



**HAL**  
open science

## Metformin and everolimus in neuroendocrine tumours: A synergic effect?

Lucia Hue-Fontaine, Annie Lemelin, Julien Forestier, Gerald Raverot, Laurent Milot, Philip Robinson, Françoise Borson-Chazot, Catherine Lombard-Bohas, Thomas Walter

### ► To cite this version:

Lucia Hue-Fontaine, Annie Lemelin, Julien Forestier, Gerald Raverot, Laurent Milot, et al.. Metformin and everolimus in neuroendocrine tumours: A synergic effect?. *Clinics and Research in Hepatology and Gastroenterology*, 2020, 44, pp.954 - 960. 10.1016/j.clinre.2020.02.011 . hal-03492643

**HAL Id: hal-03492643**

**<https://hal.science/hal-03492643>**

Submitted on 15 Dec 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution - NonCommercial 4.0 International License

1 **Metformin and everolimus in neuroendocrine tumours: a synergic effect?**

2 Lucia Hue-Fontaine<sup>1</sup>, Annie Lemelin<sup>1</sup>, Julien Forestier<sup>1</sup>, Gerald Raverot<sup>2,5</sup>, Laurent Milot<sup>3</sup>,  
3 Philip Robinson<sup>4</sup>, Françoise Borson-Chazot<sup>2,5</sup>, Catherine Lombard-Bohas<sup>1</sup>, Thomas Walter<sup>1,5</sup>

4  
5 1 - Hospices Civils de Lyon, Hôpital Edouard Herriot, Service d'Oncologie Médicale, Lyon,  
6 France

7 2 - Hospices Civils de Lyon, Hôpital Louis Pradel, Service d'Endocrinologie, Lyon, France

8 3 - Hospices Civils de Lyon, Hôpital Edouard Herriot, Service de Radiologie, Lyon, France

9 4 - Hospices Civils de Lyon, DRCI, Lyon, France

10 5 - University of Lyon, Univ Lyon 1, Lyon, France

11

12 **Corresponding author:**

13 Thomas Walter

14 Pavillon E, UJOMM, Hôpital Edouard Herriot, Hospices Civils de Lyon

15 69437 Lyon Cedex 03, France

16 phone: +33 (0) 4 72 11 73 98

17 fax: +33 (0) 4 72 11 96 91

18 E-mail address: thomas.walter@chu-lyon.fr

19

20 **Short title:** Metformin and everolimus in NET

21 **Key words:** everolimus; neuroendocrine tumors; metformin; prognosis

22

23 **Electronic word count:**

24 - Abstract: 205 words

25 - Manuscript (excluding title page, abstract, references, tables, legends to figures): 1809  
26 words

27 - 2 Figures and 4 Tables

28 - Number of references: 16

29 **ABSTRACT**

30 **Objective:** To explore potential synergy in effectiveness between metformin and everolimus,  
31 2 inhibitors of the mTOR pathway, for neuroendocrine tumours (NET).

32 **Design and Methods:** A cohort of patients with advanced gastroenteropancreatic or lung  
33 NETs treated by everolimus were stratified in to those without diabetes, those with diabetes  
34 and without metformin, and those with diabetes with metformin. The primary endpoint was  
35 the median progression-free survival (PFS).

36 **Results:** A total of 213 patients were included, 165 of which were non-diabetic; among  
37 diabetic patients, 19 were treated with metformin and 29 with others anti-diabetic drugs. No  
38 significant difference in median PFS [95%CI] was found between the three groups: 10.05  
39 months [8.27;11.83] for non-diabetic patients, 15.24 [19.88;49.43] for diabetic w/metformin,  
40 and 9.03 months [4.01;14.06] for diabetic w/o metformin group. In univariate analysis, factors  
41 significantly associated with longer PFS was a functioning NET, a number of metastatic sites  
42 <3, the absence of lung metastasis, and an uptake on Octreoscan<sup>®</sup>, but not the absence of  
43 metformin use; only uptake on Octreoscan<sup>®</sup> remained significant in multivariate analysis.

44 **Conclusions:** In contrast with the literature, we did not find a synergy between everolimus  
45 and metformin in NET. Prospective studies are underway to improve the comprehension of  
46 the potential synergy regarding population and tumour type.

## 47 **INTRODUCTION**

48 Everolimus, an inhibitor the mammalian target of rapamycin (mTOR), is an approved targeted  
49 therapy in gastroenteropancreatic (GEP) and lung neuroendocrine tumours (NET) since the  
50 RADIANT-2, -3, and -4 studies (1-3). In parallel there it is reported that metformin, the most  
51 commonly prescribed drug for type 2 diabetes mellitus (T2DM), has an anti-proliferative  
52 property (4, 5). This may be related to the known activities of metformin which are to activate  
53 AMP-activated protein kinase (AMPK), both directly and indirectly via inhibitor of  
54 mitochondrial complex 1 and the resulting elevation of AMP/ATP ratio, which then inhibits  
55 the mTOR pathway, and the direct inhibition of mTORC1 (6, 7).

56 Pusceddu et al. have recently reported that metformin use was associated with longer  
57 progression-free survival (PFS) in patients with diabetes and pancreatic NETs receiving  
58 everolimus (8). However, it is reported that the anti-proliferative effect of metformin may  
59 vary according to the origin of cancer (9, 10). We therefore further explored this synergy in  
60 pancreas NET primaries, but also in gastrointestinal tract and lung primaries.

61

## 62 **PATIENTS AND METHODS**

### 63 *Patients*

64 Patients were retrospectively selected from the neuroendocrine neoplasm (NEN) database of  
65 the Hospices Civils de Lyon (Lyon, France), a centre of excellence of the European  
66 NeuroEndocrine Tumours Society (ENETS). We included all consecutive patients with  
67 advanced/metastatic GEP or lung NETs, treated with everolimus that was initiated between  
68 July 2006 and May 2019. Patients received everolimus at the dose of 10 mg with the  
69 exception of those with comorbidities or side effects requiring dose adjustment. Patients could  
70 continue concurrent somatostatin analogs in case of functioning NET, but no other anti-  
71 tumour treatments. NETs were classified using the most recent WHO classification available:

72 GEP-NETs were re-categorized using the last WHO classification if needed; either as NET  
73 G1, NET G2, NET G3, or undefined NET (when the diagnosis was made without tumour  
74 grade or Ki67 index; often before 2000) (11); the WHO 2015 was used for lung NETs that  
75 were defined as typical carcinoid, atypical carcinoid, or undefined carcinoid (if data not  
76 available or in the absence of primary tumour specimen) (12). Patients with poorly  
77 differentiated neuroendocrine carcinoma or mixed neuroendocrine-nonneuroendocrine  
78 neoplasms (MiNEN) were not included. Patients treated with everolimus for <1 month,  
79 patients receiving everolimus a second time, and patients without information on the presence  
80 of diabetes were excluded.

81 Patient records were reviewed and the population divided according to the presence of  
82 diabetes; patients were considered diabetic at everolimus initiation if they had diabetes at  
83 baseline (diagnosis reported in medical history or under anti-diabetic drugs, elevated glycated  
84 haemoglobin with a threshold of  $\geq 6.5\%$ , fasting plasma glucose  $\geq 126$  mg/dl or 7.0 mmol/l  
85 (13). Patients with diabetes diagnosed after everolimus treatment period or resolved  
86 gestational diabetes were not included in the diabetic group; those who developed diabetes  
87 under everolimus were considered diabetics if they required a pharmacological management  
88 according to standard clinical practice. The diabetic patients were further divided into those  
89 taking metformin and those not taking metformin during the everolimus treatment period.  
90 Patients under metformin <1 month during the everolimus treatment period were not  
91 including in the metformin group (patients who developed diabetes requiring medication in  
92 the last month of the everolimus treatment period or patients who discontinued metformin  
93 within the first month of the everolimus treatment period).

94

95 **Effectiveness of everolimus**

96 The effectiveness of everolimus was assessed by the response rate according to RECIST  
97 criteria (14), PFS and overall survival (OS).

98

### 99 *Statistical Analysis*

100 Categorical variables are expressed as number (percentage) and compared using the Chi-  
101 squared test or the Fisher's exact test as appropriate. Continuous variables are presented as  
102 median [Interquartile range, IQR], and were compared using the Mann-Whitney U test. The  
103 primary end point was the PFS. Survival was estimated using the Kaplan-Meier method; PFS  
104 was calculated from the date of everolimus initiation to that of first progression according to  
105 RECIST criteria or the beginning of a new anti-tumour treatment or disease-related death, and  
106 OS to the date of disease-related death or last follow-up. For PFS, deaths not related to  
107 disease progression were not considered as an event. Median and 5-year survival rates were  
108 estimated. Univariate analyses were performed using the Log-rank test for each variable of  
109 interest. For continuous parameters, the threshold was defined as the median value of the  
110 population. Multivariate analyses using a Cox proportional hazards regression model were  
111 performed to identify factors independently associated with prognosis. All significant factors  
112 from the univariate analysis (Log-rank p-value <0.10) were included in the multivariate  
113 analyses; a p-value of <0.05 was considered statistically significant. The results from the  
114 survival analyses are presented with the effect estimates, hazard ratios (HR), and 95%  
115 confidence interval (CI). All statistical analyses were performed using IBM-SPSS version 21.  
116 Pusceddu et al. found a median PFS of 12 months in the non-metformin group and 44 months  
117 in the metformin group, which correspond to HR of 0.28 (8). However, that the present study  
118 would be positive if the HR between groups <0.65 for the primary endpoint (PFS).

119

### 120 *Ethics*

121 This study was conducted according to the World Medical Association Declaration of  
122 Helsinki. The database was approved by both the medical ethics research committee and the  
123 national data protection commission (*Commission nationale de l'informatique et des libertés*,  
124 CNIL) on 6 November 2015 (n°15-111). A consent has been obtained from each patient or  
125 subject after full explanation of the purpose and nature of all procedures used.

126

## 127 **RESULTS**

### 128 *Patients*

129 A total of 230 patients with advanced/metastatic GEP or lung NETs treated with everolimus  
130 were screened, and 213 were included: 19 diabetic patients taking metformin during treatment  
131 with everolimus (diabetic w/metformin group), 29 diabetic patients not taking metformin  
132 (diabetic w/o metformin group), and 165 non-diabetic patients (Fig. 1). Forty-six percent of  
133 patients had a duodenopancreatic NET, 52% were non-functioning, and the median Ki67 was  
134 9%. There was no significant difference in these variables for according to whether or not  
135 patients were treated metformin (Table 1). In the total population, 132 patients (62%)  
136 underwent surgery for their primary tumour before everolimus. Also, 102 patients (48%)  
137 underwent  $\geq 1$  locoregional treatment before everolimus, mainly surgery for metastases (26%)  
138 and/or a liver embolization (28%). Among the total population, 134 (63%) were treated with  
139 somatostatin analogs and/or chemotherapy for 141 patients (66%), prior to everolimus  
140 initiation. There was no significant difference in these variables for according to whether or  
141 not patients were treated metformin (Table 2).

142

### 143 *Effectiveness of everolimus*

144 The median [IQR] duration of everolimus treatment was 4.8 [2.3-13.6] months and was  
145 discontinued most frequently because of progressive disease (58%) or toxicity (31%). The

146 objective response rate was 5%, the median PFS 10.1 (95% CI [8.7; 11.5]) months, and the  
147 median OS was 33.4 (95% CI [26.3; 40.5]) months (Table 3).

148 For the diabetic w/ metformin group the median [95% CI] PFS was 15.2 [9.1; 21.3] months,  
149 for the diabetic w/o metformin group this was 9.0 [4.1; 14.1] months, and for the non-diabetic  
150 group 10.1 [8.3; 11.8] months. Despite of a trend in favour of the metformin group, the study  
151 is negative on its primary end-point (HR>0.65), with no significant difference between  
152 metformin group versus non-metformin group in terms of PFS (HR 0.87, 95% CI [0.54; 1.39],  
153 p=0.55; Fig. 2a). Factors associated with longer PFS under everolimus in univariate analysis  
154 were a functioning NET, a number of metastatic sites <3, the absence of lung metastasis, and  
155 an uptake on Octreoscan<sup>®</sup>. After multivariate analysis, an uptake on Octreoscan<sup>®</sup> remained  
156 significantly associated with longer PFS under everolimus (Table 4). The median OS was  
157 33.4 (95% CI [26.3; 40.5]) months, and there was no significant difference between groups  
158 with and without metformin (Table 3 and Fig 2b).

159

## 160 **DISCUSSION**

161 The present study did not find a significant association for a longer median PFS in patients  
162 receiving metformin plus everolimus compared to everolimus alone. This contrasts to the  
163 study performed in a more selected population that first reported the synergic effect of  
164 metformin-everolimus in diabetic patients treated with metformin (median PFS: 43.7 months,  
165 95% CI [26.4; 61.9]) in comparison to diabetics without metformin (median PFS: 15.6  
166 months, 95% CI [13.0; 22.7]), and non-diabetic patients (median PFS: 12.1 months, 95% CI  
167 [9.6; 16.7]) (8). It is of note, however, that the median PFS herein was more close to that  
168 found in three pivotal randomized studies that reported the efficacy of everolimus in GEP and  
169 lung NET (1-3).



170 There are several aspects that may have contributed to the lack of synergy found herein.  
171 Firstly, Pusceddu *et al.* found a positive association between metformin use and everolimus in  
172 pancreatic NET patients (8) while we included a wide range of primary NET locations. The  
173 synergic effect of metformin-everolimus combination could therefore be present only in  
174 pancreatic NET, but we did not include a sufficient number of patients under metformin with  
175 a pancreatic NET to perform subgroup analysis that would have allowed to investigate this  
176 point. Secondly, this may be explained by the fact that the proportion of diabetic patients in  
177 the population studied was lower than that studied by Pusceddu *et al.*, even in patients with  
178 pancreatic NET (8). This was not due to the definition of diabetic patients, which were the  
179 same, and the present study was sufficiently powered to identify the effect size reported by  
180 Pusceddu *et al.* (8), even with the low number of patients under metformin-everolimus herein.  
181 Thirdly, we were not able to retrospectively assess the duration and the dosage of metformin.  
182 We may speculate that high doses of metformin are needed to obtain this synergy. However,  
183 authors reported an anti-proliferative effect of metformin for a relatively low dose of 250-500  
184 mg (15).

185 Although the study is negative, there is a rationale for the use of metformin plus targeted  
186 therapy. Metformin is a safe and affordable drug and the plurality of its mechanisms of action  
187 does strongly suggest a potential application in the field of oncology. The present study also  
188 provides some reassuring elements about tolerance in combining metformin with everolimus.  
189 One study found a poor clinical tolerance exhorting to plan an adaptative dose in case of  
190 combination (16). In contrast, we did not find a significant difference in the frequency of  
191 discontinuation because of toxicity between the diabetic w/metformin and w/o metformin  
192 groups. Further prospective studies are warranted to assess in which tumour type and with  
193 which drug, this combination with metformin could be interesting. For instance, recently, a  
194 randomized phase 2 study in lung adenocarcinoma found a positive association between

195 metformin and epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs);  
196 the median PFS was significantly longer in the EGFR-TKI group of patients receiving  
197 metformin (13.1, 95% CI [9.8; 16.3]) than in patients not receiving metformin (9.9, 95% CI  
198 [7.5; 12.2] months; hazard ratio 0.60, 95% CI [0.40-0.94], p=0.03) (5).

199 In conclusion, we did not find a significantly better PFS under everolimus in patients taking  
200 metformin. Prospective studies are underway to improve the comprehension of the potential  
201 synergic effect of everolimus-metformin both in terms of population and tumour type.

202

### 203 **Declaration of interest:**

204 TW and CLB: board membership for Novartis, IPSEN and AAA. Other authors: None

205

206 **Funding:** This study did not receive any specific grant from any funding agency in the public  
207 commercial or not-for-profit sector.

208

209 **Acknowledgements:** None

210

### 211 **FIGURES LEGEND**

212 **Figure 1.** Flow chart.

213 **Figure 2.** Progression-free (A) overall survival (B) of patients with metastatic neuroendocrine  
214 tumour treated by everolimus, according to study groups.

215

### 216 **REFERENCES**

217 1. Yao JC, Fazio N, Singh S, Buzzoni R, Carnaghi C, Wolin E, et al. Everolimus for the  
218 treatment of advanced, non-functional neuroendocrine tumours of the lung or gastrointestinal

- 219 tract (RADIANT-4): a randomised, placebo-controlled, phase 3 study. *Lancet*. 2016 Mar  
220 05;387(10022):968-77.
- 221 2. Pavel ME, Hainsworth JD, Baudin E, Peeters M, Horsch D, Winkler RE, et al.  
222 Everolimus plus octreotide long-acting repeatable for the treatment of advanced  
223 neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised,  
224 placebo-controlled, phase 3 study. *Lancet*. 2011 Dec 10;378(9808):2005-12.
- 225 3. Yao JC, Shah MH, Ito T, Bohas CL, Wolin EM, Van Cutsem E, et al. Everolimus for  
226 advanced pancreatic neuroendocrine tumors. *N Engl J Med*. 2011 Feb 10;364(6):514-23.
- 227 4. Koritzinsky M. Metformin: A Novel Biological Modifier of Tumor Response to  
228 Radiation Therapy. *Int J Radiat Oncol Biol Phys*. 2015 Oct 1;93(2):454-64.
- 229 5. Arrieta O, Barron F, Padilla MS, Aviles-Salas A, Ramirez-Tirado LA, Arguelles  
230 Jimenez MJ, et al. Effect of Metformin Plus Tyrosine Kinase Inhibitors Compared With  
231 Tyrosine Kinase Inhibitors Alone in Patients With Epidermal Growth Factor Receptor-  
232 Mutated Lung Adenocarcinoma: A Phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2019  
233 Sep 5:e192553.
- 234 6. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin.  
235 *Diabetologia*. 2017 Sep;60(9):1577-85.
- 236 7. Laplante M, Sabatini DM. mTOR signaling in growth control and disease. *Cell*. 2012  
237 Apr 13;149(2):274-93.
- 238 8. Pusceddu S, Vernieri C, Di Maio M, Marconcini R, Spada F, Massironi S, et al.  
239 Metformin Use Is Associated With Longer Progression-Free Survival of Patients With  
240 Diabetes and Pancreatic Neuroendocrine Tumors Receiving Everolimus and/or Somatostatin  
241 Analogues. *Gastroenterology*. 2018 Aug;155(2):479-89 e7.
- 242 9. Coyle C, Cafferty FH, Vale C, Langley RE. Metformin as an adjuvant treatment for  
243 cancer: a systematic review and meta-analysis. *Ann Oncol*. 2016 Dec;27(12):2184-95.

- 244 10. Yin M, Zhou J, Gorak EJ, Quddus F. Metformin is associated with survival benefit in  
245 cancer patients with concurrent type 2 diabetes: a systematic review and meta-analysis.  
246 *Oncologist*. 2013;18(12):1248-55.
- 247 11. Rindi G, Klimstra DS, Abedi-Ardekani B, Asa SL, Bosman FT, Brambilla E, et al. A  
248 common classification framework for neuroendocrine neoplasms: an International Agency for  
249 Research on Cancer (IARC) and World Health Organization (WHO) expert consensus  
250 proposal. *Mod Pathol*. 2018 Dec;31(12):1770-86.
- 251 12. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JH, Beasley MB, et al. The  
252 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical  
253 and Radiologic Advances Since the 2004 Classification. *J Thorac Oncol*. 2015  
254 Sep;10(9):1243-60.
- 255 13. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2011 Jan;34 Suppl  
256 1:S62-9.
- 257 14. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New  
258 response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J*  
259 *Cancer*. 2009 Jan;45(2):228-47.
- 260 15. Kinaan M, Ding H, Triggle CR. Metformin: An Old Drug for the Treatment of  
261 Diabetes but a New Drug for the Protection of the Endothelium. *Med Princ Pract*.  
262 2015;24(5):401-15.
- 263 16. Molenaar RJ, van de Venne T, Weterman MJ, Mathot RA, Klumpen HJ, Richel DJ, et  
264 al. A phase Ib study of everolimus combined with metformin for patients with advanced  
265 cancer. *Invest New Drugs*. 2018 Feb;36(1):53-61.

266 **Table 1.** Patient characteristics.

	Total population, n=213	Metformin		p value
		with, n=19	without, n=194	
Median age in years [IQR]	61 [52-68]	63 [52-71]	61 [52-68]	0.06
Female sex, n (%)	107 (50)	8 (42)	99 (51)	0.46
Genetic syndrome*, n (%)	3 (1)	0 (0)	3 (2)	0.82
Primary tumour location, n (%)				0.62
Small intestine	60 (28)	4 (21)	56 (29)	
Duodenum-Pancreas	97 (46)	10 (53)	87 (45)	
Lung	31 (14)	4 (21)	27 (14)	
Other gastrointestinal**	25 (12)	1 (5)	24 (12)	
Functioning tumours, n (%)				0.29
Non-functioning	110 (52)	12 (63)	98 (51)	
Carcinoid syndrome	65 (30)	6 (32)	59 (30)	
Duodenopancreatic hormone release***	38 (18)	1 (5)	37 (19)	
Synchronous metastasis, n (%)	154 (72)	15 (79)	139 (72)	0.71
Median number of metastatic sites [IQR]	2 [1-2]	2 [1-2]	2 [1-2]	0.95
Location of metastatic sites, n (%)				
Liver	198 (93)	19 (100)	179 (92)	0.21
Distant lymph nodes	65 (30)	6 (32)	59 (30)	0.92
Bone	56 (26)	6 (32)	50 (26)	0.58
Peritoneum	35 (16)	3 (16)	32 (16)	0.94
Lung	25 (12)	0 (0)	25 (13)	0.10
Brain	4 (2)	0 (0)	4 (2)	0.53
Other	20 (9)	0 (0)	20 (10)	0.14
Uptake on SRS, n/N (% of patients with SRS)	159/183 (87)	16/17 (94)	143/166 (86)	0.35
WHO classification, n (%)				0.11
NET G1/ typical carcinoid	40 (19)	1 (5)	39 (23)	
NET G2-G3/ atypical carcinoid	146 (68)	16 (84)	130 (77)	
Not otherwise specified NET or carcinoid	27 (13)	2 (10)	25 (13)	
Median Ki67 in percentage [IQR] – 109 patients with available data	9 [4-15]	15 [5-20]	8 [3-15]	0.07

267  
268  
269  
270  
271

\* Multiple endocrine neoplasia type 1 n=1, Tuberous sclerosis complex n=2.

\*\* Other gastrointestinal primaries: stomach n=2, colon n=2, rectum n=6, gallbladder n=1, unknown n=13.

\*\*\* Zollinger-Elison syndrome n=9, Insulinoma n=9, Glucagonoma n=7, vasoactive intestinal peptide (VIPoma) n=5, Parathyroid hormone-related protein (PTHrp) n=5, Cushing n=1, Histamine n=1, growth hormone releasing hormone (GHRH) n=1

Abbreviations: IQR, interquartile range. WHO, World Health Organization; NET, neuroendocrine tumour; G, grade, SRS, somatostatin receptor scintigraphy

272 **Table 2.** Treatments received by patients before the initiation of everolimus.

	Total population, n=213	Metformin		p value
		with, n=19	without, n=194	
Primary tumour resection, n (%)	132 (62)	10 (53)	122 (63)	0.49
Median number of locoregional treatments [IQR]	0 [0-2]	0 [0-1]	0 [0-2]	0.27
≥1 locoregional treatment received before everolimus for metastatic disease, n (%)	102 (48)	6 (32)	96 (49)	0.14
Type of locoregional treatment, n (%)				
Surgery of metastases	56 (26)	3 (16)	53 (27)	0.28
Liver embolization	60 (28)	5 (26)	55 (28)	0.85
Radiofrequency ablation	17 (8)	1 (5)	16 (28)	0.65
Median number of systemic treatments [IQR]	2 [1-3]	2 [1-3]	2 [1-3]	0.85
Type of systemic treatments, n (%)				
Somatostatin analogs	134 (63)	9 (47)	125 (64)	0.14
Chemotherapy	141 (66)	14 (74)	126 (65)	0.72
Oxaliplatin-based chemotherapy	76 (36)	9 (47)	67 (35)	0.27
Temozolomide-based chemotherapy	28 (13)	0 (0)	28 (14)	0.08
Dacarbazine-based chemotherapy	40 (19)	4 (21)	36 (19)	0.79
Streptozotocin-based chemotherapy	37 (17)	4 (21)	33 (17)	0.66
Platin-etoposide chemotherapy	12 (6)	0 (0)	12 (6)	0.26
Other cytotoxic chemotherapy	12 (6)	2 (10)	10 (5)	0.33
Sunitinib	17 (8)	1 (5)	16 (8)	0.65
Peptide receptor radionuclide therapy	12 (6)	1 (5)	11 (6)	0.94
Interferon alpha	35 (16)	5 (26)	30 (16)	0.22

273 Abbreviations: IQR, interquartile range.

274

275 **Table 3.** Characteristics related to everolimus treatment.

276

	Total population, n=213	Metformin		p value
		with, n=19	without, n=194	
Median time in years between metastatic diagnosis and everolimus initiation [IQR]	2.5 [1.3-5.2]	3.1 [1.7-5.2]	2.4 [1.2-5.2]	0.64
Median time in months under treatment [IQR]	4.8 [2.3-13.6]	9.6 [2.9-15.2]	4.7 [2.2-12.9]	0.17
Reason for discontinuation, n (%)				0.64
Progressive disease and death	122 (58)	12 (63)	110 (57)	
Physician choice	17 (8)	0 (0)	17 (9)	
Toxicity	66 (31)	6 (32)	60 (31)	
Unknown	5 (2)	1 (5)	4 (2)	
Best response, n (%)				0.31
Objective response	10 (5)	2 (11)	8 (4)	
Stable disease	136 (64)	13 (68)	123 (63)	
Progressive disease	45 (21)	4 (21)	41 (21)	
Unknown	21 (10)	0 (0)	22 (11)	
Median progression-free survival in months [95% CI]	10.1 [8.7; 11.5]	15.2 [9.1; 21.3]	10.0 [8.4; 11.5]	0.55
Median overall survival in months [95% CI]	33.4 [26.3; 40.5]	34.7 [19.9; 49.4]	33.3 [25.5; 41.0]	0.43

277 Abbreviations: IQR, interquartile range; CI, confidence interval.

278

279 **Table 4.** Factors associated with progression-free survival.

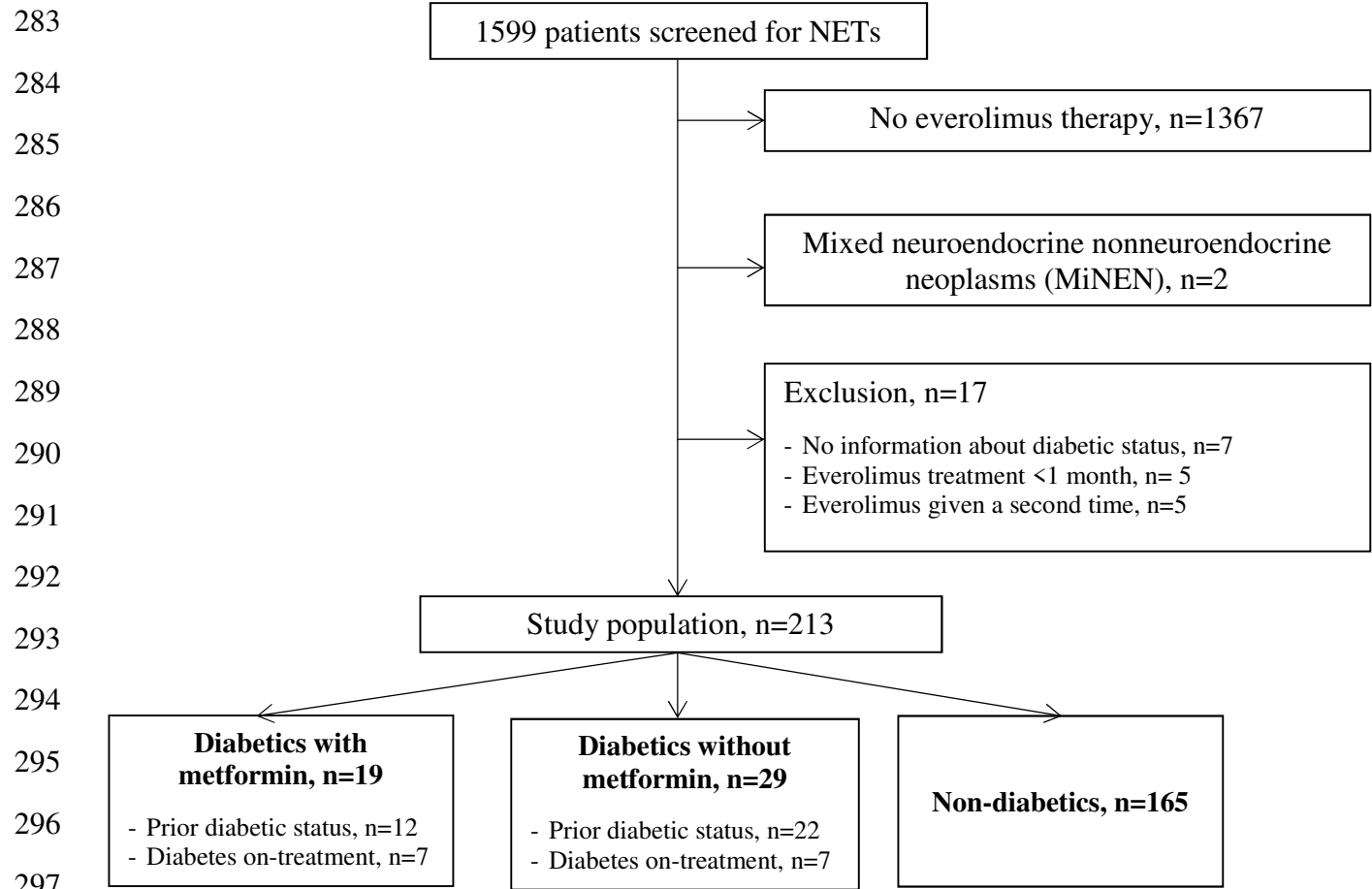
	Univariate analysis			Multivariate analysis		
	Hazard Ratio	[95%CI]	p-value	Hazard Ratio	[95%CI]	p-value
Age $\geq$ 61 vs. <61 years	1.19	[0.89; 1.57]	0.23			
Female vs. male	1.21	[0.90; 1.61]	0.20			
Primary tumour location			0.29			
Small intestine vs. lung	0.65	[0.41; 1.03]	0.07			
Duodenopancreatic vs. lung	0.79	[0.52; 1.21]	0.28			
Other gastrointestinal vs. lung	0.88	[0.51; 1.54]	0.66			
Functioning tumour, no vs. yes	1.40	[1.05; 1.86]	0.02	1.25	[0.91; 1.71]	0.17
Number of metastatic sites, 1-2 vs. $\geq$ 3	0.64	[0.45; 0.91]	0.01	0.94	[0.58; 1.53]	0.81
Liver metastasis, no vs. yes	0.80	[0.45; 1.45]	0.46			
Distant lymph nodes metastasis, no vs. yes	0.94	[0.68; 1.27]	0.67			
Bone metastasis, no vs. yes	0.77	[0.56; 1.07]	0.12			
Peritoneum metastasis, no vs. yes	1.02	[0.70; 1.51]	0.90			
Lung metastasis, no vs. yes	0.50	[0.32; 0.78]	0.002	0.60	[0.34; 1.09]	0.09
Uptake on Octreoscan <sup>®</sup> , yes vs. no	0.57	[0.37; 0.90]	0.01	0.61	[0.38; 0.95]	0.03
NETG1-typical vs. NETG2-3-atypical	0.85	[0.59; 1.22]	0.38			
Ki67 in %, <9 vs. $\geq$ 9	0.81	[0.59; 1.13]	0.22			
Patient under metformin, yes vs. no	0.87	[0.54; 1.39]	0.55			

280 Multivariate analysis effected only with the factors statistically significant (p<0.1) in univariate analysis.

281 Abbreviations: NET, neuroendocrine tumour; G, grade; CI, confidence interval.

282

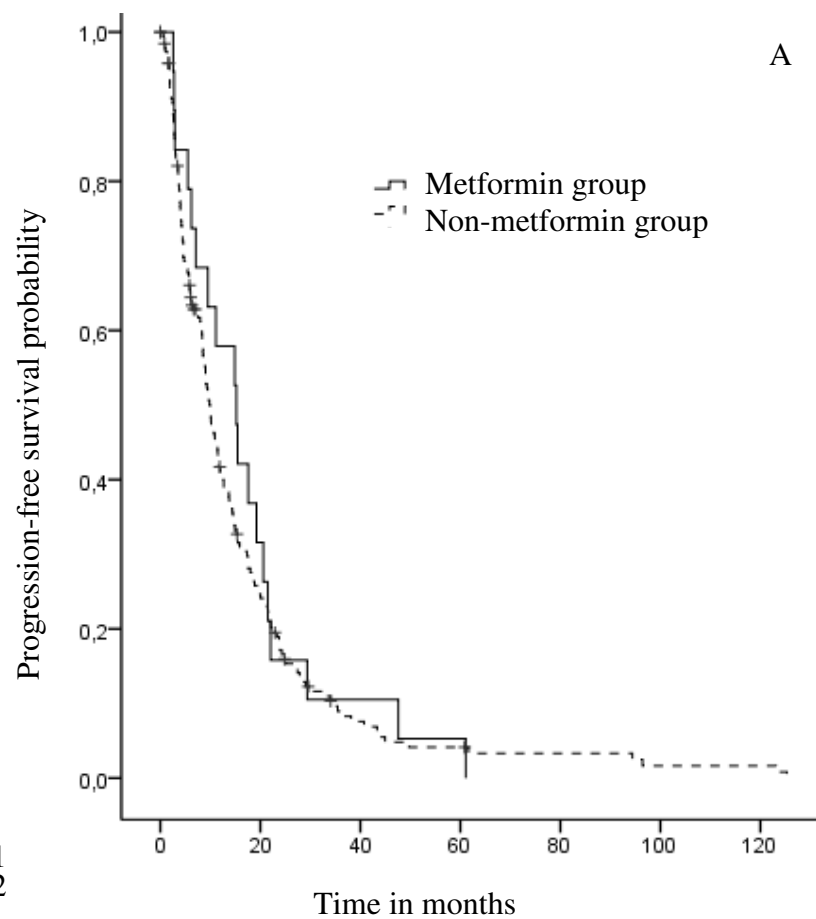




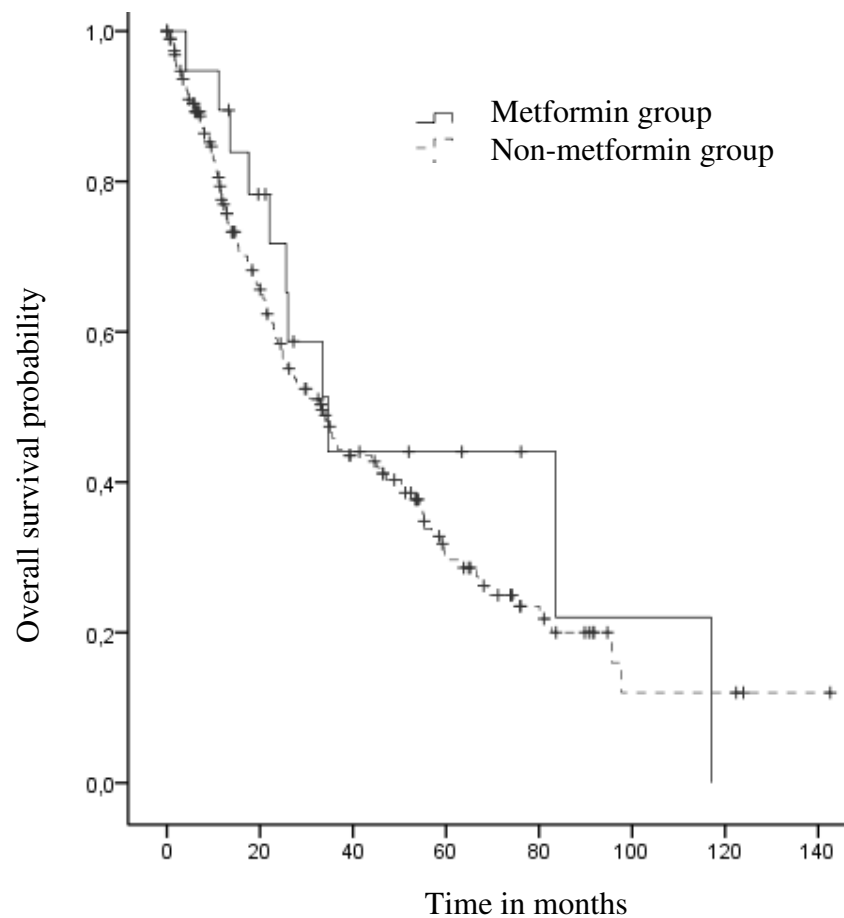
298 **Figure 1.** Flow chart.

299

300



A



B

301

302

303

304 **Figure 2.** Progression-free (A) and overall survival (B) of patients with metastatic neuroendocrine tumour treated by everolimus, according to

305 study groups.