RESEARCH

Poor outcome after systemic therapy in secondary high-grade pancreatic neuroendocrine tumors

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Abstract

Longitudinal changes in pancreatic neuroendocrine tumor (panNET) cell proliferation correlate with fast disease progression and poor prognosis. The optimal treatment strategy for secondary panNET grade (G)3 that has progressed from a previous low- or intermediate-grade to high-grade panNET G3 is currently unknown. This was a single-center retrospective cohort study aimed to characterize treatment patterns and outcomes among patients with secondary panNET-G3. Radiological responses were assessed using the Response Evaluation Criteria in Solid Tumors version 1.1. A total of 22 patients were included and received a median of 2 (range, 1–4) treatment lines in 14 different combinations. Median overall survival (OS) was 9 months (interquartile range (IQR): 4.25–17.5). For the 15 patients who received platinum–etoposide chemotherapy, median OS was 7.5 months (IQR: 3.75–10) and median progression-free survival (PFS) was 4 months (IQR: 2.5–5.5). The 15 patients who received conventional panNET therapies achieved a median OS of 8 months (IQR: 5–16.75) and median PFS was 5.5 months (IQR: 2.75–8.25). We observed one partial response on ^{177}Lu DOTA-TATE therapy. In conclusion, this hypothesis-generating study failed to identify any promising treatment alternatives for patients with secondary panNET-G3. This demonstrates the need for both improved biological understanding of this particular NET entity and for designing prospective studies to further assess its treatment in larger patient cohorts.

Key Words

- pancreatic neuroendocrine tumor
- highgrade
- systemic therapy
- treatment outcomes

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Introduction

Pancreatic neuroendocrine neoplasms (panNENs) constitute a heterogeneous group of different diseases, in terms of biology as well as in patient characteristics and outcomes. The panNENs displaying the highest proliferation rate (Ki-67 index >20%) were historically classified as neuroendocrine carcinomas (NECs) (1). The recommended first-line systemic treatment option for all metastatic NECs (1) was platinum–etoposide chemotherapy (2). In the WHO 2017 classification and grading of panNENs (3), high-grade neoplasms were separated into two categories: well-differentiated (WD) pancreatic neuroendocrine tumor grade 3 (panNET-G3) and poorly differentiated (PD) NEC (4). PanNET-G3 frequently harbors mutations in *MEN1* and *ATRX/DAXX,* similar to G1-G2 panNETs (5). Pancreatic NECs (panNEC) display distinct biology with higher proliferative indices and frequent *KRAS* and *BRAF* mutations as well as *RB* loss (6, 7). Additionally, retrospective analyses have demonstrated longer survival for panNET-G3 (range, 41–42 months) than for panNEC (range, 9–17 months) (8, 9).

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Moreover, it has been hypothesized that panNET-G3 and panNEC respond differently to systemic therapy, with higher response rates on platinum–etoposide chemotherapy for panNEC (56%, n= 49), than for panNET-G3 (0%, n= 21) (9). Conversely, conventional treatments for WD-NET showed modest responses among NEC patients, with no objective responders among those receiving either everolimus (n = 25) (10) or sunitinib (n = 5) (11). In addition, a median progression-free survival (PFS) of 4 months for peptide receptor radionuclide therapy (PRRT) has also been reported (12). Consequently, it has been hypothesized that panNET-G3 should be treated similarly to intermediate-grade panNET. European Neuroendocrine Tumor Society (ENETS) and European Society for Medical Oncology (ESMO) Guidelines (13, 14, 15) recommend that panNET-G3 should be considered for conventional NET therapy including alkylating chemotherapy, targeted agents or PRRT with ^{177}Lu-DOTA-TATE. Platinum–etoposide is not generally recommended but can be considered in certain cases such as patients with progressive high proliferative diseases (Ki-67 > 55%).

We recently characterized a cohort of panNET patients and identified a new phenomenon, which we have termed 'secondary panNET-G3' (16) defined as low- to intermediate-grade panNET that has progressed to panNET-G3 (16). This was associated with poor prognosis. As it is currently not known whether the biology of secondary panNET-G3 differs from that of primary panNET-G3, we hypothesized that secondary panNET-G3 could have different biology rendering it susceptible to some drugs that are not effective in the treatment of primary panNET-G3 (17). To the best of our knowledge, there are no data on treatment outcomes patients with secondary panNET-G3. The objective of this study was therefore to characterize the treatment patterns and outcomes in this particular patient group.

Methods

The study was approved by the Ethical Review Board in Uppsala (reference ID: 2015/544). Patients provided written informed consent. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology Guidelines (18).

Study design, setting and participants

This was a single-center retrospective cohort study at Uppsala University Hospital, Uppsala, Sweden. Patients were included when they fulfilled the following criteria: (i) histopathologically confirmed secondary panNET-G3, (ii) sporadic disease, (iii) Ki-67 analyzed at primary diagnosis and at follow-up and (iv) obtained subsequent systemic therapy. The study material consisted of a previously described cohort of 475 patients with histopathologically confirmed panNETs treated at our center, diagnosed between January 1, 1980, and December 1, 2016. In total, 382 patients had sporadic disease, and of these, 46 patients had available follow-up biopsies and 28 patients were identified with an increase in tumor grade, of them 24 had progressed into secondary panNET-G3 of

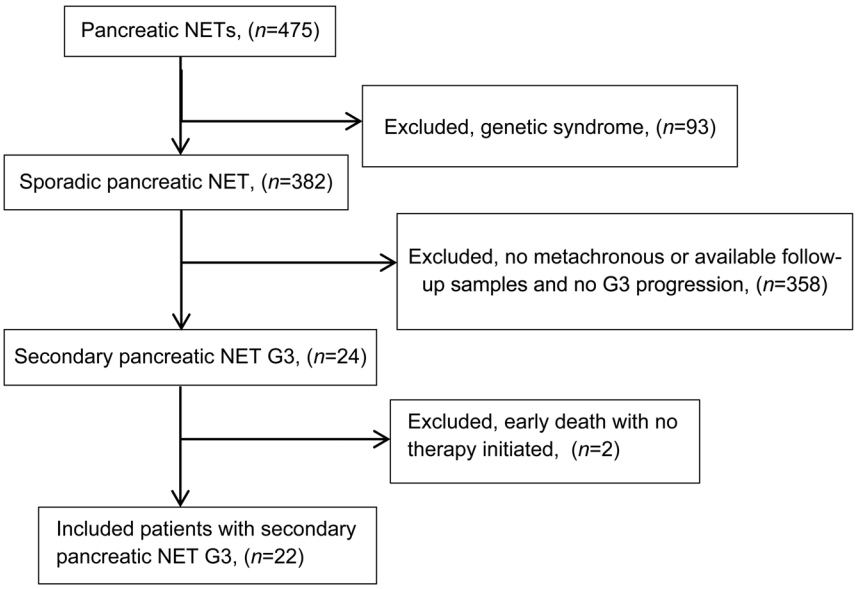

Figure 1
Flowchart for study inclusion.

which 22 were included (16). Please see Fig. 1 for details on study inclusion.

Study objectives, variables and method for outcome reporting

The objective was to characterize treatment patterns and outcomes among the patients after they had been diagnosed with secondary panNET-G3. All systemic agents administered until death were listed and outcomes were described as overall survival (OS) after the diagnosis of secondary panNET-G3. Separate analyses were additionally performed in two pre-defined subgroups of patients receiving conventional panNET treatments and platinum–etoposide chemotherapy for NEC, respectively. Conventional panNET therapies were selected based on ENETS and ESMO Guidelines (13, 14, 15): streptozotocin/5-FU, temozolomide as monotherapy or in combination with capecitabine, everolimus (mTOR inhibitor), sunitinib (tyrosine kinase inhibitor) and PRRT in somatostatin receptor-positive patients.

Patients who underwent contrast-enhanced CT (CECT) at baseline and follow-up were available for the analysis of radiological response using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (19). The PFS was determined from the initiation of new treatment until disease progression or death. The information about disease progression was based on either radiological and/or clinical findings. The patients were characterized for tumor grade according to WHO 2017 classification (4), tumor stage (UICC8) (20) and hormonal syndromes (21) at primary diagnosis and at reclassification to panNET-G3. More detailed information regarding the histopathology after G3 progression is presented in Table 1 and Supplementary Table 1 (see section on supplementary materials given at the end of this article).

Table 1 Baseline characteristics.

Patients, *n*	22
Gender, male/female	12/10
Age, median (range)	58 years (36–70)
Functional/non-functional	7/15
Ki-67, median (range)	50% (22–82)
Median time for G3 progression (range)	44 months (4–120)
Stage UICC 8th edition, *n*	
I	1
II	1
III	0
IV	19
Unknown	1
Primary grade WHO 2017, *n*	
G1	2
G2	20
Indication for new tumor sampling, *n*	
Change of disease behavior	15
Diagnostic	7
Location of biopsy, *n*	
Liver	21
Other	1
Prescence of 'NEC-like' characteristics, *n*	
Nuclear atypia	9/14
Presence of necrosis	5/14
Number of treatment lines prior to G3 progression, *n*	
0	0
1	1
2	9
3	3
4 or more	9
Treatments prior to G3 progression, *n*	
Platinum–etoposide chemotherapy	3
Alkylating chemotherapy	19
PRRT	8
mTOR inhibitor	3
Locoregional therapy	10
Other	14
Treatments reintroduced after G3 progression, *n*	
Platinum-etoposide	2
Alkylating chemotherapy	8
PRRT	1
Everolimus	0

Alkylating chemotherapy, temozolomide, temozolomide/capecitabine, streptozotocin/5-floururacil; locoregional therapy, surgery, transarterial embolization, radiofrequency ablation, selective internal radiation therapy, irreversible electroporation; mTOR, mammalian target of rapamycin;Other, somatostatin analog, taxane-based chemotherapy, bevacizumab, interferon alfa-2b, pyrimidine analog, MAB; PRRT, peptide receptor radionuclide therapy.

Results

Twenty-two patients with histopathologically confirmed secondary panNET-G3 were considered for subsequent systemic therapy and thus eligible for study inclusion. The patients' baseline characteristics and previous therapies are shown in Table 1. Briefly, there were 12 males and 10 females with a median age of 58 years (range, 36–70) at primary diagnosis. Seven patients had functioning tumors and 15 had non-functioning tumors. The patients were low- to intermediate-grade, WHO grade G1 ($n = 2$) and G2 ($n = 20$), at primary diagnosis. Median time from primary diagnosis until panNET-G3 progression was 44 months (interquartile range (IQR): 27.3–56.4). Median Ki-67 index at diagnosis of secondary panNET-G3 was 50% (range, 22–82). Six patients had Ki-67 ≥ 55% and 17 had Ki-67 < 55%. Data on previous treatments before G3 progression were available for 21 patients, of whom 23% (5/21) had undergone

Table 2 Outcome of systemic therapy after secondary panNET-G3 progression.

Therapy	Treatment line: number of patients	Median OS (months, IQR)	Median PFS (months, IQR)	Median Ki67 (%, range)	Best response (RECIST 1.1)
Conventional NEC therapy					
Platinum–etoposide	1st: 11 2nd: 5	7.5 (3.75–10)	4 (2.5–5.5)	50 (21–82)	SD: 3 PD: 4 NA: 9
Conventional NET therapy					
Alkylating chemotherapy	1st: 3 2nd: 3 3rd: 1	16 (4.5–20)	7 (3–8.5)	50 (25–50)	PD: 1 SD: 3 NA: 3
PRRT	1st: 2 2nd: 1	21 (17–22)	12 (11.5–13)	23 (22–32)	PR: 1 SD: 1 PD: 1
mTOR inhibitor	1st: 2 2nd: 2 3rd: 1	6 (6–9)	5 (5–6)	32 (25–50)	SD: 2 NA: 3
TKI	1st: 2 3rd: 1	4 (3–5.5)	2 (2–2.5)	72 (50–82)	SD: 1 PD: 1 NA: 1
Summary NET-conventional therapy	-	8 (5–16.75)	5.5 (2.75–8.25)	50 (22–82)	PR: 1 SD: 7 PD: 3 NA: 9

IQR, interquartile range; mTOR, mammalian target of rapamycin; NA, not analyzed due to lack of information and/or lack of baseline and follow-up imaging or lack of CECT; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PRRT, peptide receptor radionuclide therapy; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

surgical resection of the primary tumor. All 21 patients had received chemotherapy, 19/21 had alkylating agents and 3/21 had prior platinum–etoposide regimens. ^{177}Lu DOTA-TATE had been administered to 8/21 and an mTOR inhibitor to 3/21. Of the three patients that had progressed on platinum–etoposide before progression to secondary panNET-G3, two of them received this therapy again after progression. Eight of 19 patients who received alkylating agents before G3 progression had the therapy reintroduced after progression.

Treatment patterns

Twenty-two patients with secondary panNET-G3 were considered for systemic treatment and had various therapies administered, summarized in Table 2. After progression to panNET-G3, 16 patients received 1–2 lines of therapy and 13 patients had 3 or more treatment lines. Since some of the patients received both platinum–etoposide and conventional NET therapies, the treatment response in the same patient was evaluated separately for each treatment line. The results per patient are presented in Supplementary Tables 2 and 3 enclosed in the supplementary materials. Platinum–etoposide chemotherapy was administered to 15 patients, in 11 as first-line therapy after progression to panNET-G3, illustrated in Fig. 2 together with other

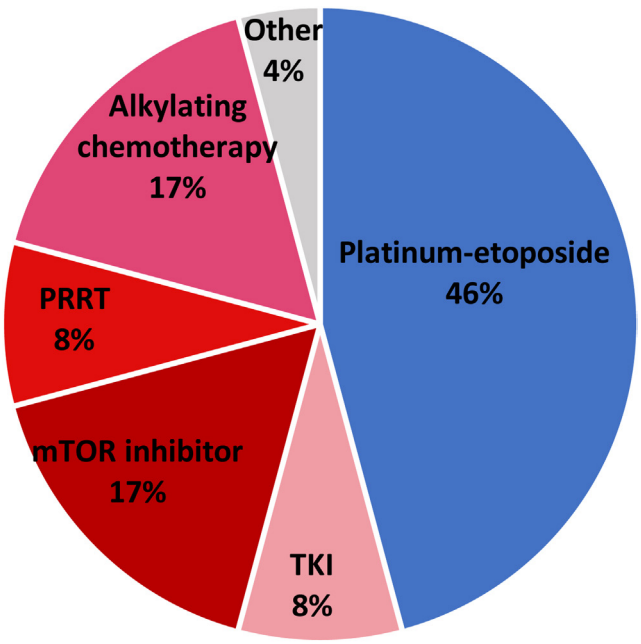

Figure 2
First-line therapies after progression to panNET-G3. Alkylating chemotherapy: temozolomide, temozolomide/capecitabine, and streptozotocin/5-Floururacil; TKI, tyrosine kinase inhibitor; mTOR, mammalian target of rapamycin; PRRT, peptide receptor radionuclide therapy; Other: locoregional therapies (surgery, transarterial embolization, radiofrequency ablation, irradiation, selective internal radiation therapy) and other systemic therapies (taxane-based, anthracycline-based, pyrimidine analogs, MAB).

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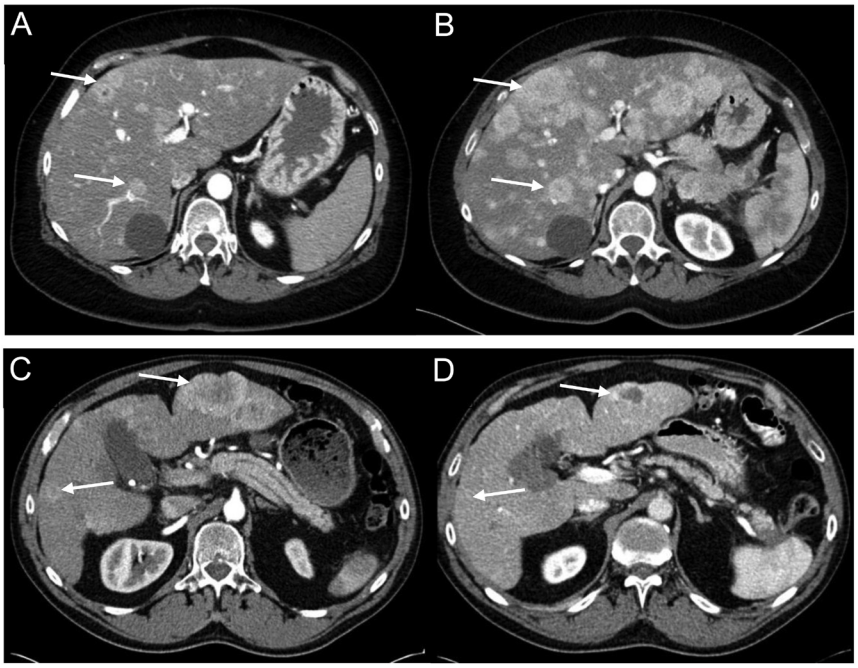

Figure 3
(A) Tumor progression in patient no. 19 treated with carboplatin–etoposide as first-line treatment after G3 progression. Ki-67 = 50%. (A) CECT at baseline was performed 4 weeks prior to treatment start. (B) CECT at first follow-up 2 months after the start of therapy, evaluation after two cycles, shows clear progressive disease with increasing size of target lesions and multiple new liver metastases. (C) Tumor response in patient no. 5 treated with ^{177}Lu DOTA-TATE therapy as first-line treatment after G3 progression. Ki-67 = 23%. (C) CECT at baseline, prior to therapy start. (D) CECT at first follow-up 5 months after the start of treatment, evaluation after two cycles of PRRT shows decreased size and disappearance, respectively, of the target lesions. Best response, PR.

administered first-line therapies. Fifteen had conventional NET therapies of whom 9 received alkylating chemotherapy, 7 mTOR inhibitors, 4 tyrosine kinase inhibitors and 3 underwent PRRT with ^{177}Lu DOTA-TATE. Other treatments included taxane- (n = 4) and anthracycline-based (n = 4) chemotherapy, locoregional therapies of the liver, including transarterial embolization and radiofrequency ablation (n = 4) and surgical resection (n = 1).

Patient outcomes

The treatment outcomes are summarized in Table 2 and more detailed information can be found in Supplementary Tables 2 and 3. Median OS for the entire cohort from therapy initiation was 9 months (IQR: 4.25–17.5).

Among 15 patients who received platinum–etoposide chemotherapy, the median OS was 7.5 months (IQR: 3.75–10). Radiological responses could not be evaluated in eight patients (three died, four lacked imaging during follow-up and one lacked CECT). Median PFS was 4 months (IQR: 2.5–5.5). Best radiological response was stable disease (SD) in three patients, and the four remaining patients had progressive disease (PD) (Fig. 3A).

The 15 patients who received conventional NET agents had median OS 8 months (IQR: 5–16.75). Radiological responses could only be analyzed in 11 patients and the median PFS was 5.5 months (IQR: 2.75–8.25). Partial response (PR) was observed as best radiological response in a patient who received ^{177}Lu DOTA-TATE (Fig. 3C), whereas the remaining patients achieved SD (n = 7) or PD (n = 3).

Discussion

Our study presents the first data on treatment selection and outcomes in a unique cohort of 22 patients with secondary panNET-G3 who had received heterogenous treatment regimens, including both conventional therapies for panNET and platinum–etoposide chemotherapy currently recommended for treatment of NEC. The OS was generally dismal with only one PR observed (Fig. 3C). Thus, we could not identify any systemic agent with promising antitumor activity for patients with secondary panNET-G3.

Our cohort was heavily pre-treated with various anti-cancer agents before progression to secondary panNET-G3. Some of the patients had already received treatment with PRRT, alkylating chemotherapy and/or platinum–etoposide regimens before progression and some were reintroduced to similar therapies after progression to G3. It is thus expected that this cohort would show poor treatment outcomes. Unfortunately, we could identify only one treatment strategy with a signal of anti-cancer effect, namely PRRT, which resulted in PR in one out of three patients. The remaining treatment strategies yielded no responders and the survival from therapy initiation was relatively short for both platinum–etoposide chemotherapy and other conventional NET therapies.

Our study had several limitations. This was a retrospective study, performed at a single tertiary referral center. A small population of patients with secondary panNET-G3 was identified, as follow-up biopsies had only

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been performed on selected cases. It is currently unknown if progression to a higher grade is representative for all panNETs or if this only occurs in special cases that run a more aggressive course. While the magnitude of selection bias is difficult to assess, it is clear that our cohort may not be fully representative of an unselected group of metastatic panNETs. Another limitation was the failure to study NEC-like features as a biomarker of treatment success, as data were only available in some patients. While NEC-like features were not a prognostic factor in our previous study, it is possible that these patients may respond differently to systemic treatments as their primary counterparts do. Further, data on objective outcomes based on radiological assessment could not be obtained for some patients, due to methodological limitations such as lack of CECT examinations, missed follow-up scans and the use of different imaging modalities during follow-up. Hence, we could not analyze treatment response in all 22 patients.

All 22 patients exhibited an increase in both Ki-67 index and grade in the first follow-up sample (Supplementary Table 1). The majority (n = 19) progressed from G2 to G3. At the second follow-up sample, three patients with G3 exhibited an increase in Ki-67 index. The progression to G3 was reflected in a poor OS of 9 months (IQR: 4.25–17.5). This is similar to what has been described in other studies, in which increases in Ki-67 index have been correlated with poor outcomes (22).

Interestingly, a higher value of Ki-67 at G3 progression within our study population did not directly correlate with a shorter OS, presented in Supplementary Table 4 where Ki-67 progression over time is summarized. This might be due to the biopsies being taken from slower-growing clone of tumor cells in lesions with intra-tumoral heterogeneity. Furthermore, as this was a historical material, the cohort had not been characterized by modern diagnostic techniques. Particularly, PET/CT imaging is currently utilized more frequently in clinical practice and plays an important diagnostic and prognostic role, especially for panNENs. Dual imaging, with both fluoro-deoxy-glucose (FDG)–PET/CT to assess tumor metabolic activity and ^{68}Ga-DOTA-somatostatin analog-PET/CT for the characterization of tumor somatostatin receptor expression, may predict whether the disease will run an indolent or more aggressive course. In our study, FDG–PET-guided biopsies of lesions with higher metabolic activity were not performed. The lack of correlation between OS and Ki-67 index may also have been due to the effects of previously administered systemic therapies. Recently, the longitudinal effects of platinum- or 5-FU-based chemotherapy were analyzed in 20 patients with PD-NEC (23) who underwent biopsy. A reduction in Ki-67 and tumor grade was observed in post-treatment tumor samples, from high grade to G1–G2.

The selection bias, incomplete data for outcome analysis and local treatment traditions should restrict any reader from generalizing our data to a wider perspective. Clearly, a prospective study design and/or a matched control group would allow for a more precise analysis of treatment responses and outcomes by reducing bias and improving data quality. Compared to previously published findings, this cohort should be regarded as a large and well-characterized group of patients with secondary panNET-G3, providing an opportunity to screen for therapeutic agents that could have promising effects in this particular NET entity. However, this study pinpoints knowledge gaps and by doing so provides a potential for gathering important information by performing longitudinal studies of panNETs.

Emerging data indicate that the genetic landscape of metastatic NETs changes during the disease course. Scott *et al.* (24) analyzed the gene expression profile in metastatic lesions of patients with WD-panNET and compared this to that of their primary tumors. They found that drugs targeting MEK and TOP2A may be the most efficient treatment for panNET metastases. Recent studies on the efficacy of PRRT in high-grade NET with positive somatostatin receptor uptake on ^{68}Ga-DOTA-TOC/TATE-PET/CT have shown promising results (12, 25) and may represent a suitable candidate for future clinical trials in secondary panNET-G3. The role of debulking surgery or localized therapies, in metastatic panNET, targeting a single growing lesion, is controversial. To date, this has not been extensively studied, and it is thus not known if it should be recommended for all patients with ^{68}Ga-DOTA-TOC/TATE-negative and FDG-positive lesions, or reserved for selected cases.

Based on these data, we propose that in future trials for panNET patients, late in their disease course, a new biopsy should be considered in order to allow for adequate tumor characterization.

Our findings in the present study have encouraged us to initiate a prospective, longitudinal, observational study, in which progressive panNET patients treated at our institution are offered inclusion for recharacterization of their disease (NCT03130205). Additional studies of a comparative nature are needed in order to identify optimal therapeutic options for this fragile patient group.

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Conclusions

In this unique cohort of secondary panNET-G3, the patients received heterogenous treatment regimens, and only one patient demonstrated an objective response. A poor OS was observed in patients receiving conventional NET therapies and platinum–etoposide, respectively. Thus, this study failed to identify any promising treatment candidate for secondary panNET-G3, thereby highlighting the unmet need for more data on this patient group, to fuel the development of new therapies.

Supplementary materials

This is linked to the online version of the paper at https://doi.org/10.1530/EC-21-0604.

Declaration of interest

J B received lecture honoraria from Novartis. A S had lecture honoraria from Ipsen and from Advanced Accelerator Applications for external imaging expert work. J C received lecture honoraria from Novartis and IPSEN and is a member of the Knowledge Network and NETConnect initiatives funded by Ipsen. The other authors declare no conflict of interest.

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Author contribution statement

K M and J C conceptualized and designed the study. K M and A S collected and analyzed radiology data. K M collected and analyzed clinical data. B S, J B, T Å, B E, S W, A S and J C contributed resources and infrastructures. K M and J C wrote the manuscript which was critically reviewed by all authors.

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