination of lanreotide and atorvastatin reduced cell viability and proliferation, increased cell death, and was associated with apoptotic activation, DNA damage, and impaired mitochondrial ATP production. So, we hypothesize that dual targeting of SSTR signaling and cholesterol biosynthesis pathways may enhance antitumor efficacy in BP-NET models. Statins, including atorvastatin, have been increasingly investigated for their antitumor properties across diverse cancer types [13,16,17]. Beyond lipid lowering, statins inhibit HMG-CoA reductase, thereby reducing the production of mevalonate intermediates required for prenylation of small GTPases such as Ras and Rho, which play central roles in cell proliferation and survival [47,48]. Statins have been shown to reduce proliferation; induce apoptosis; induce oxidative stress, cell cycle arrest, autophagy, modulation of the tumor microenvironment; and inhibit angiogenesis in various tumor models, including lung cancer, suggesting potential applicability in NETs where similar proliferative mechanisms operate [26–31]. These molecular effects are consistent with our observation of decreased viability and increased apoptosis upon combined treatment. The mechanistic basis of these findings was not specifically dissected in the present study, since our main objective was to provide a proof of concept that the combination treatment may exert antiproliferative and pro-apoptotic activity in BP-NETs. Nevertheless, a plausible biological explanation may involve the convergence of SSAs and statins on growth- and survival-related signaling pathways, including MAPK and PI3K/AKT. SSAs are known to inhibit downstream proliferative signaling through somatostatin receptors, while statins impair cholesterol biosynthesis and protein prenylation, thereby affecting small GTPases and related signaling networks. In this context, reduced ATP production, decreased proliferation, and increased apoptosis may represent interconnected consequences of a broader stress response rather than fully independent phenomena. Metabolic studies have shown that some neuroendocrine cells, including BP ones, are particularly susceptible to drugs that affect their primary energy pathways. For example, Safari M et al. demonstrated how some neuroendocrine cell lines, relying on mitochondrial respiration, were sensitive to the combination of NAMPT and HDAC inhibitors [49]. Consistent with these findings, in our study, we demonstrated that BP neuroendocrine cells could be particularly sensitive to drugs that interfere with mitochondrial respiration. Because bronchopulmonary neuroendocrine cells may depend strongly on mitochondrial respiration, disruption of energy homeostasis could contribute to decreased proliferative capacity and increased susceptibility to apoptotic death. Indeed, atorvastatin, both alone and especially in combination with lanreotide, significantly impaired mitochondrial ATP production, which, associated with an increase in cell death, supported the hypothesis of induced oxidative stress. Therefore, although no formal mechanistic experiments were performed, the observed phenotypes are biologically compatible with an integrated antitumor response involving signaling inhibition, metabolic stress, and apoptosis induction.

Several limitations should be acknowledged. First, the retrospective design and limited sample size reduce statistical power and preclude adjustment for potential confounding variables; The limited number of patients was related to the inclusion of only those treated with SSAs, which, however, reduced clinical heterogeneity. Second, the lack of comprehensive clinical data for all patients limited the ability to explore additional prognostic factors. Lastly, the in vitro findings were based on a single cell line model, and the lack of formal drug interaction analysis (e.g., combination index) limits conclusions about the nature (additive vs. synergistic) of the interaction. Third, mechanistic investigations were not included.

Despite these limitations, the study has potential clinical relevance. Both statins and SSAs are already widely used in clinical practice, and the possibility that lipid-lowering therapy may modulate tumor behavior or improve disease control in selected patients with BP-NETs is of considerable translational interest. At present, our data do not support a change in clinical management, but they do support the development of larger prospective studies and dedicated translational investigations to clarify which patients may benefit most from this therapeutic strategy.

5. Conclusions

In conclusion, this proof-of-concept study suggests that dyslipidemia may be associated with a less favorable outcome in advanced BP-NETs treated with SSAs, while statin therapy may be associated with longer PFS among dyslipidemic patients. In parallel, in vitro experiments showed that atorvastatin can support the antitumor activity of lanreotide by reducing proliferation and viability, increasing apoptosis-related cell death and impairing mitochondrial ATP production. Given the established clinical use of both classes of drugs and emerging evidence of their anti-tumor properties, future work should investigate the biological mechanism in more depth in additional NET models and in well-designed clinical trials. Although these observations support the rationale for further investigation of lipid metabolism modulation in BP-NETs, they should be interpreted in light of the exploratory, retrospective, and proof-of-concept nature of the study.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/lipidology3020012/s1, Figure S1: Bar plot showing the percentage of Ki67-positive cells treated for 48 h with ato and lan and their combination at the indicated doses. Data are presented as mean ± SD (*** $p < 0.001$; ** $0.001 < p < 0.01$); Table S1: Table showing the mean ± SD of cell viability expressed as log2 fold change relative to the control following the indicated treatments.

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Abbreviations

The following abbreviations are used in this manuscript:

NETs	Neuroendocrine tumors
GEP	Gastroenteropancreatic
BP	Bronchopulmonary

SSTRs	Linear dichroism
PRRT	Peptide Receptor Radionuclide Therapy
PFS	Progression Free Survival
SSAs	Somatostatin Analogs
ATCC	American Type Culture Collection
OCR	Oxygen Consumption Rates
ECAR	Extracellular Acidification Rates
ATO	Atorvastatin
LAN	Lanreotide

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