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The Role of Cytotoxic Chemotherapy in Advanced Pancreatic Neuroendocrine Tumors

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Abstract
Background: Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms accounting for less than 5% of all pancreatic malignancies. These tumors are characterized by clinical and prognostical heterogeneity and are predominantly diagnosed in a metastatic stage. Cytotoxic chemotherapy, along with alkylating agents and antimetabolites as well as molecular targeted agents (everolimus, sunitinib), is used in the treatment of advanced PNETs. After the approval of lanreotide for unresectable PNETs, an additional therapeutic option has become available; however, the best sequence of therapies and patient stratification to different treatments remains challenging. Furthermore, no randomized phase-3 trials or head-to-head comparisons are available to support treatment decisions. ***Summary:*** The publication of 3 large single-center retrospective studies on streptozocin-(STZ)-based chemotherapy in advanced PNETs in 2015 confirmed the effectiveness of this treatment as described in previously reported trials. All studies investigated markers for progression-free and overall survival and strongly supported the value of the Ki-67 index as a robust prognostic marker. Interestingly, chemotherapy consistently displayed antitumor efficacy in different therapeutic lines. Moreover, a recent study of dacarbazine (DTIC) in a cohort of patients predominantly with PNETs demonstrated that a once monthly infusional DTIC schedule was well tolerated and yielded similar response rates (RR) as STZ-based schedules. Given the overall good tolerability of a monthly infusion and RR similar to STZ schedules, DTIC thus represents a feasible alternative or additional treatment option for PNETs. In this article, we review the current standard and summarize the most recent advances in the field of cytotoxic chemotherapy for PNET patients. ***Key Messages:*** (1) Despite the lack of phase3 trials, cytotoxic chemotherapy offers efficacy for patients with advanced PNETs; (2) the best therapeutic option and sequence remain open since comparable randomized studies are lacking; (3) careful patient selection and treatment stratification may increase overall outcome; and (4) currently, no biomarkers for clinical routine exist to predict response to chemotherapy.

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Introduction and Epidemiology

Neuroendocrine tumors (NET) form a heterogeneous group of neoplasms with increasing incidence over the last decades [1, 2]. Compared to other malignancies, their indolent course and biological behavior are mostly associated with better prognosis. Pancreatic neuroendocrine tumors (PNETs) account for less than 3% of all pancreatic malignancies with estimated incidences of <0.5/100,000 worldwide [1, 3]. Interestingly, the incidence of PNETs varies depending on region and data acquisition. Recently, a systemic review compared epidemiological data obtained in North America, Western Europe, and Japan. The incidence rates of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) seem to have significantly increased over the last decades revealing major differences in the incidence rates of PNETs according to gender, race, and country [4]. Surprisingly, different analyses of the SEER database yielded variable PNET incidence rates, most likely based on interobserver bias and inappropriate evaluation strategies [5, 6]. Data from a cohort of patients with newly diagnosed GEP-NETs prospectively collected over one year revealed an overall incidence rate for GEP-NETs of 2.39 per 100,000 inhabitants, of which only a small fraction of 11.6% (incidence of 0.25 per 100,000) had a PNET [7]. Overall these results were in line with those of previous publications and confirm that PNETs are a rare tumor entity and only represent a small subfraction of all GEP-NETs.

Current Standard of Treatment

Several characteristics such as functionality, proliferation index, stage, and spontaneous tumor growth influence the prognosis of PNET patients, which renders this disease a diagnostic and therapeutic challenge (Fig. 1). As symptoms often occur late, 60–90% of patients with PNETs present in an advanced stage with distant metastases at the time of the initial diagnosis [8–10]. Whether resection of the primary tumor in metastatic disease or synchronous resection of hepatic metastases is indicated is still a matter of debate. In retrospective studies that are limited by patient selection, primary tumor resection done with the intention to limit the disease, to deliver, and to avoid local complications, as well as surgical treatment of liver metastases have shown to improve the long-term outcome of PNET patients [11–13]. However, this approach needs validation in prospective controlled trials. [10]. When multiple unresectable liver metastases are present or multiple distant organs are involved, systemic treatment is indicated. The CLARINET trial introduced somatostatin analogues (SSA) for PNETs with Ki-67 values of up to 10% and revealed an improvement of the progression-free survival (PFS; 29.7 months in the lanreotide group vs. 12.1 in the placebo group) [14, 15]; however, the limitation of the study was that the majority of patients had stable disease (96%) prior to study entry. Despite their effectiveness and good safety profile, SSA should thus be used only in carefully selected patients with metastatic PNETs. The ENETS guidelines recommend the initiation of SSA treatment rather than to watch and wait at the time of diagnosis in patients with NET of pancreatic origin, extended disease, and higher liver burden, since these criteria are indicative of an inferior prognosis [16].

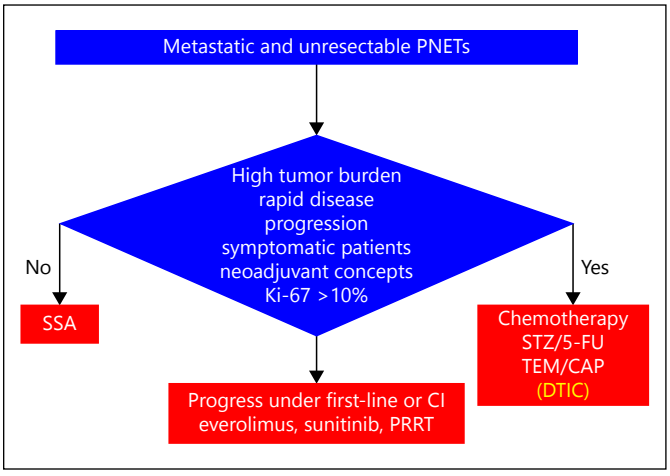

Fig. 1. Treatment algorithm for metastatic and unresectable pancreatic neuroendocrine tumors.

However, particularly for PNETS, the spontaneous clinical course and the growth rate using the Ki-67 value (<10%) as its surrogate are important criteria to stratify which patients are the best suited to be given a first-line treatment with SSA.

When patients progress under SSA therapy or exhibit features of a symptomatic or aggressive disease and/or Ki-67 values >10%, cytotoxic chemotherapy should be considered first-line treatment of choice [16]. Two classes of drugs are used to treat well-differentiated PNETs comprising alkylating agents such as streptozocin (STZ), temozolomide (TEM), dacarbazine (DTIC), and antimetabolites such as 5-fluorouracil (5-FU) and capecitabine (CAP). The use of the anthracycline doxorubicine (Dox)

Table 1. Dacarbazin-based chemotherapy, response rates, and outcomes

Author	Year	Protocol	Patients, *n*	RR, %	mPFS, months	mOS, months
Kessinger et al. [32]	1983	DTIC 5 days 250 mg/m^2 every 28 days	11	27	3–53	–
van Hazel et al. [33]	1983	DTIC 5 days 250 mg/m^2 every 28–35 days	50	4	4.2	11
Altimari et al. [34]	1987	DTIC 5 days 250 mg/m^2 every 28 days	14	50	–	–
Bukowski et al. [35]	1994	DTIC 650/850 mg/m^2 day 1 every 21 days	56	16	–	20
Hatton and Reed [36]	1997	DTIC 600 mg/m^2 day 1 every 21 days	19	53	10	–
Ramanathan et al. [37]	2001	DTIC 850 mg/m^2 every 28 days	50	34	10	19.3
Sun et al. [38]	2005	DTIC crossover 1–5 days 250 mg/m^2 every 28 days after 5-FU/DOX or 5-FU/STZ	249 (91)	8.2	4.1	11.9

RR, response rate; mPFS, median progression-free survival; mOS, median overall survival; DTIC, dacarbazine.

is limited due to cardiotoxicity occurring after a cumulative dose of 500 mg/m^2 has been reached. At present, the combination of STZ and 5-FU is recommended as the standard combination regimen rather than STZ combined with Dox. Two STZ/5-FU schedules are presently used in clinical care, comprising the Moertel protocol (500 mg/m^2 STZ on day 1–5 and 400 mg/m^2 5-FU on day 1–5, repeated every 6 weeks) and the Uppsala protocol (500 mg/m^2 STZ on day 1–5 and 400 mg/m^2 5-FU on day 1–3 followed by 1-day treatment with 1,000 mg/m^2 STZ and 1-day treatment with 400 mg/m^2 5-FU every 3 weeks) [17, 18]. STZ was initially described as diabetogenic substance, though the underlying mechanism remained unclear for decades [19]. STZ is a glucose analogue, which is selectively incorporated into the beta cells of the pancreas via GLUT2 transporters [20]. After incorporation, STZ accumulates in β-cells and leads to cytotoxicity and finally to diabetes via the alkylating activity of STZ and the generation of ROS [21]. Interestingly, common side effects of STZ in kidney and liver could mechanistically be explained by the expression of GLUT2 transporters in these organs [22]. Several studies have assessed the efficacy of STZ combined with 5-FU for the treatment of PNETS. Response rates were reported to be as high as 69%; however, major variations in efficacy and outcome were reported [17, 18, 23–25]. TEM and CAP represent attractive alternatives to intravenous chemotherapy and have recently gained popularity over the last years. Both drugs are available as orally active compounds and thus are far more convenient for patients. TEM monotherapy has a long tradition in glioblastoma and melanoma, though in PNETs it was described to have only marginal benefits [26]. Therefore, combination regimens were evaluated revealing impressive objective response rates (RR) and good tolerability for the TEM-CAP combination therapy [27–31]. However, due to the limited availability of data and prospective clinical trials, the current guidelines recommend the TEM-CAP combination only as an alternative but not superior treatment to STZ/5-FU. Further ongoing studies will contribute to clarify this situation and may change our practice in the future (NCT01824875, NCT01525082, NCT01465659, NCT02231762). The alkylating agent DTIC, which shares the active metabolite MTIC with TEM, has also been used for the treatment of advanced NET. Most studies were conducted using triple combinations with 5-FU, epirubicin, or leucovorin, though some studies well evaluated the efficacy of DTIC monotherapy (Table 1). Despite heterogeneous application schedules and dosages, RR of up to 50% and median PFS of 10 months have been reported [32–38]. However, the enthusiasm to recommend DTIC-based regimens for the treatment of patients with PNETs

has been low, since different schedules and dosages have been associated with severe toxicities. At present, only one controlled trial using a DTIC-5-FU combination together with an experimental drug has been done in PNET patients (NCT01845675). In fact, the current guidelines do not recommend DTIC for the treatment of advanced PNET stages and only limited efforts have been taken so far to increase the knowledge of efficacy of this chemotherapeutic agent.

Besides cytotoxic chemotherapy, targeted therapies such as everolimus and sunitinib were approved for the treatment of metastatic PNETs [39, 40] 5 years ago. Although, with both drugs most patients achieved disease stabilization with less than 10% objective responses, median PFS improved from 6 to approximately 12 months as compared to placebo controls. Both drugs are approved and recommended for second-and third-line treatment of well-differentiated PNETS after disease progression either to chemotherapy or SSA-treatment. Thus, several therapeutic options are now available for advanced PNETs, though there is no evidence in which sequence they should be used. In this context, the SEQTOR trial currently assesses the activity of chemotherapy with STZ/5-FU followed by everolimus versus the reverse sequence until disease progression occurs. The results of this European multicenter study have to be awaited and similar study approaches are mandatory for a better understanding of the optimal sequence of available treatment options. Furthermore, no trials comparing the efficacy of targeted therapies, chemotherapy, or SSA treatment are available. In light of the available evidence, an interdisciplinary discussion in a specialized GEP-NET tumor board at present is still the best way to determine the most suited treatment for each individual patient at a given time (Fig. 1).

Recently Published Studies Confirming the Role of Chemotherapy in PNETs

In 2015, 3 studies on the use of STZ-based cytotoxic chemotherapy in patients with advanced well differentiated PNETs were published [41–43] (Table 2). All 3 studies were carried out at ENETS centers of excellence (Uppsala, Berlin, Marburg) and represent retrospective single-arm observations without a control group (Table 2). The number of included patients ranged between 77 and 133 and all studies reported radiological objective RR based on RECIST 1.1 criteria. Whereas the Uppsala and Berlin cohorts exclusively comprised PNETs, the Marburg cohort additionally included a fraction of 15% NETs from other primary locations. As mentioned above, different STZ-based treatment schedules were employed. Whereas the Uppsala protocol was used in Sweden and the Moertel protocol in Berlin, in Marburg, besides STZ/5-FU, the combination of STZ and Dox was used in 40% of the patients. In terms of patient characteristics, most patients presented with metastatic disease (90%) and liver was the primary organ of manifestation (Berlin: 90.6%, Marburg: 88.3%, Uppsala: not reported). Seventy-nine percent of the patients in the Marburg cohort had ≥2 distant disease sites (66.2% lymph nodes, 39% bone lesions), whereas only 32.3% of the patients in the Berlin cohort presented at least 2 distant sites. In all 3 cohorts, the majority of patients had well differentiated (73.7–90.7%) and nonfunctional tumors (54.1–77.1%). Prior therapies were not evenly distributed in the 3 cohorts. Although 20–30% of patients received SSA, chemotherapy and loco-regional approaches were more frequently used prior to chemotherapy in Marburg; thus, only 19.5% of the patients in this cohort were treatment naive as compared to approximately 60% in the 2 other cohorts. Besides prior systemic treatments, some patients underwent surgical resection of the primary tumor (Uppsala 28.6%; Marburg: 29.9%) and surgery intended to reduce the tumor mass (Berlin: 44.8%). The objective RR reported in the 3 studies were similar and ranged between 28 and 42%, with a high rate of disease control ranging between 72 and 92%. All groups provided evidence for a correlation between radiological and biochemical response, though definitions of biochemical response were variable (reduction of serum chromogranin A levels >30% or >50%). Additional potential predictive clinical, biochemical, and imaging markers were studied, but only a positive somatostatin receptor status was reported to be of predictive value in the Marburg cohort. The reported outcome measures median PFS, and overall survival (OS) appeared to be superior in the Uppsala and Berlin cohorts as compared to patients in the Marburg cohort (median PFS/TTP: 23 vs. 19.4 vs. 16 months; median overall survival: 51.9 vs. 54.8 vs. 28 months). The reason for this discrepancy became obvious when comparing the patient criteria of the different cohorts. At the start of chemotherapy treatment, the Marburg patients had received more prior treatments resulting in a median time to cytotoxic therapy of approximately 3 years. Moreover, patients endured more advanced diseases with a higher involvement of additional organ sites besides the liver, which was reported to be an important prognostic factor in the Berlin cohort. Fur-

Table 2. Characteristics of recently published studies of chemotherapy in advanced pancreatic neuroendocrine tumors

	Clewemar et al. [41], 2015	Dilz et al. [42], 2015	Krug et al. [43], 2015	Mueller et al. [46], 2016
Regimen	STZ/5-FU 1981–2014	STZ/5-FU 1998–2014	STZ/Dox/5-FU 1995–2013	DTIC 1998–2013
Number of patients	133 (100 radiologically evaluable)	96 All radiologically evaluable	77 (66 radiologically evaluable)	75
Localization	100% pancreas	100% pancreas	84.4% pancreas	66.6% pancreas
Population	88% stage IV 54.1% FNA 73.7% G1/2 6% MEN-1	93.8% stage IV 77.1% FNA 90.7% G1/G2 90.6% liver metastases	90.9% stage IV 71.5% FNA 77.9% G1/G2 88.3% liver metastases	97.4% stage IV 81% G1/G2 97% liver
Objective response rate	28%	42.7%	34%	27% (32% pancreas)
Disease control rate	92%	83.3%	72%	66% (66% pancreas)
Markers of response	CgA decrease >50%	CgA decrease >30%	CgA decrease >30% positive Octreo-Scan	–
mPFS/TTP	23 months	19.4 months	16 months	10 months
mOS	51.9 months	54.8 months	28 months	–
Survival rates	5-year: 38.3% 10-year: 16.5%	5-Year: 44.9%	–	–
Prognostic factors PFS/TTP (univariate)	Gender Functionality Grading	Ki-67 >15%	Ki-67 >10% Objective response Biochemical response	Grading Objective response Biochemical response
Prognostic factors PFS/TTP (multivariate)	Grading Stage IV	Ki-67 >15%	Ki-67 >10%	–
Prognostic factors OS (univariate)	Grading Previous surgery	Ki-67 >15% Liver burden >10% ≥2 metastatic sites	Ki-67 >10% Performance status Primary tumor resection Disease control	
Prognostic factors OS (multivariate)	Grading Previous surgery	Ki-67 >15% Metastatic sites ≥2	–	–
Prior therapies	23.3% SSA 16.5% chemotherapy	31.3% SSA 6.3% chemotherapy	29.9% SSA 27.4% chemotherapy 20.8% loco-regional	–
No prior treatment	63.2%	56.3%	19.5%	5.3%
Discontinuation due to side effects	29/133 (21.8%)	16/96 (16.6%)	10/77 (13%)	2/75 (3%)
Specifics	27.8% SSA synchronous with CTx 28.6% primary tumor resection	44.8% prior surgical resection 64.7% liver burden <25%	29.9% primary tumor resection time to CTx 33m	44% liver only disease

STZ, streptocozin; 5-FU, 5-fluorouracil; Dox, doxorubicin; DTIC, dacarbazine; RR, response rate; mPFS, median progression-free survival; mOS, median overall survival; TTP, time to progression; CTx, chemotherapy.

thermore, since chemotherapy was mostly the second- or third-line of treatment in the Marburg cohort, it is obvious that more disease progressions must have occurred. The impact of disease progression and Ki-67 values on the outcome of patients with PNETs is well known [9, 44]. All 3 studies confirmed the value of Ki-67 values as prognostic markers with a major impact on PFS and OS. Whereas in the Uppsala cohort the grading according to the WHO 2010 classification was a robust prognostic parameter, the other 2 groups presented Ki-67

Table 3. Toxic reactions of different chemotherapy protocols

Toxic reactions	STZ/5-FU		TEM-CAP		DTIC	
	500 mg/m^2 STZ days 1–5, 400 mg/m^2 5-FU days 1–5 every 6 weeks		750–1,000 mg/m^2 CAP twice daily days 1–14, 150–200 mg/m^2 TEM once daily days 10–14 every 4 weeks		650 mg/m^2 every 4 weeks	
	grades 1–2	grades 3–4	grades 1–2	grades 3–4	grades 1–2	grades 3–4
Hematologic, *n* (%)						
Leukopenia	5–60	<5	10–50	5–10	<10	
Thrombocytopenia	5–15		10–20	10	<5	
Anemia	25–35		<10	<5	<5	
Gastrointestinal, *n* (%)						
Nausea or vomiting	30–40	<10	15–25		45–70	5–15
Diarrhea	10–20		<5	<5	15–20	
Hepatologic, *n* (%)	60	<5	<5	<5	5–15	
Renal, *n* (%)	25–50	<5				
Fatigue, *n* (%)	20–25		10–50	<5	<5	
Hand-foot syndrome, *n* (%)	<5		15–35			

STZ, streptocozin; 5-FU, 5-fluorouracil; DTIC, dacarbazine.

cutoff values of 10 and 15% as surrogates for poor outcome in the PFS and OS analyses. Although Ki-67 values were shown to predict response [45], this is most likely due to their strong prognostic impact. Even so, published data suggest that STZ-based chemotherapy is effective in patients with PNET regardless of the line of treatment applied.

Very recently, Mueller et al. [46] published a large retrospective study of patients treated with DTIC (650 mg/m^2 every 4 weeks). This report reintroduced DTIC as effective, safe, and cost-effective therapeutic option in a cohort of PNET patients predominantly with advanced stages of disease. The objective response and disease control rates were 32 and 66%, respectively, and thus quite similar to the STZ combination regimens. For patients who achieved objective response or disease stabilization with DTIC, median PFS times ranging from 18 to 27 months were observed. Since DTIC was applied in heavily pretreated patients with progressive disease, remarkable efficacy is underscored. However, further studies are required to characterize the role of DTIC monotherapy in a more homogenous and well-defined collective.

Finally, 2 series of the TEM-CAP combination therapy in PNET patients were published in 2016. A Spanish multicenter study and the single-center experience of Cives et al. [30] revealed very similar results in terms of response and outcome [31]. Response rates were 47.7 and 54% with additional disease stabilization rates of 41.5 and 35% respectively. Whereas the median PFS reached approximately 17 months in both studies, large differences were reported for OS (38.3 vs. 73.2 months). However, it remains to be clarified whether TEM-CAP oral combination therapy is more than just a more convenient alternative therapeutic option for the present standard: STZ-based combination chemotherapy.

Chemotherapy-Related Adverse Events

Besides its efficacy, cytotoxic chemotherapy is commonly associated with toxic reactions (Table 3). When assessing side effects, we have to take into consideration that the majority of studies are of retrospective design. Thus, evaluable patients for side effects differ between 50 and 100% in the studies and the quality of documentation may vary and lead to quite different results [41–43]. In addition, inadequate information is presented about supportive treatment and older studies may not reach the current standard, for instance, in preventing nausea and vomiting. From this point of view, it is ambitious to compare the rate and severity of side effects of the protocols reported in different studies. However, it is mandatory to explain major complications that can impair quality of life and lead to the discontinuation of the treatment [31, 41–43, 46]. Low-dose DTIC monotherapy was well tolerated with a lower rate of side effects compared to the com-

bination schedules. Whereas hematological events occurred less frequently (<10% grades 1–2, no grades 3–4), major complications were documented for gastrointestinal toxicities. Almost all patients experienced nausea and vomiting with some grades 3–4 events (5–15%), which can currently be reduced by the use of a 3-drug prophylactic regimen (neurokinin 1 antagonist, a 5-hydroxytryptamine-3 antagonist and dexamethasone) for highly emetogenic agents like DTIC. Moderate hematotoxicity was seen in about half of the patients treated with the combination schedules STZ/5-FU and TEM-CAP. Hematological grades 3–4 toxicities occurred in less than 5 and 3–11% in STZ/5-FU and TEM-CAP-treated patients respectively. The STZ/5-FU combination frequently exhibited renal and hepatological adverse events (50–60%) followed by nausea and vomiting (30–40%) and diarrhea (10–20%). Although these events were grades 1–2, special attention has to be paid to nephrotoxicity of STZ, which should lead to the discontinuation of this treatment if adverse effects persist despite prophylactic hydration. TEM-CAP treatment was better tolerated in terms of vomiting, nausea (<25%), diarrhea (<5%), and renal and hepatological events (<5%). Relevant major side effects were caused by fatigue (10–50%) and hand-foot syndrome (up to 35%). The hand-foot syndrome also known as palmar-plantar erythrodysesthesia is a common adverse event caused by CAP. Besides dose reduction and treatment interruption, local and systemic anti-inflammatory therapies along with lifestyle changing factor like reduce friction and heat exposure are treatment options.

Predictive Markers for Chemotherapy in PNETs

Well-established biomarkers in pancreatic neuroendocrine tumors are the Ki-67 proliferation index and chromogranin A serum levels which, however, have no role to play as predictive biomarkers for response to chemotherapy. Recently, the group of Marinoni et al. [47] and Schmitt et al. [48] described that DAXX, ATRX, and MGMT (O[6]-methylguanine DNA methyltransferase) expression are associated with impaired outcome. The value of MGMT, however, in predicting chemotherapy response to alkylating agents is still a matter of debate. One major problem is the determination of MGMT activity either by immunohistochemistry or by promoter methylation assays. Unfortunately, no consistent correlation between both methods could be detected [48]. While Kulke and coworkers [49] observed significant correlations between MGMT protein expression and response to TEM, the articles of Schmitt et al. [48] and Walter et al. [50] only confirmed this correlation with respect to promoter methylation status. Very recently, Cives et al. [30] analyzed 143 patients treated with TEM-CAP with regard to their MGMT and ALT (alternative lengthening of telomeres) status as potential predictive biomarkers. However, treatment efficacy did not appear to be influenced by these markers. In conclusion, studies are warranted to systematically correlate new biomarkers and response to chemotherapy in prospective trials.

Perspectives

The therapy of PNETs is increasingly complex involving multimodal therapy algorithms requiring close interactions within a multidisciplinary team including surgeons, nuclear physicians, gastroenterologists, and oncologists. To date, only 3 randomized phase-3 trials were published for patients with advanced or recurrent disease. All studies were performed with placebo arms. Furthermore, no comparative trials of SSA, molecular targeted treatments, peptide receptor radionuclide therapy, or cytotoxic chemotherapy are available. At present, the SEQTOR trial is the sole European study to assess the best sequence of STZ/5-FU followed by everolimus versus the reverse sequence. The next generation of clinical trials must be designed to address the pivotal challenge of comparison and sequence studies to improve the care for PNET patients.

Disclosure Statement

The authors declare no conflicts of interest.

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