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

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## ABSTRACT

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

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

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

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

## INTRODUCTION

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

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

## PATIENTS AND METHODS

### *Patients*

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

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

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

## **Effectiveness of everolimus**

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

### ***Statistical Analysis***

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

### ***Ethics***

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

## RESULTS

### *Patients*

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

### *Effectiveness of everolimus*

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

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

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

## DISCUSSION

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

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

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

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

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

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

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

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#### **FIGURES LEGEND**

**Figure 1.** Flow chart.

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

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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

\* 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.

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

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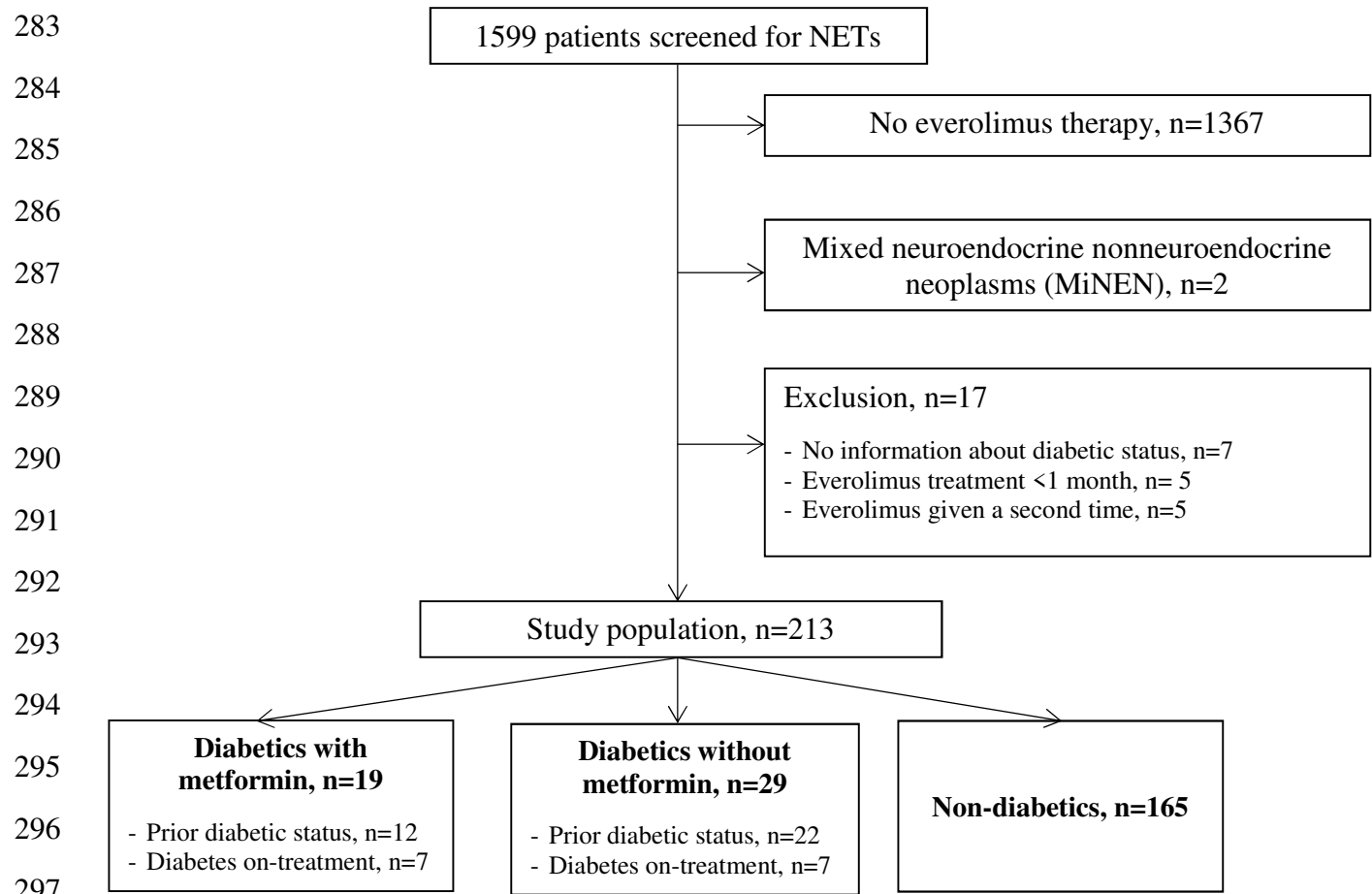
279 **Table 4.** Factors associated with progression-free survival.

	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.

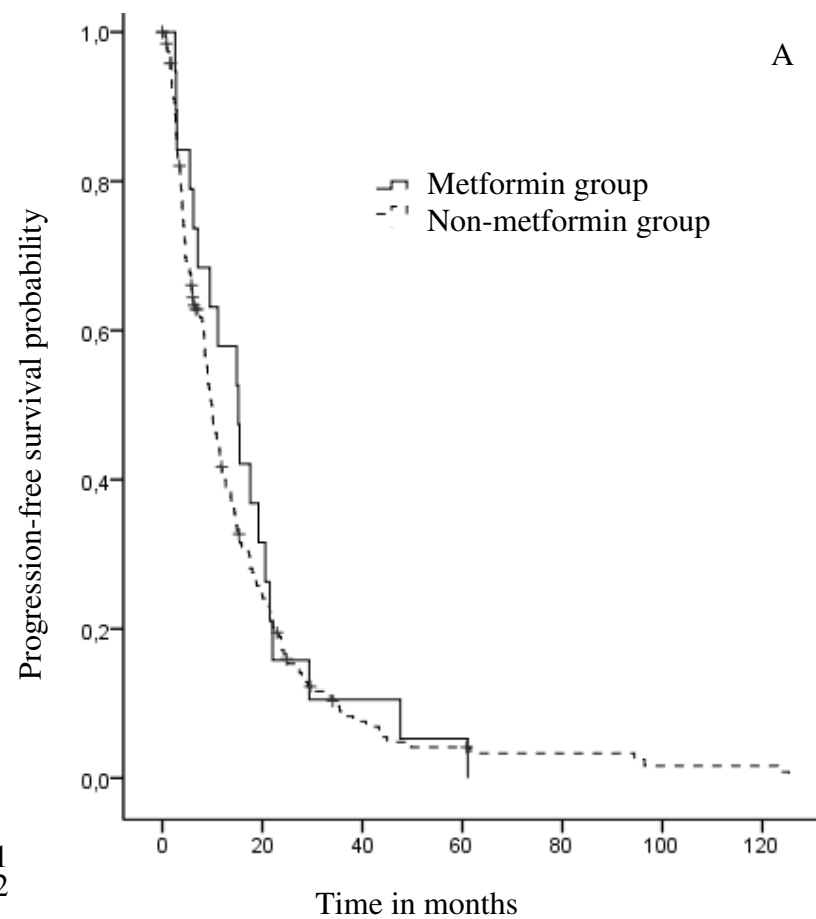
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298 **Figure 1.** Flow chart.

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

305 study groups.

