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Understanding the treatment algorithm of patients with metastatic pancreatic neuroendocrine neoplasms: A single-institution retrospective analysis comparing outcomes of chemotherapy, molecular targeted therapy and peptide receptor radionuclide therapy in 255 patients

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ABSTRACT

Background

The number of therapeutic options for patients with pancreatic neuroendocrine neoplasms (PNEN) has increased, but the optimal therapeutic algorithm has not been defined due to lack of randomised trials comparing different modalities.

Methods

We performed a retrospective study in patients with metastatic PNEN treated with ≥1 line of systemic therapy. The relationship between baseline characteristics, treatment type and time to treatment failure (TTF), time to progression (TTP) and overall survival (OS) was analysed using the Kaplan-Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards model.

Results

Two hundred and fifty-five patients with metastatic PNEN had 491 evaluable lines of therapy. Independent predictors of TTF included treatment type, Ki-67, tumour grade and chromogranin A. To reduce selection bias, a subgroup of 114 patients with grade 2 (G2) metastatic pancreatic neuroendocrine tumours (PNET) was analysed separately. These patients had received 234 lines of treatment (105 chemotherapy, 82 molecular targeted therapy, and 47 peptide receptor radionuclide therapy [PRRT]). In the G2 cohort, TTF and TTP were superior for PRRT compared with both chemotherapy and molecular targeted therapy. OS in the G2 cohort was also superior for those that had received PRRT compared with those that had not (median 84 vs 56 months; HR 0.55, 95%CI 0.31-0.98, p=0.04).

Conclusions

This study suggests that PRRT is associated with superior clinical outcomes relative to other systemic therapies for G2 metastatic PNET. Prospective studies are required to confirm these observations.

INTRODUCTION

Pancreatic neuroendocrine neoplasms (PNEN) are rare and account for 1 to 2% of all pancreatic tumours [1–3]. They have an incidence of ≤1 case per 100,000 persons per year [4,5]; however, their prevalence is likely to be higher given the relatively long patient survival compared with other malignancies. At presentation, 55-75% of patients have unresectable or metastatic disease [3,5–7]. Furthermore, the majority of patients with node-positive resections will eventually show recurrence [8,9]. Hence, most patients with PNEN will be considered for systemic therapy during the course of their disease.

PNEN are widely heterogeneous in their biological behaviour, and treatment decisions are based on a variety of features including histological grade and morphology, functional status, somatostatin receptor expression and patient factors such as performance status and renal function. Nevertheless, survival has been increasing and this likely reflects an improvement in therapies [5]. Historically, cytotoxic chemotherapy with streptozocin-based regimens has been a standard of care for pancreatic neuroendocrine tumours (PNET) [10–13], but in the past decade, randomised trials in selected patients have demonstrated efficacy for somatostatin analogues [14] and the molecularly targeted agents, sunitinib and everolimus [15,16]. Most recently, peptide receptor radionuclide therapy (PRRT) with ^{177}Lutetium (^{177}Lu)-DOTATATE has been approved for somatostatin receptor-positive gastroenteropancreatic NETs by the US Food and Drug Administration and European Medicines Agency following the phase III NETTER-1 trial published in 2017 [17]. While the NETTER-1 trial exclusively studied patients with metastatic midgut NET, most

other phase II and retrospective series assessing the efficacy and toxicity of ^{177}Lu DOTATATE included both gastrointestinal and pancreatic NET [18–20].

While these phase III trials have expanded the treatment options for metastatic PNET, the optimal sequencing of these therapies remains largely unanswered due to the lack of randomised comparative trials. The ENETS expert consensus guidelines [21,22], recommend first-line therapy with somatostatin analogues in grade 1(G1)/low G2 (Ki-67 <5-10%) non-functional PNET in asymptomatic patients with low tumour burden, followed by molecular targeted therapy or cytotoxic chemotherapy in the second line. For non-functional G2 PNET with higher tumour burden and/or progressive disease or symptoms, first-line cytotoxic chemotherapy is recommended followed by molecular targeted therapy in the second line. PRRT is recommended as a potential third-line treatment option in non-functional, somatostatin receptor-expressing G1/G2 PNET and also as a treatment option in patients with functional tumours and refractory syndrome. These guidelines however were published in 2016 [22] prior to the approval of PRRT, and based on efficacy and toxicity data [20] ^{177}Lu DOTATATE therapy could also potentially be considered in earlier lines of treatment; for example, in the second-line setting in G1/G2 patients with somatostatin receptor positive disease who have progressed on somatostatin analogue therapy. First-line cytotoxic chemotherapy is recommended for patients with metastatic G3 pancreatic neuroendocrine tumours or neuroendocrine carcinomas but PRRT could also be considered in the newly-defined G3 well-differentiated NET subgroup [23], provided there is evidence of sufficient somatostatin receptor expression [24,25].

The increase in available systemic therapies coupled with the wide biological heterogeneity of PNEN has created a challenging treatment landscape. Randomised, comparative trials will be critical to inform the optimal sequencing of therapy and to guide the treatment algorithm. To aid current management decisions, we performed a retrospective study to compare the performance of systemic therapies and determine predictors of treatment response and survival in patients with advanced PNEN, with a focus on the G2 cohort.

METHODS

Population

We retrospectively identified patients with histologically confirmed PNEN and metastatic disease treated with ≥1 line of systemic therapy registered on our institution database between January 1998 and December 2018. All pathology was reviewed centrally; morphology, Ki67 and mitotic index were consistently reported allowing reclassification according to the WHO 2017 PNEN classification [23]. Mixed neuroendocrine neoplasms (i.e. MiNEN) were excluded. Data collected comprised demographics (gender, date of birth, date of histological diagnosis), presentation (presence of hormonal syndrome, previous surgical resection of primary, presence of hepatic metastases at time of diagnosis and at time of first-line systemic therapy, presence of germline mutation, presence of second malignancy), pathology (WHO 2017 grade [23], proliferative indices, immunohistochemistry), biochemistry (chromogranin A measured using a DAKO immunoassay), imaging (computed tomography [CT], magnetic resonance imaging [MRI], somatostatin receptor imaging

[SSRI] including ^{68}Ga DOTATATE PET or octreotide scans) and treatment (lines of therapy, date of commencement, date of treatment failure, reason for treatment failure). A positive ^{68}Ga DOTATATE PET or octreotide scan was defined as disease avidity above background liver.

Treatment and assessment

Treatment lines were included in the analysis of time to treatment failure (TTF) if dates of treatment commencement and treatment failure were identified, and in the analysis of time to progression (TTP) if date of first radiological progression was identified as per RECIST version 1.1 [26] assessed in the multidisciplinary team meeting. Treatment arms included chemotherapy (5-fluorouracil/cisplatin/streptozocin (FCiSt) [27], 5-fluorouracil/carboplatin/streptozocin (FCarboStrep), capecitabine/streptozocin (CapStrep) [10], cisplatin/etoposide (CisEtop), carboplatin/etoposide (CarboEtop), capecitabine/temozolomide (CAPTEM) [28] and 5-fluorouracil/leucovorin/irinotecan (FOLFIRI), molecular targeted therapy (sunitinib, everolimus) and PRRT (^{177}Lu-DOTATATE, ^{90}Y-DOTATATE). ENETS guidelines [22] were generally followed to guide sequencing of treatment however treatment plans were made in the multidisciplinary team meeting according to patient preferences and current evidence base. Patients were followed for disease progression and survival every 3-6 months. Tumour assessment was performed with contrast-enhanced CT or MRI at baseline and then every 3-6 months.

Statistical analysis

Categorical variables were expressed as percentages and compared using the Chi squared test or Fisher exact test. Continuous variables were expressed as median and range or mean and standard deviation and compared with the Kruskal-Wallis test.

Time to treatment failure (TTF), time to progression (TTP) and overall survival (OS) were estimated by the Kaplan-Meier method and comparison of curves was performed using the log-rank test. The continuous variables Ki-67 and age were analysed in quartiles with cut-off points chosen in order to create four groups with approximately equal numbers of events (failures). TTF was defined as time from date of cycle 1 for each line of therapy to date of first radiological progression, treatment cessation due to toxicity or clinical deterioration, or death. Patients without treatment failure were censored at date of last known alive. TTP was defined as time from date of cycle 1 to date of first radiological progression. Outcomes for each treatment were compared irrespective of sequence in which they were given. Overall survival was calculated from date of first identified metastasis to date of death, given the long latency between curative intent surgery and development of recurrent disease in some patients. There was significant biological heterogeneity of the study cohort and we performed a separate analysis on the G2 cohort to minimise the impact of tumour grade on treatment outcomes and to remove the potential bias of treatment selection based on grade.

Univariate and multivariate analyses were performed using the Cox proportional hazards model to determine the relationship between baseline characteristics and TTF, TTP and OS. Variables with a p value <0.1 were included in the multivariate Cox model. Variables with high collinearity (e.g. Ki-67 and grade) were not included in the

same regression model. For all analyses, a p value <0.05 was considered to be statistically significant. All statistical analyses were performed using SAS (version 9.4).

RESULTS

Patients

Three hundred and eleven patients identified as having metastatic PNEN were searched from our institution database. Fifty-six patients were excluded due to pathology other than PNEN or MiNEN, non-pancreas primary, absence of metastases or absence of residual/recurrent disease after resection, no lines of systemic therapy received or inadequate clinical data (Fig. 1). Two hundred and fifty-five patients were included and their characteristics are summarised in Table 1. The median age at diagnosis was 54 years (range 13-82) and the majority of patients were male (60%). One hundred and forty-five (57%) patients had WHO 2017 [23] G2 disease and 48 (19%) patients had functional tumours (most frequently, insulinoma [15 patients], followed by gastrinoma [13 patients]). The majority of patients (71%) had the primary pancreatic tumour *in situ* and the presence of hepatic metastases (94%) at the time of first-line systemic therapy. Chromogranin A was greater than five times normal in 49% of the study cohort and in the 186 patients that had ^{68}Ga DOTATATE PET or octreotide scans, 92% were positive. Fourteen (5%) patients had a germline mutation (9 *MEN1*, 2 *BRCA2*, 1 *NF1*, 1 *VHL*, 1 Tuberous Sclerosis). Nineteen (7%) patients, excluding those with a germline mutation, had a second primary malignancy.

Time to treatment failure

Entire cohort

Two hundred and fifty-five patients had 491 evaluable lines of systemic therapy with a median of 3 (range 1-9) lines of treatment per patient. The majority of patients had somatostatin analogue therapy (104/255; 41%) or chemotherapy (134/255; 53%) in the first-line setting. Across all treatments, overall median TTF was 9 months (95%CI 8-11). Median TTF in the G1 cohort was 15 months compared with 10 months in the G2 cohort, 6 months in the G3 NET cohort and 4 months in the G3 NEC cohort (log-rank p<0.0001). Independent predictors of TTF included Ki-67, tumour grade, treatment type and chromogranin A (Table 2).

Grade 2 cohort

One hundred and fourteen patients with G2 disease had 234 evaluable lines of systemic therapy to determine TTF (105 lines of chemotherapy, 82 lines of molecular targeted therapy and 47 lines of PRRT). There was no significant difference in baseline characteristics including age, gender, mean Ki-67, chromogranin A, presence of hepatic metastases or SSRI positivity between the three treatment arms (Table 3). The majority (80%) of lines of chemotherapy were given in the first or second line. In contrast, molecular targeted therapy (50% of lines) and PRRT (55% of lines) were more frequently given in the third or fourth-line setting.

After a median of 9 months follow-up, 91% of chemotherapy treatments, 88% of molecular targeted therapy treatments and 74% of PRRT treatments had failed (Table 3). In the chemotherapy arm, 91% of treatment failures were due to radiological progression compared with 86% and 68% in the PRRT and molecular targeted therapy arms respectively. The molecular targeted therapy arm had the highest rate of toxicity leading to treatment cessation (22% vs 2% in the chemotherapy arm and 0% in the

PRRT arm). The PRRT arm had the highest rate of treatment failure due to death (5/35, 14%); however, all five of these deaths occurred when PRRT was given in the 5th or 6th line setting and is likely to represent a subcohort of patients with poorer performance status.

Of the G2 cohort, median TTF was 10 months (95%CI 8-12). The independent variables associated with TTF included chromogranin A, treatment type and resection of primary (Table 4). Patients with chromogranin A <5 times normal had prolonged TTF (median 14 vs 9 months, HR 0.71, 95%CI 0.52-0.97, p=0.03). In terms of treatment type, PRRT had prolonged TTF compared with both chemotherapy (median TTF 21 months vs 11 months, HR 0.56, 95%CI 0.34-0.84, p=0.005) and molecular targeted therapy (median TTF 21 months vs 6 months, HR 0.47, 95%CI 0.31-0.72, p=0.0005). Patients that had prior resection of the pancreatic primary also had prolonged TTF in this cohort (median 17 vs 9 months, HR 0.73, 95%CI 0.48-0.99, p=0.04).

A separate analysis was performed on the G2 cohort to estimate TTP (Table 5). Radiological progression was evaluable in 197 lines of therapy (96 lines of chemotherapy, 59 lines of molecular targeted therapy, 42 lines of PRRT). The median TTP was 13 months (95%CI 11-16). The only independent predictor of TTP was treatment type. Similar to TTF, PRRT had prolonged TTP compared with both chemotherapy (median TTP 24 months vs 12 months, HR 0.46, 95%CI 0.29-0.73, p=0.0009; Fig. 2) and molecular targeted therapy (median TTP 24 months vs 12 months, HR 0.59, 95%CI 0.35-0.98, p=0.04; Fig. 2).

Overall survival

Entire cohort (n=255)

After a median follow-up of 40 months, the median overall survival of the entire cohort was 59 months (95%CI 45-72). The 5-year and 10-year survival rates were 47% and 29% respectively. Based on tumour grade, median overall survival was 97 months in the G1 cohort, 77 months in the G2 cohort, 20 months in the G3 NET cohort and 19 months in the G3 NEC cohort. Variables that were independently associated with poorer overall survival included older age (>63 years), high tumour grade, high Ki-67, chromogranin A ≥5 times normal, presence of hepatic metastases at diagnosis and absence of avidity on SSRI (Table 6).

Grade 2 cohort (n=114)

Of the G2 cohort, 51 (45%) patients received a treatment sequence that included PRRT compared to 63 (55%) patients that did not. Patients that received a treatment sequence that included PRRT had improved overall survival (median 84 vs 56 months, HR 0.55, 95%CI 0.31-0.98, p=0.04) (Table 7 and Fig. 3a). Other independent predictors of survival in the G2 cohort included chromogranin A (CgA <5x normal vs ≥5x normal; median OS 121 vs 60 months, HR 0.47, 95%CI 0.24-0.92, p=0.03), number of lines of therapy received per patient (1 or 2 lines of therapy vs 5 or more lines of therapy; median OS 64 months vs 97 months, HR 0.38 95%CI 0.15-0.97, p=0.04; Fig. 3b) and Ki-67 (Ki-67 15-20% vs Ki-67 3-4%; median OS 37 months vs 97 months, HR 3.53, 95%CI 1.30-9.59, p=0.01 and Ki67 5-9% vs 3-4%; median OS 60 months vs 97 months, HR 3.17 (1.14-8.79), p=0.03). Treatment sequence and number of lines of therapy were collinear and were handled separately in the regression analysis.

DISCUSSION

This single institution, retrospective study of 255 patients with metastatic PNEN provides significant insight into the predictors of treatment response and outcomes of chemotherapy, molecular targeted therapy and PRRT administered in a real-world setting. The separate analysis of the G2 cohort is of clinical interest given its prevalence, biological heterogeneity and broad treatment options.

The overall characteristics of the study population (Table 1) including male predominance, diagnosis in the sixth decade of life and up to 20% functional tumours, with the most common functional types being insulinoma and gastrinoma, are representative of PNEN data previously reported in the literature [7,21,29,30]. Of the entire cohort, 186 (73%) patients had SSRI performed, of which 92% were positive. The most frequent WHO tumour grade [23] in our study population, was G2 (57%). The newly defined well-differentiated G3 NET cohort, which has little descriptive data in the literature to date, accounted for almost 20% of our study cohort and 25 out of 32 (78%) G3 NET patients had SSRI-positive disease suggesting a potential role for PRRT.

Of the entire cohort, the median OS was 59 months with a 5-year survival rate of 47%. This reflects previous Surveillance, Epidemiology and End Results (SEER) data [5] which reported a median OS of 60 months and 5-year survival rate of 50% in patients diagnosed with metastatic G1/G2 PNET between 2000 and 2012. Independent predictors of poor survival included older age (>63 years), high tumour grade, high Ki-

67, chromogranin A ≥5 times normal and presence of hepatic metastases at diagnosis (Table 6). These variables are well-defined NET prognostic factors in the literature [5,31–34]. Absence of avidity on SSRI was also independently associated with poorer overall survival, and the concept of using functional imaging, including both SSRI and ^{18}F-FDG PET, as prognostic biomarkers in metastatic NET is supported by previous studies [35–40]. It is likely in the future that functional imaging, especially the combination of ^{68}Ga DOTATATE and ^{18}F-FDG PET, will also play a greater role in guiding treatment decisions in patients with metastatic NET, and prospective validation is warranted. Furthermore, of the G2 cohort, patients that received a treatment sequence that included PRRT had significantly prolonged survival compared with those patients who had not received PRRT. Given the baseline characteristics of the G2 cohort, including mean Ki-67 and SSRI positivity, were comparable between the treatment arms this is an interesting finding. Other variables independently associated with overall survival in the G2 cohort included chromogranin A, number of lines of therapy and Ki67 (3-4% vs 15-20% and 3-4% vs 5-9%). Previous studies also suggest that a Ki-67 threshold of 5% could better distinguish G1 from G2 PNET and this warrants further exploration [41,42].

Less studied in the literature are predictors of treatment response. In our study, the independent predictors of prolonged TTF in the entire cohort not unexpectedly mirrored those of prolonged overall survival, including Ki-67, histological grade and chromogranin A (Table 2). In addition, treatment type was also independently associated with TTF. In the G2 cohort, despite no significant difference in patient baseline characteristics, treatment type remained an independent predictor of TTF. PRRT had prolonged TTF compared with both chemotherapy and molecular targeted

therapy. This finding was replicated in the analysis of TTP in the G2 cohort in which the median TTP of PRRT was 24 months versus 12 months for chemotherapy and 12 months for molecular targeted therapy. Notably, patients treated with molecular targeted therapy had the highest rate of treatment cessation due to toxicity and measures to ameliorate toxicity should be pursued early and aggressively in patients treated with molecular targeted therapy. Resection of primary was an independent predictor of TTF in the G2 cohort but it did not attain independent significance in the TTP analysis nor the survival analyses.

These findings, however, must be interpreted with caution given the retrospective design of our study and inherent limitations including potential unmeasured confounders. Potential confounders include clinical factors that denote a poorer prognosis. Whilst some of our patients were treated prior to the availability of PRRT in the United Kingdom, thus resulting in less treatment choice, in more recent times patients with poorer prognostic factors such as faster pace of disease progression or bulky, symptomatic disease, may have preferentially been treated with chemotherapy over PRRT. A poorer prognosis in the chemotherapy cohort is supported by the fact that patients who only received 1 or 2 lines of therapy in total (most frequently incorporating chemotherapy in our study [Table 3]) had poorer overall survival compared with those patients who survived long enough to receive 5 or 6 lines of therapy which more frequently included molecular targeted therapy or PRRT. However, this does not fully explain the persistent difference in TTP between molecular targeted therapy and PRRT in patients with presumably more similar indications for these two treatments. Furthermore, our median TTP estimates (24 months for PRRT vs 12 months for molecular targeted therapy) are consistent with

progression free survival (PFS) estimates reported in the experimental arms of the NETTER-1 (median 28.4 months), sunitinib (median 11.4 months) and everolimus (median 11 months) phase III trials [15–17,43].

In conclusion, PRRT is associated with encouraging TTF and TTP relative to other systemic therapies for G2 metastatic PNET and it should be considered early in the treatment algorithm. Furthermore, access to PRRT as part of a therapeutic sequence appears to improve overall survival in patients with metastatic PNET. Our study is unique in its approach and provides insight into potential variables that should be studied in future trials to help understand the optimal treatment algorithm for metastatic PNET. Predictors of prognosis and treatment response will be expanded with the further development of molecular profiling of these tumours. Randomised trials comparing chemotherapy, molecular targeted therapy and PRRT (Table 8) are ongoing and may validate these findings. Such studies will be critical to inform the optimal treatment algorithm in these challenging tumours.

Statement of Ethics

This study was approved by the Quality Governance and Clinical Audit Committee of the Royal Free Hospital NHS Foundation Trust.

Disclosure Statement

The authors have no conflicts of interest to declare with regards to this manuscript.

BK is a member of the UK National Institute for Clinical Excellence Technology Appraisal Committees.

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Figure legends

Fig. 1. Flow diagram for patient selection

Fig. 2. Kaplan-Meier plot of time to progression in the G2 PNET cohort

Fig. 3. Kaplan-Meier plots of overall survival stratified by a) treatment sequence and b) number of lines of therapy per patient in the G2 PNET cohort *(n=114)*

Fig. 1. Flow diagram for patient selection

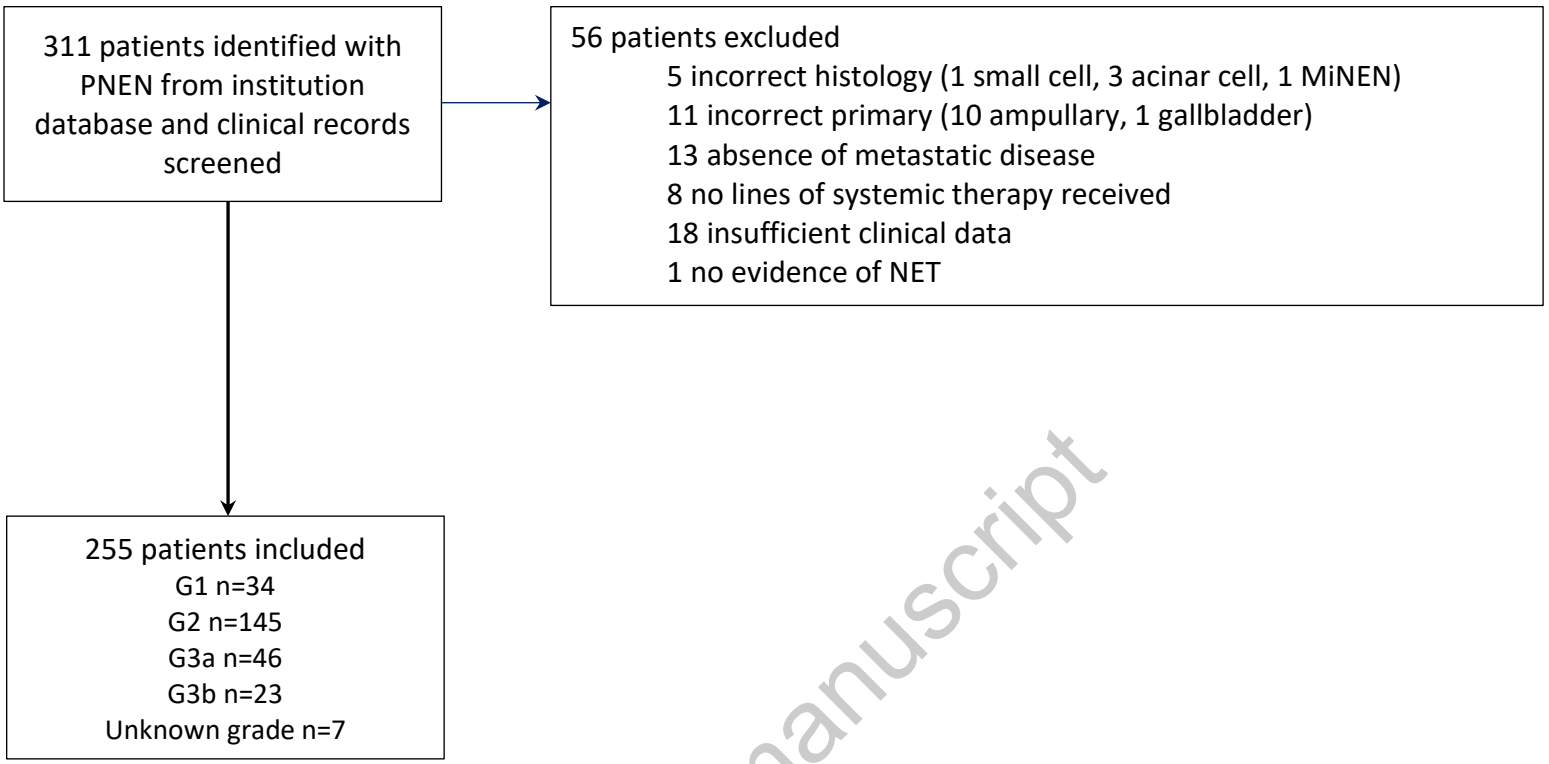


Fig. 2. Kaplan-Meier plot of time to progression in the G2 PNET cohort

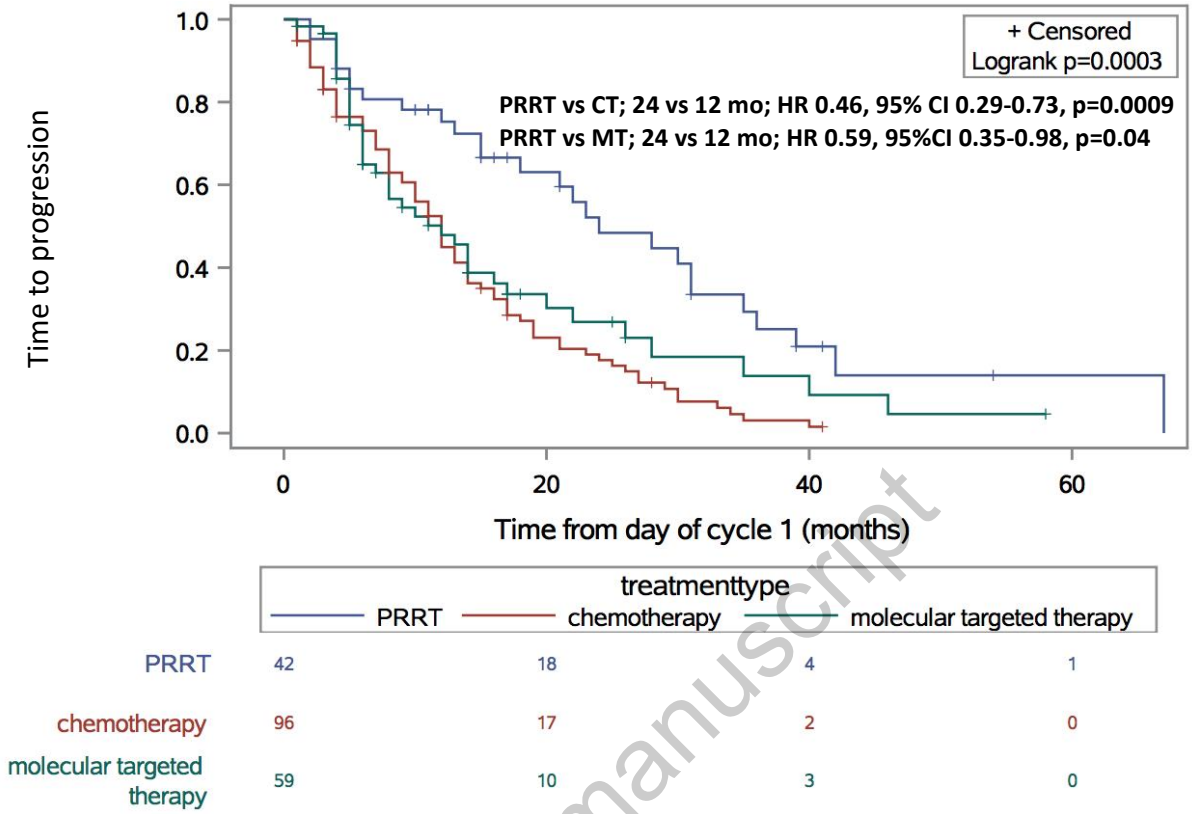
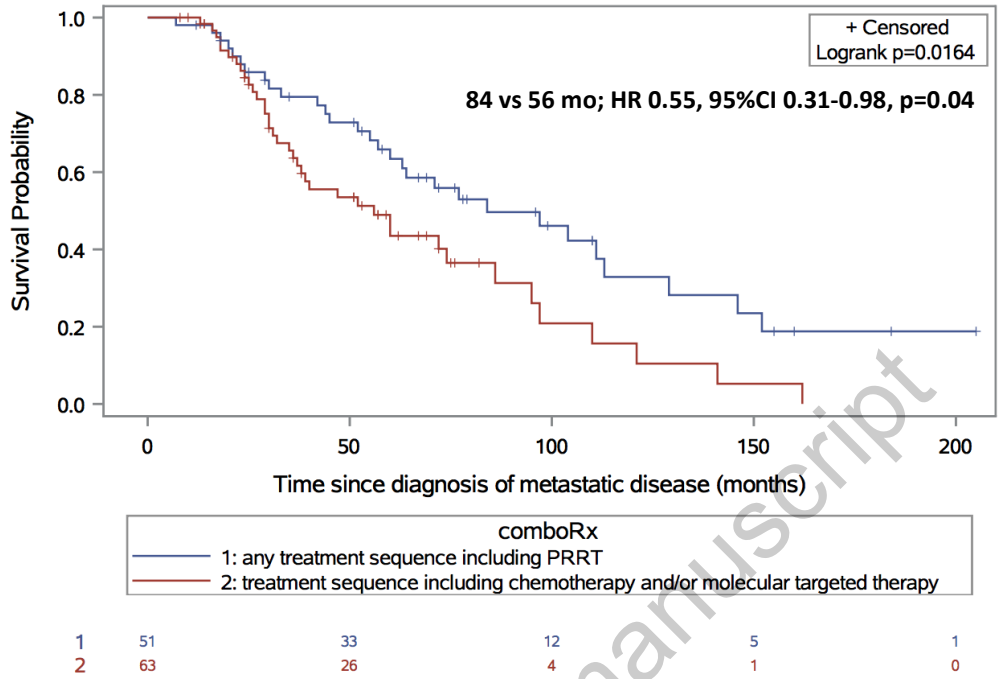


Figure 3. Kaplan-Meier plots of overall survival stratified by a) treatment sequence and b) number of lines of therapy per patient in the G2 PNET cohort *(n=114)*

a)



b)

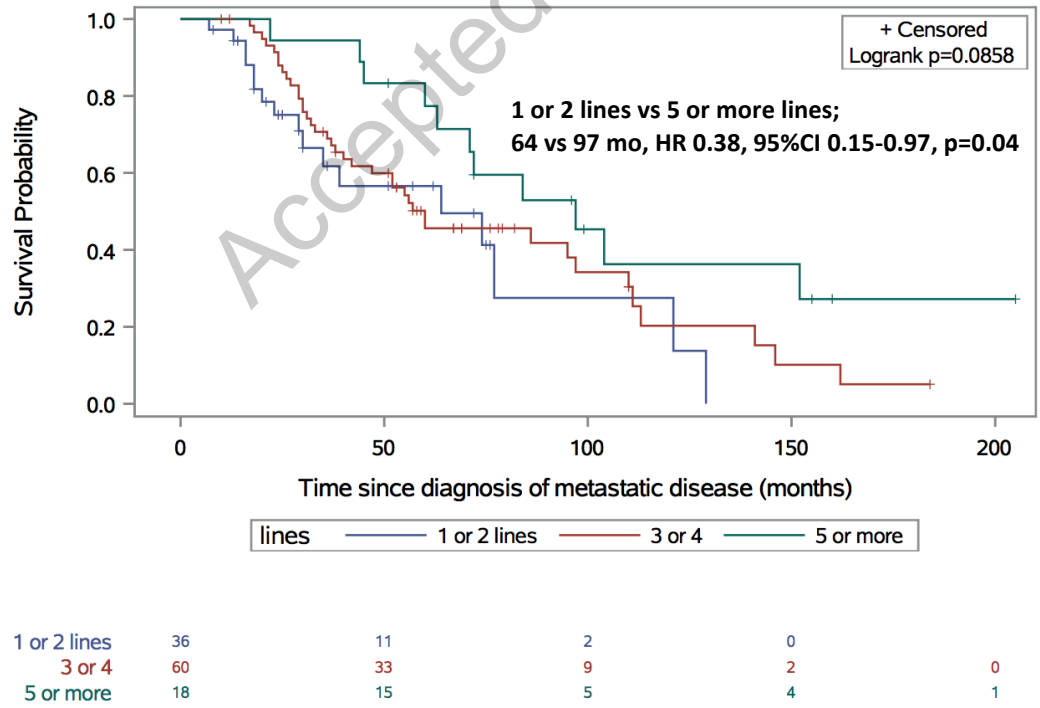


Table 1. Characteristics of study cohort at baseline (*n=255*)

Characteristic	*n*
Median age at diagnosis, yrs (range)	54 (13-82)
Gender	
Female	102 (40%)
Male	153 (60%)
WHO 2017 grade[1]	
G1	34 (13%)
G2	145 (57%)
G3 NET	46 (18%)
G3 NEC	23 (9%)
Unknown	7 (3%)
Functional	
No	207 (81%)
Yes	48 (19%)
Known germline mutation	
No	241 (95%)
Yes	14 (5%)
Resection of primary	
No	180 (71%)
Yes	71 (28%)
Unknown	4 (2%)
Presence of hepatic metastases at time of diagnosis	
No	79 (31%)
Yes	148 (58%)
Unknown	28 (11%)
Presence of hepatic metastases at time of first line systemic therapy	
No	13 (5%)
Yes	240 (94%)
Unknown	2 (1%)
Chromogranin A	
< 5x normal	94 (37%)
≥ 5x normal	126 (49%
Unknown	35 (14%)
SSRI imaging	
Positive	172 (67%)
Negative	14 (6%)
Unknown	69 (27%)
Second primary malignancy*	19 (7%)

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**excluding patients with a germline mutation*

Table 2. Univariate and multivariate analyses showing relationship between baseline characteristics and time to treatment failure (TTF) of entire cohort *(491 lines of therapy in 255 patients)*

Variable	Univariate analysis	Multivariate analysis Cox regression	
	p value	Model 1 HR (95% CI), p value	Model 2 HR (95% CI), p value
Age, quartiles by event Grp 1 (0-44 yrs) Grp 2 (45-52 yrs) Grp 3 (53-61 yrs) Grp 4 (≥62 yrs)	 Reference 0.80 0.29 0.50		
Gender, M vs F	0.48		
WHO 2017 grade*; G1 G2 G3 NET G3 NEC	 Reference **0.002** **<0.0001** **<0.0001**	 1.0 **1.38 (1.01-1.91), p=0.046** **2.47 (1.68-3.62), p<0.0001** **3.30 (1.90-5.73), p<0.0001**	
Ki67*, quartiles by event; Grp 1 (Ki67 0-4%) Grp 2 (Ki67 5-9%) Grp 3 (Ki67 10-24%) Grp 4 (Ki67 ≥25%)	 Reference 0.10 **0.003** **<0.0001**		 1.0 1.18 (0.86-1.63), p=0.30 1.33 (1.00-1.77), p=0.05 **2.33 (1.70-3.20), p<0.0001**
CgA; <5x normal vs ≥5x normal	**0.0001**	**0.74 (0.60-0.91), p=0.005**	**0.73 (0.59-0.91), p=0.005**
SSRI; avid vs non-avid	0.78		
Functional; yes vs no	0.57		
Presence of hepatic metastases; yes vs no	0.86		
Resection of primary; yes vs no	**0.003**	0.82 (0.65-1.04), p=0.11	0.80 (0.63-1.01), p=0.06
Treatment type; PRRT vs chemotherapy	**<0.001**	**0.56 (0.43-0.80), p=0.0008**	**0.62 (0.45-0.85), p=0.003**
Treatment type; PRRT vs molecular targeted therapy	**<0.001**	**0.48 (0.35-0.68), p<0.0001**	**0.50 (0.35-0.70), p<0.0001**

***Ki67 and grade are collinear and were handled separately in the regression analysis*

Table 3. Evaluable lines of systemic therapy in the G2 cohort *(114 patients; 234 evaluable lines of systemic therapy)*

Characteristic	Chemotherapy	Molecular targeted therapy	PRRT	p value
Therapy	105 *(FCiSt/FCarboStrep/CapStrep 89, Cis/CarboEtop 9, CAPTEM 6, FOLFIRI 1)*	82 *(Sunitinib 46, Everolimus 36)*	47 *(^{177}Lu 33, ^{90}Y 14)*	
Age, mean (±SD)	52.62 (±10.95)	50.96 (±9.80)	54.0 (±10.80)	0.27†
Gender				
Female	38 (36%)	35 (43%)	24 (52%)	0.22‡
Male	67 (64%)	47 (57%)	23 (48%)	
Ki67, mean (±SD)	10.06 (±5.38)	9.02 (±5.15)	8.49 (±5.01)	0.22†
Chromogranin A				
< 5x normal	33 (31%)	31 (38%)	18 (38%)	0.54§
≥ 5x normal	64 (61%)	44 (54%)	28 (60%)	
Unknown	8 (8%)	7 (9%)	1 (2%)	
Presence of hepatic metastases				
No	4 (4%)	1 (1%)	2 (4%)	0.54§
Yes	101 (96%)	81 (99%)	45 (96%)	
SSRI imaging				
Positive	78 (74%)	62 (76%)	37 (78%)	0.85§
Negative	3 (3%)	3 (4%)	0	
Unknown	24 (23%)	17 (21%)	10 (21%)	
Line of treatment				
1 or 2	84 (80%)	34 (41%)	11 (23%)	**<0.0001**‡
3 or 4	16 (15%)	41 (50%)	26 (55%)	
5 or 6	5 (5%)	7 (9%)	10 (21%)	
Treatment failure				
Total	96 (91%)	72 (88%)	35 (74%)	**0.02**‡
Radiological	*87 (91%)*	*49 (68%)*	*30 (86%)*	**<0.0001**§
Toxicity*	*2 (2%)*	*16 (22%)*	*0*	
Clinical deterioration*	*6 (6%)*	*6 (8%)*	*0*	
Death	*1 (1%*	*1 (1%)*	*5 (14%)*	

**necessitating treatment cessation*

† Kruskal-Wallis test

‡ Chi –squared test

§ Fisher-Freeman-Halton exact test

Table 4. Univariate and multivariate analyses showing relationship between baseline characteristics and TTF in the G2 cohort *(234 lines of therapy in 114 patients)*

Variable	Univariate analysis	Multivariate analysis Cox regression
	p value	**HR (95% CI), p value**
Age, quartiles by event; Grp 1 (0-44 yrs) Grp 2 (45-52 yrs) Grp 3 (53-61 yrs) Grp 4 (≥62 yrs)	 Reference 0.69 0.16 0.34	
Gender, M vs F	0.16	
Ki67, quartiles by event; Grp 1 (Ki67 3-4%) Grp 2 (Ki67 5-9%) Grp 3 (Ki67 10-14%) Grp 4 (Ki67 15-20%)	 Reference 0.66 0.46 0.41	
CgA; <5x normal vs ≥ 5x normal	**0.005**	**0.71 (0.52-0.97), p=0.03**
SSRI; avid vs non-avid*	0.72	
Functional; yes vs no	0.54	
Presence of hepatic metastases at time of 1st line systemic therapy; yes vs no	0.22	
Resection of primary; yes vs no	**0.01**	**0.73 (0.48-0.99), p=0.04**
Treatment type; PRRT vs chemotherapy	**0.0007**	**0.56 (0.34-0.84), p=0.005**
Treatment type; PRRT vs molecular targeted therapy	**<0.0001**	**0.47 (0.31-0.72), p=0.0005**

Table 5. Univariate and multivariate analyses showing relationship between baseline characteristics and time to progression (TTP) in the G2 cohort *(197 evaluable lines of therapy)*

Variable	Univariate analysis	Multivariate analysis Cox regression
	p value	**HR (95% CI), p value**
Age, quartiles by event; Grp 1 (0-44 yrs) Grp 2 (45-49 yrs) Grp 3 (50-60 yrs) Grp 4 (≥61 yrs)	 Reference 0.42 **0.006** **0.06**	 1.00 1.12 (0.68-1.85), p=0.66 1.60 (0.97-2.65), p=0.06 1.52 (0.92-2.46), p=0.1
Gender, M vs F	0.29	
Ki67, quartiles by event; Grp 1 (Ki67 3-4%) Grp 2 (Ki67 5-9%) Grp 3 (Ki67 10-14%) Grp 4 (Ki67 15-20%)	 Reference 0.30 0.79 0.44	
CgA; <5x normal vs ≥ 5x normal	**0.007**	0.72 (0.50-1.03), p=0.07
SSRI; avid vs non-avid*	0.79	
Functional; yes vs no	0.94	
Presence of hepatic metastases at time of 1st line systemic therapy*; yes vs no	0.78	
Resection of primary; yes vs no	0.07	0.73 (0.48-1.13), p=0.16
Treatment type; PRRT vs chemotherapy	**0.0001**	**0.46 (0.29-0.73), p=0.0009**
Treatment type; PRRT vs molecular targeted therapy	**0.01**	**0.59 (0.35-0.98), p=0.04**

Table 6. Association between baseline characteristics and overall survival of entire cohort *(255 patients)*

Variable	Univariate analysis	Multivariate analysis Cox regression	
	p value	Model 1 HR (95% CI), p value	Model 2 HR (95% CI), p value
Age, quartiles by event; Grp 1 (0-45 yrs) Grp 2 (46-55 yrs) Grp 3 (56-63 yrs) Grp 4 (≥64 yrs)	 Reference 0.14 0.52 **0.02**	 1.00 1.79 (0.88-3.66), p=0.12 1.47 (0.71-3.07), p=0.30 **2.10 (1.003-4.47), p=0.049**	 1.00 1.93 (0.96-3.88), p=0.07 1.51 (0.73-3.12), p=0.27 **2.58 (1.28-5.21), p=0.008**
Gender, M vs F	0.90		
Ki67*, quartiles by event; Grp 1 (Ki67 0-4%) Grp 2 (Ki67 5-14%) Grp 3 (Ki67 15-29%) Grp 4 (Ki67 ≥30%)	 Reference 0.21 **0.0002** **<0.0001**	 1.00 1.60 (0.77-3.31), p=0.21 **2.99 (1.32-6.74), p=0.009** **10.1 (4.34-23.55), p<0.0001**	
CgA; <5x normal vs ≥ 5x normal	**0.009**	**0.51 (0.29-0.88), p=0.02**	**0.49 (0.29-0.84), p=0.01**
SSRI; avid vs non-avid	**0.04**	**0.27 (0.1-0.75), p=0.01**	**0.23 (0.1-0.65), p=0.006**
Functional; yes vs no	**0.02**	0.96 (0.54-1.60), p=0.89	1.06 (0.61-1.85), p=0.83
Presence of hepatic metastases at diagnosis; yes vs no	**0.003**	**1.62 (1.06-2.49), p=0.03**	**1.60 (1.04-2.44), p=0.03**
Resection of primary; yes vs no	**<0.0001**	0.65 (0.35-1.23), p=0.19	0.63 (0.34-1.17), p=0.14
Presence of germline mutation; yes vs no	0.057	0.98 (0.33-2.95), p=0.97	0.76 (0.28-2.10), p=0.60
Presence of second malignancy; yes vs no	0.062	0.43 (0.16-1.15), p=0.09	0.96 (0.23-1.53), p=0.28
WHO 2017 grade*; G1 G2 G3 NET G3 NEC	 Reference 0.089 **<0.0001** **<0.0001**		 1.00 1.78 (0.78-4.02), p=0.17 **5.59 (2.26-13.80), p=0.0002** **9.27 (2.19-39.2), p=0.003**

***Ki67 and grade are collinear and were handled separately in the regression analysis*

Table 7. Association between baseline characteristics and overall survival in the G2 cohort (*114 patients*). Cox regression multivariate analysis.

Variable	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	
		Model 1	**Model 2**
Ki67, quartiles by event; Grp 1 (3-4%) Grp 2 (5-9%) Grp 3 (10-14%) Grp 4 (15-20%)	 Reference 1.96 (0.76-5.05), p=0.17 2.05 (0.81-5.16), p=0.13 2.48 (0.99-6.2), p=0.052	 1.00 **3.17 (1.14-8.79), p=0.03** 2.60 (0.99-6.89), p=0.054 **3.53 (1.30-9.59), p=0.01**	 1.00 2.75 (0.99-7.56), p=0.051 2.17 (0.82-5.76), p=0.12 **3.23 (1.18-8.85), p=0.02**
Presence of hepatic metastases at diagnosis; yes vs no	**1.62 (1.14-2.3), p=0.008**	1.66 (1.0-2.76), p=0.052	1.37 (0.82-2.28), p=0.23
Chromogranin A; <5x normal vs ≥5x normal	**0.45 (0.25-0.81), p=0.008**	**0.47 (0.24-0.92), p=0.03**	**0.36 (0.18-0.72), p=0.004**
Resection of primary; yes vs no	**0.38 (0.21-0.71), p=0.002**	0.57 (0.24-1.31), p=0.18	0.53 (0.23-1.23), p=0.14
Treatment*; any sequence including PRRT vs sequences that did not include PRRT	**0.55 (0.34-0.90), p=0.02**	**0.55 (0.31-0.98), p=0.04**	
Total number of lines of therapy per patient*; 1 or 2 3 or 4 5 or more	 Reference 0.78 (0.44-1.39), p=0.71 **0.43 (0.19-0.93), p=0.03**		 1.0 0.70 (0.37-1.35), p=0.29 **0.38 (0.15-0.97), p=0.04**

**Treatment and number lines of therapy are collinear and were handled separately in the regression analysis*

Table 8. Summary of randomised, comparative trials in progress

Trial	Phase	Predefined sample size	Primary	Grade	Functional tumours eligible	Experimental arm	Comparator arm	Primary endpoint
COMPETE (NCT03049189)	III	300	Gastroentero pancreatic	Well-differentiated	Functional PNET eligible, functional GI NET ineligible	177Lu DOTATOC	Everolimus	PFS
OCCLURANDOM (NCT02230176)	II	80	Pancreatic	Well-differentiated	Yes	177Lu DOTATATE	Sunitinib	PFS
SEQTOR (NCT02246127)	III	180	Pancreatic	G1/G2	Yes	STZ-5FU followed by everolimus	Everolimus followed by STZ-5FU	Second PFS
CONTROL NETS (NCT02358356)	II (two parallel phase II)	72	Midgut or pancreatic	G1/G2	No	177Lu DOTATATE and CAPTEM	i) vs CAPTEM alone in the treatment of PNET; ii) vs 177Lu DOTATATE alone in the treatment of midgut NET	PFS