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The efficacy of streptozotocin in managing pancreatic neuroendocrine neoplasms – A systematic review

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ABSTRACT

Pancreatic neuroendocrine tumors (pan-NETs) represent a highly heterogeneous and complex pathology, with therapeutic management and prognosis influenced by several biological and clinical characteristics. Chemotherapy, including regimens based on capecitabine and temozolomide (CAPTEM) or the combination of streptozotocin and 5-fluorouracil (STZ-5FU), is indicated for rapidly growing, symptomatic, or high-burden disease requiring swift cytoreduction. Historical studies provide scientific evidence for the STZ-5FU regimen, often retrospective and frequently analyzing small series. Despite these limitations, the efficacy of this treatment is well-established, and it is included in all guidelines as a therapeutic option. This systematic review aims to gather scientific evidence on using STZ-based chemotherapy to assess its real impact in managing well-differentiated metastatic or unresectable pan-NETs.

Introduction

Pancreatic neuroendocrine neoplasms (pan-NENs) are rare and heterogeneous tumors. Although their incidence has increased over the past few decades, there are still only approximately 0.3–0.8 new cases per 100,000 individuals per year [1,2]. These highly complex diseases can exhibit various biological characteristics significantly affecting patient prognosis. Like all NENs of the digestive system, they are divided into four main categories according to the WHO 2022 classification: neuroendocrine tumors (NET) G1 (well-differentiated, with Ki67 < 3 %), NET G2 (well-differentiated, with Ki67 3–20 %), NET G3 (well-differentiated, with Ki67 > 20 %), and neuroendocrine carcinomas (NEC or poorly differentiated, with Ki67 always > 20 %) [3]. This classification serves as the cornerstone for most therapeutic decisions.

In the majority of cases (approximately 60 %), pancreatic NETs (pan-NETs) are already metastatic or otherwise non-resectable at the time of diagnosis, necessitating systemic medical therapy [4]. In cases of G1 or G2 NETs (preferably with Ki67 < 10 %) where there is neither rapid growth nor an extensive disease burden, first-line therapy typically involves somatostatin analogs (SSA), provided the tumor expresses somatostatin receptors [5]. In cases of disease progression with SSA, international guidelines allow for several alternative approaches, including peptide-receptor radionuclide therapy (PRRT), targeted therapies such as everolimus or sunitinib, or chemotherapy [4,6]. For well-differentiated pan-NETs, chemotherapy may include regimens based on capecitabine and temozolomide (CAPTEM) or combinations of streptozotocin and 5-fluorouracil (STZ-5FU) [4,6].

These systemic chemotherapy options can also be used as upfront treatments in cases of rapid disease progression, where patients exhibit symptoms related to tumor presence or growth, where somatostatin receptor expression is suboptimal, or in certain subgroups of patients with locally advanced tumors that are borderline resectable. In these

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scenarios, a primary goal is rapid tumor mass reduction. Regarding the scientific evidence for the STZ-5FU regimen, much of the available data is from older studies, often retrospective and with small sample sizes [7]. Nevertheless, the efficacy of this treatment is well-documented, and it remains a feasible therapeutic option for pan-NETs in current guidelines, although a notable degree of disagreement exists among guidelines regarding the therapeutic sequence for pan-NETs beyond the first-line approach [8].

This systematic review aims to compile scientific evidence on chemotherapy regimens that include streptozotocin to understand better its impact on the management of patients with well-differentiated, metastatic, or non-resectable pan-NETs.

Methods

Eligibility criteria

We included retrospective, prospective, randomized, and non-randomized trials that investigated the efficacy, activity, and toxicity profile of STZ-based regimens in pan-NETs. The primary endpoint was to assess overall response rates (ORR), defined as the percentage of patients achieving either partial response (PR) or complete response (CR) according to RECIST 1.1 criteria.

Secondary endpoints included: a) disease control rate (DCR), defined as the percentage of patients with PR, CR, or stable disease (SD) per RECIST 1.1 criteria; b) progression-free survival (PFS), measured from study enrollment to the first evidence of disease progression or death from any cause; c) overall survival (OS), defined as the time from study enrollment to death from any cause; and d) safety profile, evaluated according to CTCAE criteria.

The search was limited to English-language studies on humans. Case reports, case series, editorials, commentaries, *meta*-analyses, and review articles were excluded.

Search strategy and data Extraction

We performed a systematic search, according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [9], on PubMed and Scopus until March 2024 to identify available articles investigating the use of streptozotocin in NENs (PROSPERO registration code: 541168). The search strategy was (streptozotocin OR STZ OR "streptozocin"[MeSH Terms]) AND (pancreatic[tiab] AND (neuroendocrine[tiab] OR "Neuroendocrine Tumors"[MeSH Terms] OR "Neuroendocrine Neoplasms"[tiab] OR NEN [tiab] OR NET[tiab])) on PubMed, while was "(TITLE-ABS-KEY(streptozotocin) OR TITLE-ABS-KEY(STZ)) AND(TITLE-ABS-KEY(pancreatic) AND (TITLE-ABS-KEY(neuroendocrine) OR TITLE-ABS-KEY("Neuroendocrine Tumors") OR TITLE-ABS-KEY("Neuroendocrine Neoplasms"))) on Scopus. Other articles not comprising the initial search but relevant to our topic were included in our analysis.

Two investigators (G.A. and F.P.) independently reviewed titles and abstracts of the manuscripts of included studies and extracted data for inclusion and exclusion criteria, study design, and endpoints.

Results

Studies selection

Using the specified search strategy, a total of 263 articles were identified (165 from PubMed and 98 from Scopus), with an additional 11 records found through other sources. Screening titles and abstracts led to the exclusion of 179 articles due to irrelevant topics. Among the 95 remaining potentially relevant articles, we removed 24 duplicates, leaving 71 articles for eligibility assessment. After further exclusions—nineteen reviews, seven case reports, two preclinical studies, four articles on irrelevant topics, one article lacking available endpoints, and one non-English full-text article—37 articles were included in the final analysis. The PRISMA 2020 flow diagram illustrating the search strategy is shown in Fig. 1.

Characteristics of included studies and population

Of the 37 articles included in the final analysis, published between 1974 and 2024, 28 were retrospective studies, 2 prospective studies, 1 retrospective/prospective study, 1 phase I-II study, 2 phase II studies, and 3 randomized trials. In the two randomized trials by Moertel, the 5FU-STZ regimen was compared with the combination of Doxorubicin-STZ or chlorozotocin [10] and with STZ alone [11]; in Meyer's trial [12], STZ plus capecitabine was compared to STZ-capecitabine-cisplatin.

Our analysis included a total of 2,184 patients. Regarding the primary tumor site, 70 % of the studies (n = 26) enrolled exclusively patients with pan-NETs, totaling 1,927 patients, while 30 % (n = 11) included non-pancreatic gastrointestinal NETs, totaling 120 patients. Additionally, seven trials included patients with lung carcinoids and neuroendocrine tumors of unknown or other origins, comprising 35 and 69 patients, respectively. Focusing on histopathological classification, seven studies reported a diagnosis of "pancreatic islet cell carcinoma," while eight records referred to "neuroendocrine tumors" or "well-differentiated neuroendocrine tumors" without specifying tumor grade. Most patients treated with STZ-based chemotherapy were diagnosed with G1-2 NETs (n = 883); 121 patients had G3 NETs, and 24 had poorly differentiated or NEC.

The most commonly used combination regimens were STZ-5FU (n = 25 studies, 67.5 %) and STZ-anthracyclines (n = 18 studies, 48.6 %), primarily administered in advanced, non-resectable, or metastatic disease as first-line or subsequent therapy (n = 35 studies, 94.6 %). Other STZ combination regimens investigated included CDDP, S-1, tegafur, bevacizumab, and everolimus or sunitinib.

Two studies specifically investigated the STZ-doxorubicin combination in metastatic disease, targeting either cases with potentially resectable liver-only involvement or localized disease [13,14]. Table 1 provides a list of all studies included in the review.

Efficacy outcomes: Progression-free survival and overall survival

The median PFS in metastatic diseases was 14.5 months (range 3.9 to 31 months), as reported in 23 studies. In contrast, in studies investigating STZ-based chemotherapy as a perioperative treatment [13,14], the median recurrence-free survival (RFS) was 25.1 months in liver-only resectable metastatic pan-NETs and 38 months in locally advanced pan-NETs.

The median OS, reported in 30 studies, ranged from 10.9 to 69 months, reaching up to 108.2 months in liver-only resectable metastatic pan-NETs—with better outcomes observed for resected patients—and 107 months in locally advanced pan-NETs. The median OS across all patients included in this review was 37.5 months. Table 2 summarizes the efficacy outcomes.

Objective response

The median DCR for the entire population, reported in 36 of 37 studies, was 79 % (range: 12.5 %-100 %), while the median ORR (CR + PR), assessed in 35 studies, was 33 % (range: 4 %-63 %).

In the context of advanced, non-resectable, or metastatic NENs, STZ-based chemotherapy used as first-line or beyond achieved a median DCR of 76.9 % and a median ORR of 33 %. Median values for CR, PR, and SD were 0 %, 30 %, and 45 %, respectively. Progressive disease was observed in 18.2 % of cases. In the two trials investigating STZ-based regimens in a preoperative setting, a DCR of 92.6 % and ORR of 63 % were observed in liver-only, potentially resectable pan-NETs [13]. In contrast, in locally advanced pan-NETs, DCR and ORR were 97 % and 7

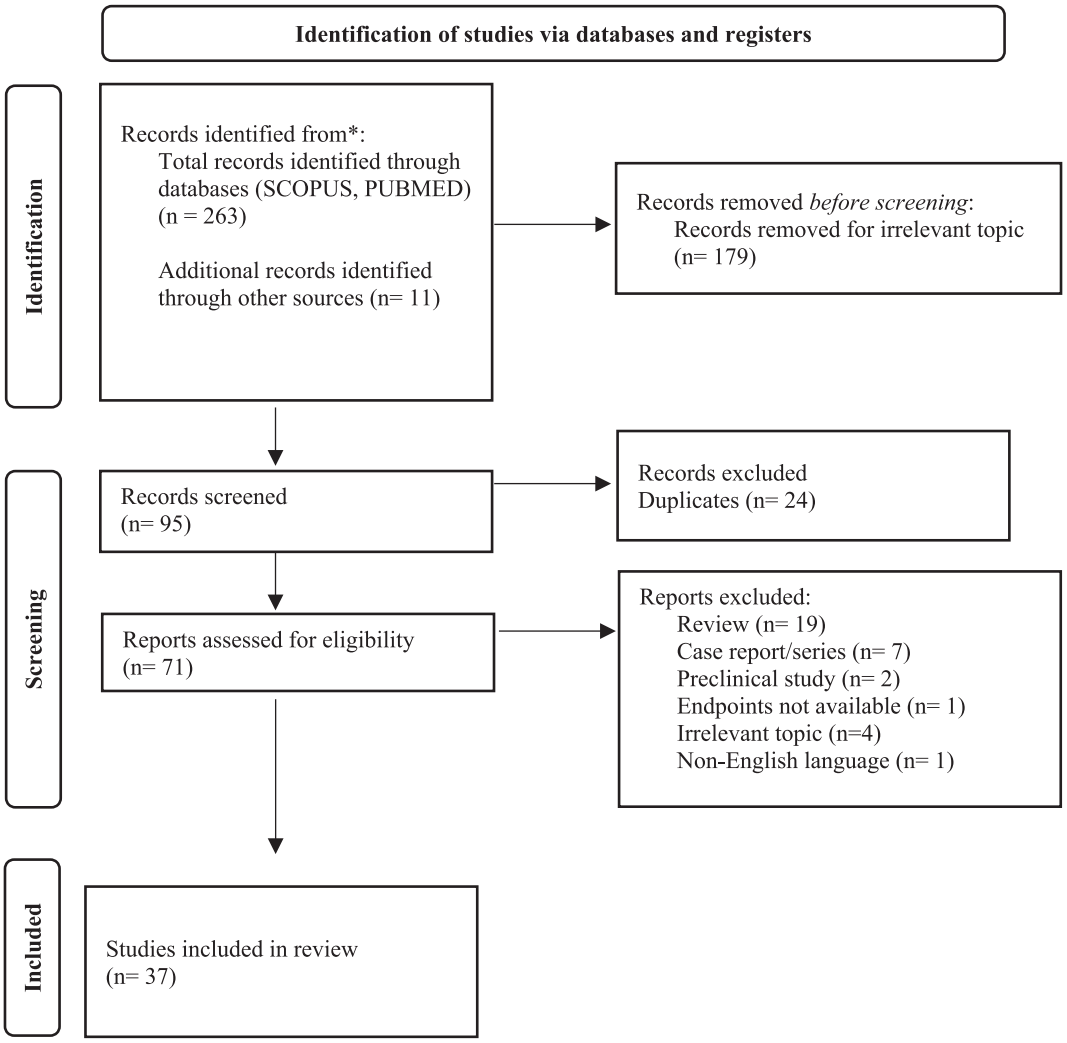

Fig. 1. PRISMA 2020 flow diagram for the search strategy.

%, respectively [14]. Most responses were SD at 29.6 % and 90 %, respectively, with no CR achieved in either study.

When grouped by treatment protocol, response data for triplet chemotherapy with STZ, 5-FU, and doxorubicin were available in two trials [22,42], showing a DCR of 87.5 % and an ORR of 40 %. For doublet chemotherapy, 13 studies reported a DCR of 80 % and an ORR of 33 % for the STZ plus 5-FU regimen, while seven studies reported a DCR of 61 % and an ORR of 14 % for the STZ plus anthracycline regimen.

Response rates across all studies are summarized in Tables 3 and 4. In Fig. 2, we reported the DCR and ORR values of the studies on a histogram graphic.

Discussion

This structured discussion addresses five key questions, focusing on critical aspects of pan-NET treatment as informed by clinical trials, retrospective studies, and current guidelines. The topics explored include:

1. A comparison between STZ and CAPTEM regimens in progressive G1-G2 pan-NETs
2. The optimal placement of STZ-based chemotherapy within the treatment algorithm
3. Recommended regimens, scheduling, and duration of treatment
4. The potential role of STZ in neoadjuvant therapy
5. Predictive factors influencing the efficacy of STZ regimens

Which treatment is more effective for progressive pancreatic G1-G2 NETs: STZ or CAPTEM?

Chemotherapy remains the gold standard for treating NECs [47,48], yet it is also widely used to manage well-differentiated G1-G2-G3 pan-NETs. Most available data, however, derive from retrospective studies [49–51], with few randomized trials published [10–12]. Commonly used regimens in current practice include CAPTEM, 5-FU, oxaliplatin-based regimens, platinum/etoposide, and STZ-based chemotherapy. As no direct comparative studies among chemotherapy regimens exist, the therapeutic algorithm remains somewhat controversial, with treatment options and schedules often adjusted based on tumor grade, primary location, and patient characteristics.

Regardless of the primary tumor location, the CAPTEM regimen is considered safe and effective for patients with advanced NENs, demonstrating a median DCR of 77 % and a median PFS of 4 to 38.5 months [52]. Due to the increased chemosensitivity of pan-NETs [53,54] and findings from the recent randomized phase II E2211 trial [55], which established CAPTEM over temozolomide monotherapy as the standard chemotherapy for advanced low/intermediate-grade pan-NETs, this combination has become the preferred regimen for pan-NETs.

The clinical-pathological profile of pan-NETs suitable for STZ-based

Table 1
Articles included in the review.

First author, year of publication	Type of the study	Patients (N)	Age or median age	Site of primary tumor	Histotypes of primary tumor (WHO)	Treatment Regimen	Setting Treatment	Outcomes
Broder LE, 1973 [15]	retrospective	52	–-	Pancreatic Islet-cells carcinoma	Islet-cells carcinoma	STZ 0.1 to 80.0 g/m^2 (ev or intra-arterial + ev)	Advanced (> I Line)	RR mOSsafety
Schein PS, 1974 [16]	retrospective	16(tot 106)	–-	GEP/lung carcinoid	CarcinoidPancreatic islet cell carcinoma	STZ 1.0 to 7.5 g/m2 weekly STZ 500–1600 mg/m2 (d1-5) biweekly	(> I Line)	RRSafety
Moertel CG, 1980 [11]	RCT	84(tot 103)	53	Pancreatic Islet-cells carcinoma	Islet-cells carcinoma	STZ 500 mg/m2 (d1-5) +/- 5-FU 400 mg/m2 (d1-5) q6w	Advanced (> I Line)	RR
Frame J, 1988 [17]	Phase II	33#*	51	GEP/H&N/unknown carcinoid, Pancreatic islet-cells carcinoma, medullary tiroid carcinoma	carcinoid, pancreatic islet-cells carcinoma, medullary tiroid carcinoma	STZ 1000 mg/m^2 + Adriamycin 20 mg/m^2 (weekly for first 4 weeks, then biweekly)	(≥ I line)	RRSafety
Eriksson B, 1990 [18]	prospective	44(total 84)	53	Pan-NETs	Neuroendocrine tumors	STZ 500 mg/m^2 (d1-5) + 40 mg/m2 (d3) /5-FU 400 mg/m2 (d1-5) → STZ 1000 mg/m^2 + doxo/5-FU q21(maintenance)	Advanced(I line)	RRmOS
Moertel CG, 1992 [10]	RCT	72	51–53	Pancreatic Islet-cells carcinoma	Islet-cells carcinoma	STZ 500 mg/m^2 (d1-5) +/- 5-FU 400 mg/m^2 (d1-5) q6w +/- Doxo 50 mg/m^2 (d1-22)	Advanced(I line)	RR mOSSafety
Rivera E, 1998 [19]	retrospective	12	–-	Pancreatic Islet-cells carcinoma	Islet-cells carcinoma	STZ 400 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) q28		RRsafety
Cheng PN, 1999 [20]	retrospective	16	58	Pancreatic Islet-cells carcinoma	Islet-cells carcinoma	STZ 500 mg/m^2 (d1-5) + Doxo 50 mg/m^2 (d1-22)	Advanced (≥ I line)	RR mOSsafety
McCollum AD, 2004 [21]	retrospective	16	52	Pancreatic neuroendocrine tumors	Neuroendocrine tumors	STZ 500 mg/m2 (d1-5) +/- Doxo 50 mg/m2 (d1-22)	Advanced (≥I line)	RR mOSsafety
Kouvaraki MA, 2004 [22]	retrospective	84	54	Pancreatic neuroendocrine carcinoma	Neuroendocrine tumors	STZ 400 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) q28	Advanced (≥ I line)	RR mPFS mOSsafety
Delaunoit T, 2004 [23]	retrospective	45	54	Pan-NETs	WD-NETs	STZ 500 mg/m2 (d1-5) + Doxo 50 mg/m2 (d1 and d22) q6w	Advanced (≥ I Line)	RR mOSsafety
Fjallskog ML, 2008 [24]						STZ 1000 mg/m^2 (d1-5) + doxo 30 mg/m2 q3w (maintenance q6w in case of response)	(I line)	RR mOS mPFSsafety
Turner NC, 2010 [25]	retrospective	82	55.4	GEP-NETsLung, unknown, ovarian	NETs(G1-G2-G3) WD/poorly differentited	STZ 1000 mg/m^2 + 5-FU 500 mg/m2 + CDDP 70 mg/m^2q3w	(≥ I line)	RR mPFSmOS
Ducreux M, 2014 [26]	phase II (non randomized)	34	55	Pan-NETs	WD-NETs	STZ 500 mg/m^2 + 5-FU 400 mg/m2 (d1-5) q6w + bevacizumab 7.5 mg/kg d1 q 3w	Advanced (≥ I Line)	mPFS mOS RRsafety QoL
Meyer T, 2014 [12]	RCT	44(cap-STZ) 42 (Cap-STZ-CDDP)	57 (cap-STZ) 59(Cap-STZ-CDDP)	GEP-NETs, unknown	NETs(G1-G2-G3, unknown)	capecitabine 625 mg/m^2 (d1-21) + STZ 1000 mg/m^2 +/- CDDP 70 mg/m^2	(≥ I line)	RR mPFS, mOSQoL
Aoki T, 2015 [27]	retrospective	54	54	GEP-NETs	WD-NETsNEC	STZ 350–500 mg/m2 (d1-5) q6w or STZ 350–1000 mg/m^2 weekly/ biweekly+/- tegafur/S-1/5-FU	(≥ I line)	RR mOS mPFSsafety
Dilz LM, 2015 [28]	retrospective	96	57.6	Pan-NETs	NETs(G1-G2-G3, unknown)	STZ 500 mg/m^2 + 5-FU 400 mg/m2 (d1-5) q6w	(≥ I Line)	RR TTP mOSsafety
Dussol AS, 2015 [29]	retrospective	63 (104 total)	58	GEP-NETs Lungunknown	WD-NETs(G1-G2-G3)	STZ based regimen (+ doxo/5-FU) TMZ +/- capecitabineDacarbazine +/- 5-FU/epirubicin	(≥ I line)	RRmPFS
Krug S, 2015 [30]	retrospective	77	53	GEP-NETs Lung	NETs(G1-G2-G3) NEC	STZ 500 mg/m2 (d1-5) + Doxo 50 mg/m2 (d1 and 22) / 5-FU 400 mg/m2 (d1-5) q6w	(≥ I line)	RR mPFS mOS

(*continued on next page*)

Table 1 (*continued*)

First author, year of publication	Type of the study	Patients (N)	Age or median age	Site of primary tumor	Histotypes of primary tumor (WHO)	Treatment Regimen	Setting Treatment	Outcomes
Clewemar Antonodimitrakis P, 2016 [31]	retrospective	133	57	Pan-NETs	NETs(G1-G2-G3)	STZ 1000 mg (d1-5) + 5-FU 400 mg/m^2 (d1-3) I cycle → STZ 2000 mg + 5-FU 400 mg/m^2 q21	(≥ I Line)	RR mOS mPFSsafety
Krug S, 2017 [32]	retrospective	41	54	Pan-NETs	NETs(G1-G2-G3, unknown)	STZ 500 mg/m^2 + 5-FU 400 mg/m^2 (d1-5) q6w	(≥ I line)	RR mPFS mOSPrgnostic factors
Krug S, 2017 [33]	retrospective	28*	53	GEP-NETsLung	NETs (G1-G2)	STZ 500 mg/m^2 (d1-5) + Doxo 50 mg/m^2 (d1 and 22) / 5-FU 400 mg/m^2 (d1-5) q6w	Advanced(I-II Line)	RR TTPRole of MGMT
Prakash L, 2017 [14]	retrospective	29	55	Pan-NETs	NETs	STZ 500 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) + 5-FU 400 mg/m^2 (d1-5) q28		RR Surgical outcomesmOS
Cloyd JM, 2018 [13]	retrospective	27 (67 total)	52	Pan-NETs (M + only liver)	NETs (G1/G2/G3/unknown)	STZ 400 mg/m^2 + 5-FU 400 mg/m^2 (d1-5) + doxo 40 mg/mq^2 q28		mOS RFS
Hijioka S, 2018 [34]	retrospective	13	64	Pan-NETs	WD-NETs	STZ based regimen	(≥ I line)	RR mPFS mOS role of MGMT
Roquin G, 2018 [35]	retrospective	74	55.5	Pan-NETs	WD-NETs (Ki-67 ≥ 10 %)	STZ + doxo/5-FU/5-FU bevacizumab/ epirubicin	Advanced(I line)	mPFSRR
Shibuya H, 2018 [36]	retrospective	110	59–60	Pan-NETs	NETs(G1-G2-G3) NEC G3	STZ 500 mg/m^2 (d1-5) or STZ 1000 mg/m^2/week q6w +/- Doxo 50 mg/m^2 (d1-22)/ 5-FU 400 mg/m^2 (d1-5) q6w/S-1	(≥ I line)	RR mPFSmOS
Ono H, 2019 [37]	retrospective	20	61.5	Pan-NETs	NETs(G1-G2-G3) NECs	STZ 1000 mg/m^2 weekly + S-1 100 mg per day q21	Advanced (≥ I line)	RR mPFSmOS
Schrader J, 2019 [38]	retrospective	32	–-	Pan-NETs	NETs(G1-G2-G3)	STZ 500 mg/m2 (d1-5) +/- 5-FU 400 mg/m2 (d1-5) q6w	Advanced (≥ I line)	RR mPFSmOS
Lahner H, 2021 [39]	retrospective	50	61	Pan-NETs	NETs (G1-G2-G3, unknown)	STZ 500 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) q6w	(≥ I line)	RR mPFS mOS
Legoux JL, 2021 [40]	retrospective/ prospective	110/30‡	54.5/65	GEP-NETs	NETs	STZ 500 mg/m^2 (d1-5) + doxo/5-FU/ epirubicin/ 5-FU bevacizumab	Advanced (> I Line)	Pts < 25 % eGFRRR
Komoto I, 2022 [41]	phase I-II (non randomized)	22	59	GEP-NETs	NETs(G1-G2)	STZ 500 mg/m^2 (d1-5) q6w (4 cycles) or STZ 1000–1500 mg/m^2 weekly q6w (weekly regimen, 6 weeks)	Advanced (≥ I line)	RR SafetyPharmacokinetics
Rogers JE, 2022 [42]	retrospective	243	56	Pan-NETs	WD-NETs	STZ 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) + 5-FU 400 mg/m^2 (d1-5) q28	Advanced (≥ I line)	RR mPFSmOS
Reher D, 2022 [43]	retrospective	84	59	Pan-NETs	NETs (G1-G2-G3)	STZ 500 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) q6w	(≥ I line)	RR mPFSmOS
Yagi K, 2023 [44]	retrospective	19 (tot 392)	52	Pan-NETs	NETs (G2-G3)	STZ +/-S-1	(> I Line)	RR mPFSMGMT role
Murakami M, 2024 [45]	retrospective	53	63.8	GEP-NETs	NETs(G1-G2-G3)	STZ 500 mg/m^2 (d1-5) q6w/ STZ 1000 mg/m^2 weekly +/- 5-FU/eve/ sunitinib	(≥ I line)	RR mPFS mOSsafety
Petersen SS, 2024 [46]	retrospective	70 (total 192)	64 ± 13	Pan-NETs	NETs NEC	STZ 500 mg/m^2 (d1-5) +/ 5-FU 400 mg/m^2 (d1-3) → STZ 1000 mg/m^2 + 5FU 400 mg/m^2 q3w	Advanced (≥ I line)	mOSmPFS

Abbreviations: RCT: randomized clinical trial; STZ: streptozotocin; CDDP: cisplatin; 5-FU: 5-Fluorouracil; Doxo: doxorubicin; eve: everolimus; S-1: oral dihydropyrimidine dehydrogenase; TMZ: temozolomide; DTIC: dacarbazine; mPFS: median progression-free survival; mOS: median overall survival; mTTP: median time to progression; mRFS: median relapse free survival; RR: response rate; MGMT: O6-methylguanine–DNA methyltransferase; pNENs: pancreatic NENs; GEP-NENs: gastro-entero-pancreatic NENs.

[#] 31 patients analyzed for endpoints.

[*] 24 patients analyzed for endpoints

[‡] 84/27 patients analyzed for endpoints.

Table 2
Survival outcomes in studies included in the review.

Study (first author, year)	Interventional regimen	Comparator regimen	PFS Interventional regimen	PFS Comparator regimen	OS Interventional regimen	OS Comparator regimen
Broder LE, 1973 [15]	STZ 8.1 to 10.0 g/m^2	NA	NA	NA	mOS 1268 days (responders) mOS 518 days (non responders)	NA
Schein PS, 1974 [16]	STZ 1.0 g/m2 weekly STZ 500 mg/m2 (d1-5) biweekly	NA	NA	NA	NA	NA
Moertel CG, 1980 [11]	STZ 500 mg/m2 (d1-5) + 5-FU 400 mg/m2 (d1-5) q6w	STZ 500 mg/m2(d1-5)	NA	NA	mOS 26 mo	16.4 mo
Frame J, 1988 [17]	STZ 1000 mg/m^2 + Adriamycin 20 mg/m^2 (weekly for first 4 weeks, then biweekly)	NA	NA	NA	mOS 10.9 mo (responders:16.2 mo; non responders:7.82 mo)	NA
Eriksson B, 1990 [18]	STZ 500 mg/m^2 (d1-5) + doxo 40 mg/m2 (d3) /5-FU 400 mg/m2 (d1-5) → STZ 1000 mg/m^2 + doxo/5-FU q21(maintenance)	NA	NA	NA	5y OS (STZ based regimen) 50 %	NA
Moertel CG, 1992 [10]	STZ 500 mg/m2 (d1-5) +/- 5-FU 400 mg/m2 (d1-5) q6w	STZ 500 mg/m2 (d1-5) +/- Doxo 50 mg/m2 (d1-22)	NA	NA P = 0.001	mOS 16 mo	2.2 y
Rivera E, 1998 [19]	STZ 400 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) q28	NA	NA	NA	mOS 21 mo (3–32.5)	NA
Cheng PN, 1999 [20]	STZ 500 mg/m^2 (d1-5) + Doxo 50 mg/m^2 (d1-22)	NA	NA	NA	mOS NR (2–65 mo)	NA
McCollum AD, 2004 [21]	STZ 500 mg/m2 (d1-5) +/- Doxo 50 mg/m2 (d1-22)	NA	mPFS 3.9 (2.8–8.8)	NA	mOS 20.2 (9.7–37.4)	NA
Kouvaraki MA, 2004 [22]	STZ 400 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) q28	NA	mPFS 18 mo	NA	mOS 37 mo	NA
Delaunoit T, 2004 [23]	STZ 500 mg/m2 (d1-5) + Doxo 50 mg/m2 (d1 and d22) q6w	NA	mPFS 16 mo	NA	mOS 24 mo	NA
Fjallskog ML, 2008 [24]	STZ 1000 mg/m^2 (d1-5) + doxo 30 mg/m2 q3w (maintenance q6w in case of response)	NA	mPFS 13 mo (2–46)	NA	mOS 66 mo (10–166)	NA
Turner NC, 2010 [25]	STZ 1000 mg/m^2 + 5-FU 500 mg/m2 + CDDP 70 mg/m^{2}q3w	NA	mPFS 9.1 mo	NA	mOS 31.5 mo	NA
Ducreux M, 2014 [26]	STZ 500 mg/m^2 + 5-FU 400 mg/m2 (d1-5) q6w + bevacizumab 7.5 mg/kg d1 q 3w	NA	mPFS 23.7 mo	NA	mOS NR 12 mo OS 94 % 24 mo OS 88 %	NA
Meyer T, 2014 [12]	capecitabine 625 mg/m^2 (d1-21) + STZ 1000 mg/m^2 + CDDP 70 mg/m^2	capecitabine 625 mg/m^2 (d1-21) + STZ 1000 mg/m^2	mPFS 9.7 mo	mPFS 10.2 mo	mOS 27.5	mOS 26.7 mo
Aoki T, 2015 [27]	STZ 350–500 mg/m2 (d1-5) q6w or STZ 350–1000 mg/m^2 weekly/ biweekly+/- tegafur/S-1/5-FU	NA	mPFS 11.8 mo	NA	mOS 38.7 mo	NA
Dilz LM, 2015 [28]	STZ 500 mg/m^2 + 5-FU 400 mg/m2 (d1-5) q6w	NA	mTTP 19.4 mo	NA	mOS 54.8 mo 2y OS 82.4 % 5y OS 44.9 %	NA
Dussol AS, 2015 [29]	STZ based regimen (+ doxo/5-FU)	GEMOX gem 1000 mg/m^2 + oxa 100 mg/m^2 q2w	mPFS 7.5 (5.3–9.6)	mPFS 7.8 (6.4–9.2)	mOS 62.8 (55.2–70.4)	mOS 31.6 (28.6–34.6)
Krug S, 2015 [30]	STZ 500 mg/m2 (d1-5) + Doxo 50 mg/m2 (d1 and 22) / 5-FU 400 mg/m2 (d1-5) q6w	NA	mPFS 16 mo	NA	mOS 28 mo	NA
Clewemar Antonodimitrakis P, 2016 [31]	STZ 1000 mg (d1-5) + 5-FU 400 mg/m^2 (d1-3) I cycle → STZ 2000 mg + 5-FU 400 mg/m^2 q21	NA	mPFS 23 mo (14.5—31.5)	NA	mOS 86 mo 2y OS 66.9 % 5y OS 38.3 %	NA
Krug S, 2017 [32]	STZ 500 mg/m^2 + 5-FU 400 mg/m^2 (d1-5) q6w	NA	mPFS 17 mo (5.5–28.5)	NA	mOS 50 mo (20.0–79.9)	NA
Krug S, 2017 [33]	STZ → DTIC (N = 15)	DTIC → STZ (N = 13)	mTTP 21 mo	mTTP 21 mo	NA	NA
Prakash L, 2017 [14]	STZ 500 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) + 5-FU 400 mg/m^2 (d1-5) q28	NA	mRFS 38 mo	NA	mOS 107 mo(resected 112 mo; non resected 41 mo)	NA
Cloyd JM, 2018 [13]	STZ 400 mg/m^2 + 5-FU 400 mg/m^2 (d1-5) + doxo 40 mg/mq^2 q28	NA	mRFS 25.1 mo (23.2–27)	NA	mOS 108.2 mo (78–136)	NA
Hijioka S, 2018 [34]	STZ based regimen	NA	mPFS 141 days (61–1246)	NA	mOS MGMTp 447 days mOS MGMTd 827 days	NA
Roquin G, 2018 [35]	STZ + doxo/5-FU/5-FU bevacizumab/epirubicin	CDDP-etoposideTMZ/ DTIC	mPFS 7.2(5.2-11.0)	mPFS 7.5 momPFS 7.2 mo	mOS 37.9(20.8-NE)	mOS 27.1mOS 40.9

(*continued on next page*)

Table 2 (*continued*)

Study (first author, year)	Interventional regimen	Comparator regimen	PFS Interventional regimen	PFS Comparator regimen	OS Interventional regimen	OS Comparator regimen
Shibuya H, 2018 [36]	STZ 500 mg/m^2 (d1-5) or STZ 1000 mg/m^2/week q6w +/- Doxo 50 mg/m^2 (d1-22)/ 5-FU 400 mg/m^2 (d1-5) q6w/S-1	NA	mPFS 9.8 mo	NA	NA	NA
Ono H, 2019 [37]	STZ 1000 mg/m^2 weekly + S-1 100 mg per day q21	NA	mPFS 19 mo (13.3–26.1)	NA	mOS NR(23.1–32.0)	NA
Schrader J, 2019 [38]	STZ 500 mg/m2 (d1-5) +/- 5-FU 400 mg/m2 (d1-5) q6w	Maintenance extended 3-mo cycle (N = 13)	mPFS 21 mo (3–128)	mPFS 44 mo	mOS 69 mo (3–157)	mOS 69 mo (21–157)
Lahner H, 2021 [39]	STZ 500 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) q6w	NA	mPFS 12 mo (8.5–15.5)	NA	mOS 64 mo(35.6–92.5)	NA
Legoux JL, 2021 [40]	STZ 500 mg/m^2 (d1-5) + doxo/5-FU/epirubicin/ 5-FU bevacizumab	NA	NA	NA	NA	NA
Komoto I, 2022 [41]	STZ 500 mg/m^2 (d1-5) q6w (4 cycles) or STZ 1000–1500 mg/m^2 weekly q6w (weekly regimen, 6 weeks)	NA	NA	NA	NA	NA
Rogers JE, 2022 [42]	STZ 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) + 5-FU 400 mg/m^2 (d1-5) q28	NA	mPFS 20 mo (15–23)	NA	mOS 63 mo (60–71)	NA
Reher D, 2022 [43]	STZ 500 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) q6w	NA	mPFS 31 mo (2–164)	NA	mOS 42 (2–169)	NA
Yagi K, 2023 [44]	STZ +/-S-1	NA	mPFS (MGMT-) 20.8 momPFS (MGMT +) 9.4 mo	NA	mOS (MGMT-) NRmOS (MGMT +) NR	NA
Murakami M, 2024 [45]	STZ 500 mg/m^2 (d1-5) q6w/ STZ 1000 mg/m^2 weekly +/- 5-FU/ eve/sunitinib	NA	mPFS 7.1 mo (4.7–15.6)	NA	mOS 20.3 (15.8–32.1)	NA
Petersen SS, 2024 [46]	STZ 500 mg/m^2 (d1-5) +/ 5-FU 400 mg/m^2 (d1-3) → STZ 1000 mg/m^2 + 5FU 400 mg/m^2 q3w	NA	mPFS 20 mo 2y PFS 35 % 5y PFS 9 %	NA	NA	NA

Abbreviations: STZ: streptozotocin; CDDP: cisplatin; 5-FU: 5-Fluorouracil; Doxo: doxorubicin; GEMOX: gemcitabine + oxaliplatin; DTIC: dacarbazine; eve: everolimus; S-1: oral dihydropyrimidine dehydrogenase; TMZ: temozolomide; DTIC: dacarbazine; mPFS: median progression-free survival; mOS: median overall survival; mTTP: median time to progression; mRFS: median relapse free survival; RR: response rate; MGMT: O6-methylguanine–DNA methyltransferase; mo: months; NA: not available; NR: not reached.

or TEM-based chemotherapy is similar, typically involving well-differentiated tumors, relatively high tumor burden, and/or rapidly progressing disease. Both regimens have shown higher ORR in pan-NETs with a Ki-67 index above 5 % [56,36]. Stratified by treatment line and Ki-67 index, treatment-naïve patients and those with NETs featuring Ki-67 below 55 % demonstrated a more favorable survival profile, supporting CAPTEM's role as a first-line option for G3 NETs with Ki-67 between 20 and 54 % [57] and for NENs with Ki-67 between 2 and 20 % [58]. While CAPTEM's use in G3 NETs is well supported by consistent evidence [59–61], most studies on STZ-based regimens focus on well-differentiated G1-G2 pan-NETs. Among the studies in this review, a total of 121 G3 NETs and 24 NEC cases were described. Still, due to a lack of sub-analyses on efficacy and activity, conclusive evidence for STZ use in G3 NENs is unavailable. Platinum and 5-FU based regimens still represent the chemotherapy regimens routinely used in therapeutic scenario of G3 NETs and NECs, even though, we must consider the growing use of the FOLFIRINOX (leucovorin, 5-FU, and oxaliplatin, irinotecan) schedule due to ORR of 46–77 % in some retrospective analysis [62,63].

The toxicity profiles of STZ-based (notably emesis, myelotoxicity, and renal damage) and CAPTEM regimens (gastrointestinal, hematological, and hand-foot syndrome) differ significantly and are currently major factors in treatment decision-making. A recent pooled analysis of CAPTEM toxicity revealed G3-G4 toxicities in 16.4 % of patients, with 27.2 % hematological, 8.3 % gastrointestinal, and 3.2 % cutaneous adverse events [52]. Specific safety data for STZ are limited, as no dedicated trials have been conducted apart from the Streptotox-FFCD 0906 study [40], and standardized reporting of AEs is lacking. Additionally, the impact of combination regimens (STZ/anthracycline/5-FU) warrants consideration.

No head-to-head studies are available to recommend one treatment over the other definitively. Still, the final results from two trials are anticipated: the phase II BETTER II trial (NCT03351296), which compares CAPTEM or STZ-5-FU alone or in combination with bevacizumab in pre-treated or treatment-naïve, well-differentiated G1-G2-G3 pan-NETs, and the phase III randomized SEQTOR study (NCT02246127), which assesses the efficacy and safety of everolimus followed by STZ-5-FU chemotherapy upon progression or the reverse sequence in advanced, progressive pan-NETs.

What is the optimal place for STZ-based chemotherapy in the therapeutic algorithm for advanced panNETs?

Although most studies in our review proposed STZ-based chemotherapy as a first-line treatment and beyond, there is currently insufficient data to establish a definitive position for this regimen within the advanced pan-NET treatment algorithm [8].

In routine clinical practice, the placement of STZ or chemotherapy in general within the treatment sequence is primarily influenced by several factors: the safety and toxicity profiles of available drugs, the clinicopathological characteristics and behavior of the disease, the patient's comorbidities, and the objectives of current and prior treatments administered.

The ENETS guidelines [6] recommend alkylating-based treatments as systemic first-line options for metastatic, progressive, and/or symptomatic non-functioning G1–G2 pan-NETs, with a moderate grade of recommendation. In contrast, the NCCN guidelines [64] suggest that STZ or temozolomide may be more effective treatment options than other cytotoxic agents for pan-NETs.

The SEQTOR study [65] is the only trial examining therapeutic sequencing, comparing two treatment sequences: everolimus followed by STZ-5FU upon progression and the reverse sequence. The primary

Table 3
Efficacy outcomes in studies included in the review.

Study (first author, year)	Therapeutic Setting	Interventional regimen	Comparator regimen	DCR Interventional regimen	DCR Comparator regimen	ORR Interventional regimen	ORR Comparator regimen
Broder LE, 1973 [15]	Advanced (> I Line)	STZ 8.1 to 10.0 g/m^2	NA	F 100 % (N = 30/30) NF 100 % (N = 8/8)	NA	F 50 % (N = 15/30) NF 63 % (N = 5/8)	NA
Schein PS, 1974 [16]	Advanced (> I Line)	STZ 1.0 g/m2 weekly STZ 500 mg/m2 (d1-5) biweekly	NA	12.5 % (N = 2/16)	NA	% (N = 1/16)	
Moertel CG, 1980 [11]	Advanced (> I Line)	STZ 500 mg/m2 (d1-5) + 5-FU 400 mg/m2 (d1-5) q6w	STZ 500 mg/m2 (d1-5)	63 % (N = 25/40)	36 % (N = 15/42)	33 % (N = 13/40)	12 % (N = 5/42)
Frame J, 1988 [17]	Advanced (≥I line)	STZ 1000 mg/m^2 + Adriamycin 20 mg/m^2 (weekly for first 4 weeks, then biweekly)	NA	42 % (N = 13/31)	NA	19 % (N = 6/31)	NA
Eriksson B, 1990 [18]	Advanced(I line)	STZ 500 mg/m^2 (d1-5) + doxo 40 mg/m^2 (d3) /5-FU 400 mg/m^2 (d1-5) → STZ 1000 mg/m^2 + doxo/5-FU q21(maintenance)	NA	STZ + 5-FU 42 % (N = 8/19) STZ + doxo 48 % (N = 12/25)	NA	STZ + 5-FU 31.6 % (N = 6/19) STZ + doxo 8 % (N = 2/25)	NA
Moertel CG, 1992 [10]	Advanced(I line)	STZ 500 mg/m^2 (d1-5) +/- 5-FU 400 mg/m^2 (d1-5) q6w	STZ 500 mg/m^2 (d1-5) +/- Doxo 50 mg/m^2 (d1-22)	45 %	69 %	4 %	14 %
Rivera E, 1998 [19]	Advanced	STZ 400 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) q28	NA	82 % (N = 9/11)	NA	54.5 % (N = 6/11)	NA
Cheng PN, 1999 [20]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) + Doxo 50 mg/m^2 (d1-22)	NA	62 % (N = 10/16)	NA	6 % (N = 1/16)	NA
McCollum AD, 2004 [21]	Advanced (≥I line)	STZ 500 mg/m2 (d1-5) +/- Doxo 50 mg/m2 (d1-22)	NA	44 % (N = 7/16)	NA	6 % (N = 1/16)	
Kouvaraki MA, 2004 [22]	Advanced (≥I line)	STZ 400 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) q28	NA	89 % (N = 75/84)	NA	39 % (N = 33/84)	NA
Delaunoit T, 2004 [23]	Advanced (≥ I Line)	STZ 500 mg/m2 (d1-5) + Doxo 50 mg/m2 (d1 and d22) q6w	NA	61 % (N = 27/45)	NA	36 % (N = 16/45)	NA
Fjallskog ML, 2008 [24]	Advanced(I line)	STZ 1000 mg/m^2 (d1-5) + doxo 30 mg/m2 q3w (maintenance q6w in case of response)	NA	97 % (N = 29/30)	NA	40 % (N = 12/30)	NA
Turner NC, 2010 [25]	Advanced (≥ I Line)	STZ 1000 mg/m^2 + 5-FU 500 mg/m2 + CDDP 70 mg/m^2 q3w	NA	83.5 % (N = 66/79)	NA	33 % (N = 26/79)	NA
Ducreux M, 2014 [26]	Advanced (≥ I Line)	STZ 500 mg/m^2 + 5-FU 400 mg/m2 (d1-5) q6w + bevacizumab 7.5 mg/kg d1 q 3w	NA	100 % (N = 34/34)	NA	56 % (N = 19/34)	NA
Meyer T, 2014 [12]	Advanced (≥I line)	capecitabine 625 mg/m^2 (d1-21) + STZ 1000 mg/m^2 + CDDP 70 mg/m^2	capecitabine 625 mg/m^2 (d1-21) + STZ 1000 mg/m^2	74 % (N = 28/38)	80 % (N = 33/41)	16 % (N = 6/38)	12 % (N = 5/41)
Aoki T, 2015 [27]	Advanced (≥I line)	STZ 350–500 mg/m2 (d1-5) q6w or STZ 350–1000 mg/m^2 weekly/biweekly+/- tegafur/S-1/5-FU	NA	40.7 % (N = 22/54)	NA	27.7 % (N = 13/54)	NA
Dilz LM, 2015 [28]	Advanced (≥I line)	STZ 500 mg/m^2 + 5-FU 400 mg/m2 (d1-5) q6w	NA	83.3 % (N = 80/96)	NA	% (N = 41/96)	NA
Dussol AS, 2015 [29]	Advanced (≥I line)	STZ based regimen (+ doxo/5-FU)	GEMOX gem 1000 mg/m^2 + oxa 100 mg/m^2 q2w	73 % (N = 46/63)	83 % (N = 86/104)	22 % (N = 14/63)	23 % (N = 24/104)
Krug S, 2015 [30]	Advanced (≥I line)	STZ 500 mg/m2 (d1-5) + Doxo 50 mg/m2 (d1 and 22) / 5-FU 400 mg/m2 (d1-5) q6w	NA	71.9 % (N = 46/64)	NA	34.4 % (N = 22/64)	NA
Clewemar Antonodimitrakis P, 2016 [31]	Advanced (≥I line)	STZ 1000 mg (d1-5) + 5-FU 400 mg/m^2 (d1-3) I cycle → STZ 2000 mg + 5-FU 400 mg/m^2 q21	NA	92 % (N = 92/100)	NA	28 % (N = 28/100)	NA
Krug S, 2017 [32]	Advanced (≥I line)	STZ 500 mg/m^2 + 5-FU 400 mg/m^2 (d1-5) q6w	NA	76.9 % (N = 26/39) °	NA	33.3 % (N = 13/39)°	
Krug S, 2017 [33]	Advanced (≥I line)	STZ → DTIC (N = 15)	DTIC → STZ (N = 13)	87 %	62 %	47 %	23 %

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Table 3 (*continued*)

Study (first author, year)	Therapeutic Setting	Interventional regimen	Comparator regimen	DCR Interventional regimen	DCR Comparator regimen	ORR Interventional regimen	ORR Comparator regimen
Prakash L, 2017 [14]	Localized (preoperative setting)	STZ 500 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) + 5-FU 400 mg/m^2 (d1-5) q28	NA	97 % (N = 28/29)	NA	7% (N = 2/29)	
Cloyd JM, 2018 [13]	Advanced (preoperative)	STZ 400 mg/m^2 + 5-FU 400 mg/m^2 (d1-5) + doxo 40 mg/mq^2 q28	NA	92.6 % (N = 25/27)	NA	63 % (N = 17/27)	NA
Hijioka S, 2018 [34]	Advanced (≥I line)	STZ based regimen	NA	69.1 % (N = 9/13)	NA	46.1 % (N = 6/13)	NA
Roquin G, 2018 [35]	Advanced(I line)	STZ + doxo/5-FU/5-FU bevacizumab/epirubicin	CDDP-etoposideTMZ/DTIC	56 % (N = 24/44)	78 % (N = 14/18) 67 % (N = 8/12)	26 % (N = 11/44)	22 % (N = 4/18) 50 % (N = 6/12)
Shibuya H, 2018 [36]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) or STZ 1000 mg/m^2/week q6w +/- Doxo 50 mg/m^2 (d1-22)/ 5-FU 400 mg/m^2 (d1-5) q6w/ S-1	NA	61.9 %	NA	21.8 %	NA
Ono H, 2019 [37]	Advanced (≥I line)	STZ 1000 mg/m^2 weekly + S-1 100 mg per day q21	NA	90 % (N = 18/20)	NA	30 % (N = 6/20)	NA
Schrader J, 2019 [38]	Advanced (≥I line)	STZ 500 mg/m2 (d1-5) +/- 5-FU 400 mg/m2 (d1-5) q6w	Maintenance extended 3-month cycle (N = 13)	86 % (N = 24/28)	84.6 % (N = 11/13)	36 % (N = 10/28)	23 % (N = 3/13)
Lahner H, 2021 [39]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) q6w	NA	76 % (N = 38/50)	NA	38 % (N = 19/50)	NA
Legoux JL, 2021 [40]	Advanced (>I line)	STZ 500 mg/m^2 (d1-5) + doxo/5-FU/epirubicin/ 5-FU bevacizumab	NA	pNETs 74.5 % – 90 % [§] sbNETs 83.3 % – 100 % [§] other NETs 72.2 % – NA [§]	NA	NA	NA
Komoto I, 2022 [41]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) q6w (4 cycles) or STZ 1000–1500 mg/m^2 weekly q6w (weekly regimen, 6 weeks)	NA	86.4 % (N = 19/22)	NA	9.1 % (N = 2/22)	NA
Rogers JE, 2022 [42]	Advanced (≥I line)	STZ 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) + 5-FU 400 mg/m^2 (d1-5) q28	NA	86 %	NA	41 %	NA
Reher D, 2022 [43]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) q6w	NA	88 % (N = 74/84)^	NA	34 % (N = 29/84) ^	NA
Yagi K, 2023 [44]	Advanced (>I line)	STZ +/-S-1	NA	79 % (N = 15/19)	NA	26 % (N = 5/19)	NA
Murakami M, 2024 [45]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) q6w/ STZ 1000 mg/m^2 weekly +/- 5-FU/eve/sunitinib	NA	74.5 % (N = 35/53)	NA	27.7 % (N = 13/53)	NA
Petersen SS, 2024 [46]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) +/ 5-FU 400 mg/m^2 (d1-3) → STZ 1000 mg/m^2 + 5FU 400 mg/m^2 q3w	NA	NA	NA	NA	NA

Abbreviations: DCR: disease control rate; ORR: overall response rate; STZ: streptozotocin; CDDP: cisplatin; 5-FU: 5-Fluorouracil; Doxo: doxorubicin; GEMOX: gemcitabine + oxaliplatin; DTIC: dacarbazine; eve: everolimus; S-1: oral dihydropyrimidine dehydrogenase; TMZ: temozolomide; DTIC: dacarbazine; mPFS: median progression-free survival; mOS: median overall survival; mTTP: median time to progression; mRFS: median relapse-free survival; RR: response rate; F: functioning; NF: non-functioning; NA: not available.

[§] the first value refers to the retrospective cohort, the second value to the prospective cohort. ° RR evaluated in first-line STZ-based regimen. ^ RR evaluated on primary tumor

endpoint was progression-free survival at first progression (PFS-1) at one year. Recently, a post hoc analysis of this phase III trial revealed no significant difference in 12-month PFS rates between the two approaches (19.4 months for everolimus → STZ/5-FU vs. 22.5 months for STZ/5-FU → everolimus; p = 0.476). Although these post hoc findings should be interpreted with caution, certain factors were associated with worse PFS-1 regardless of treatment sequence, including female sex (p = 0.010), ECOG performance status of 1–2 (p = 0.035), and high tumor burden (p = 0.279).

First-line chemotherapy achieved a higher ORR compared to first-line everolimus (30 % vs. 12 %), though there was no difference in PFS, and OS was lower in this group. These preliminary results further support the role of first-line chemotherapy in G2 pan-NETs when cytoreduction is needed.

Is there an optimal regimen or schedule for treatment, and is there evidence on the ideal duration or maintenance of therapy?

This review observed a median DCR of 87.5 % and a median ORR of 40 % for the triplet chemotherapy regimen of STZ, 5-FU, and doxorubicin. For doublet chemotherapy, better activity outcomes were reported for the STZ plus 5-FU combination (DCR 80 %; ORR 33 %) compared to STZ plus anthracycline (DCR 61 %; ORR 14 %). Notably, response rates were reported in only seven studies for the anthracycline combination, compared to thirteen for 5-FU, suggesting an imbalance that warrants cautious interpretation of these results.

Conversely, two phase III randomized trials showed a superior ORR with STZ plus doxorubicin compared to STZ plus 5-FU (69 % vs. 45 %, p = 0.05) and improved ORR (33 % vs. 12 %) and survival outcomes

Table 4
Details of efficacy outcomes in studies included in the review.

Study (first author, year)	Therapeutic Setting	Interventional regimen	CR	PR	SD	PD
Broder LE, 1973 [15]	Advanced (> I Line)	STZ 8.1 to 10.0 g/m^2	F 17 % (N = 5/30) NF 13 % (N = 1/8)	F 33 % (N = 10/30) NF 50 % (N = 4/8)	F 50 % (N = 15/30)* NF 37 % (N = 3/8)*	F 0 % (N = 0/30) NF 0 % (N = 0/8)
Schein PS, 1974 [16]	Advanced (> I Line)	STZ 1.0 g/m2 weekly STZ 500 mg/m2 (d1-5) biweekly	6.2 % (N = 1/16)	6.2 % (N = 1/16)	0 % (N = 0/16)	0 % (N = 0/16)
Moertel CG, 1980 [11]	Advanced (> I Line)	STZ 500 mg/m2 (d1-5) + 5-FU 400 mg/m2 (d1-5) q6w VS STZ 500 mg/m2(d1-5)	33 % (N = 13/40) VS 12 % (N = 5/42)	NA	NA	NA
Frame J, 1988 [17]	Advanced (≥I line)	STZ 1000 mg/m^2 + Adriamycin 20 mg/m^2 (weekly for first 4 weeks, then biweekly)	0 % (N = 0/31)	19.4 % (N = 6/31)	22.6 % (N = 7/31)	55 % (N = 17/31)
Eriksson B, 1990 [18]	Advanced(I line)	STZ 500 mg/m^2 (d1-5) + doxo 40 mg/m^2 (d3) /5-FU 400 mg/m^2 (d1-5) → STZ 1000 mg/m^2 + doxo/5-FU q21 (maintenance)	STZ + 5-FU 0 % (N = 0/19) STZ + doxo 0 % (N = 0/25)	STZ + 5-FU 31.6 % (N = 6/19) STZ + doxo 8 % (N = 2/25)	STZ + 5-FU 10.5 % (N = 2/19) STZ + doxo 40 % (N = 10/25)	STZ + 5-FU 31.5 % (N = 6/19) STZ + doxo 24 % (N = 6/25)
Moertel CG, 1992 [10]	Advanced(I line)	STZ 500 mg/m^2 (d1-5) +/- 5-FU 400 mg/m^2 (d1-5) q6w VS STZ 500 mg/m^2 (d1-5) +/- Doxo 50 mg/m^2(d1-22)	4 % VS 14 %	41 % VS 55 %		
Rivera E, 1998 [19]	Advanced	STZ 400 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) q28	0 % (N = 0/11)	54.5 % (N = 6/11)	18.2 % (N = 2/11)	18.2 % (N = 2/11)
Cheng PN, 1999 [20]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) + Doxo 50 mg/m^2 (d1-22)	0 % (N = 0/16)	6 % (N = 1/16)	56 % (N = 9/16)	38 % (N = 6/16)
McCollum AD, 2004 [21]	Advanced (≥I line)	STZ 500 mg/m2 (d1-5) +/- Doxo 50 mg/m2 (d1-22)	0 % (N = 0/16)	6 % (N = 1/16)	38 % (N = 6/16)	56 % (N = 9/16)
Kouvaraki MA, 2004 [22]	Advanced (≥I line)	STZ 400 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) q28	0 % (N = 0/84)	39 % (N = 33/84)	50 % (N = 42/84)	11 % (N = 9/84)
Delaunoit T, 2004 [23]	Advanced (≥ I Line)	STZ 500 mg/m2 (d1-5) + Doxo 50 mg/m2 (d1 and d22) q6w	0 % (N = 0/45)	36 % (N = 16/45)	9 % (N = 4/45)	40 % (N = 18/45)
Fjallskog ML, 2008 [24]	Advanced(I line)	STZ 1000 mg/m^2 (d1-5) + doxo 30 mg/m2 q3w (maintenance q6w in case of response)	0 % (N = 0/30)	40 % (N = 12/30)	57 % (N = 17/30)	3 % (N = 1/30)
Turner NC, 2010 [25]	Advanced (≥ I Line)	STZ 1000 mg/m^2 + 5-FU 500 mg/m2 + CDDP 70 mg/m^2 q3w	0 % (N = 0/79)	33 % (N = 26/79)	50.6 % (N = 40/79)	16.4 % (N = 13/79)
Ducreux M, 2014 [26]	Advanced (≥ I Line)	STZ 500 mg/m^2 + 5-FU 400 mg/m2 (d1-5) q6w + bevacizumab 7.5 mg/kg d1 q 3w	0 % (N = 0/34)	56 % (N = 19/34)	44 % (N = 15/34)	0 % (N= 0/34)
Meyer T, 2014 [12]	Advanced (≥I line)	capecitabine 625 mg/m^2 (d1-21) + STZ 1000 mg/m^2 + CDDP 70 mg/m^2 VS capecitabine 625 mg/m^2 (d1-21) + STZ 1000 mg/m^2	0 % (N = 0/38) VS 0 % (N = 0/41)	16 % (N = 6/38) VS 12 % (N = 5/41)	58 % (N = 22/38) VS 68 % (N = 28/41)	26 % (N = 10/38) VS 20 % (N = 8/41)
Aoki T, 2015 [27]	Advanced (≥I line)	STZ 350–500 mg/m2 (d1-5) q6w or STZ 350–1000 mg/m^2 weekly/biweekly+/- tegafur/S-1/5-FU	4.3 % (N = 2/54)	23.9 % (N = 11/54)	19.6 % (N = 9/54)	54.3 % (N = 25/54)
Dilz LM, 2015 [28]	Advanced (≥I line)	STZ 500 mg/m^2 + 5-FU 400 mg/m2 (d1-5) q6w	1 % (N = 1/96)	41.7 % (N = 40/96)	40.6 % (N = 39/96)	16.7 % (N = 16/96)
Dussol AS, 2015 [29]	Advanced (≥I line)	+ doxo/5-FU)	0 % (N = 0/63)	22 % (N = 14/63)	51 % (N = 32/63)	27 % (N = 17/63)
Krug S, 2015 [30]	Advanced (≥I line)	STZ 500 mg/m2 (d1-5) + Doxo 50 mg/m2 (d1 and 22) / 5-FU 400 mg/m2 (d1-5) q6w	3.1 % (N = 2/64)	31.3 % (N = 20/64)	37.5 % (N = 24/64)	28.1 % (N = 18/64)
Clewemar Antonodimitrakis P, 2016 [31]	Advanced (≥I line)	STZ 1000 mg (d1-5) + 5-FU 400 mg/m^2 (d1-3) I cycle → STZ 2000 mg + 5-FU 400 mg/m^2 q21	3 % (N = 3/100)	25 % (N = 25/100)	64 % (N = 64/100)	% (N = 8/100)
Krug S, 2017 [32]	Advanced (≥I line)	STZ 500 mg/m^2 + 5-FU 400 mg/m^2 (d1-5) q6w	2.3 % (N = 1/39)°	31 % (N = 12/39)°	43.6 % (N = 17/39)°	23.1 % (N = 9/39)°
Krug S, 2017 [33]	Advanced (≥I line)	STZ → DTIC (N = 15) VS DTIC → STZ (N = 13)	0 % (N = 0/15) VS 0 % (N = 0/13)	47 % (N = 7/15) VS 23 % (N = 3/13)	40 % (N = 6/15) VS 38.5 % (N = 5/13)	13 % (N = 2/15) VS 38.5 % (N = 5/13)
Prakash L, 2017 [14]	Localized (preoperative setting)	STZ 500 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) + 5-FU 400 mg/m^2 (d1-5) q28	0 % (N = 0/29)	7 % (N = 2/29)	90 % (N = 26/29)	3 % (N = 1/29)
Cloyd JM, 2018 [13]	Advanced (preoperative)	STZ 400 mg/m^2 + 5-FU 400 mg/m^2 (d1-5) + doxo 40 mg/mq^2 q28	0 % (N = 0/27)	63 % (N = 17/27)	29.6 % (N = 8/27)	7.4 % (N = 2/27)
Hijioka S, 2018 [34]	Advanced (≥I line)	STZ based regimen	0 % (N = 0/13)	46.1 % (N = 6/13)	23 % (N = 3/13)	30.7 % (N = 4/13)

(*continued on next page*)

Table 4 (*continued*)

Study (first author, year)	Therapeutic Setting	Interventional regimen	CR	PR	SD	PD
Roquin G, 2018 [35]	Advanced(I line)	STZ + doxo/5-FU/5-FU bevacizumab/epirubicin VS CDDP-etoposideTMZ/DTIC	0 % (N = 0/44) VS 0 % (N = 0/18) 0 % (N = 0/12)	26 % (N = 11/44) VS 22 % (N = 4/18) 50 % (N = 6/12)	30 % (N = 13/44) VS 56 % (N = 10/18) 17 % (N = 2/12)	44 % (N = 19/44) VS 22 % (N = 4/18) 33 % (N = 4/12)
Shibuya H, 2018 [36]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) or STZ 1000 mg/m^2/week q6w +/- Doxo 50 mg/m^2 (d1-22)/ 5-FU 400 mg/m^2 (d1-5) q6w/S-1	NA	NA	NA	NA
Ono H, 2019 [37]	Advanced (≥I line)	STZ 1000 mg/m^2 weekly + S-1 100 mg per day q21	0 % (N = 0/20)	30 % (N = 6/20)	60 % (N = 12/20)	10 % (N = 2/20)
Schrader J, 2019 [38]	Advanced (≥I line)	STZ 500 mg/m2 (d1-5) +/- 5-FU 400 mg/m2 (d1-5) q6w VSMaintenance extended 3-month cycle (N = 13)	7.2 % (N = 2/28) VS 15.3 % (N = 2/13)	28.8 % (N = 8/28) VS 7.7 % (N = 1/13)	50 % (N = 14/28) VS 61.6 % (N = 8/13)	14 % (N = 4/28) VS 15.4 % (N = 2/13)
Lahner H, 2021 [39]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) q6w	0 % (N = 0/50)	38 % (N = 19/50)	38 % (N = 19/50)	24 % (N = 12/50)
Legoux JL, 2021 [40]	Advanced (>I line)	STZ 500 mg/m^2 (d1-5) + doxo/5-FU/epirubicin/ 5-FU bevacizumab	pNETs 5.9 % – 0 % [§] sbNETs NA – 0 % [§] others NETs NA- 0 % [§]	19.6 % – 30 % 5.5 % – NA NA – NA	49 % – 60 % 77.8 % – 100 % 72.2 % – NA	25.5 % – 10 % 16.7 % – NA 27.3 % – NA
Komoto I, 2022 [41]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) q6w (4 cycles) or STZ 1000–1500 mg/m^2 weekly q6w (weekly regimen, 6 weeks)	0 % (N = 0/22)	9.1 % (N = 2/22)	77.3 % (N = 17/22)	0 % (N = 0/22)
Rogers JE, 2022 [42]	Advanced (≥I line)	STZ 400 mg/m^2 (d1-5) + Doxo 40 mg/m^2 (d1) + 5-FU 400 mg/m^2 (d1-5) q28	13.6 % (N = 3/220)	27.4 %	45 %	NA
Reher D, 2022 [43]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) + 5-FU 400 mg/m^2 (d1-5) q6w	2 % (N = 2/84)^	32 % (N = 27/84)^	54 % (N = 45/84)^	7 % (N = 6/84)^
Yagi K, 2023 [44]	Advanced (>I line)	STZ +/-S-1	0 % (N = 0/19)	26 % (N = 5/19)	53 % (N = 10/19)	21 % (N = 4/19)
Murakami M, 2024 [45]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) q6w/ STZ 1000 mg/m^2 weekly +/- 5-FU/eve/sunitinib	0 % (N = 0/53)	27.7 % (N = 13/53)	46.8 % (N = 22/53)	25.5 % (N = 12/53)
Petersen SS, 2024 [46]	Advanced (≥I line)	STZ 500 mg/m^2 (d1-5) +/ 5-FU 400 mg/m^2 (d1-3) → STZ 1000 mg/m^2 + 5FU 400 mg/m^2 q3w	NA	NA	NA	NA

Abbreviations: STZ: streptozotocin; CDDP: cisplatin; 5-FU: 5-Fluorouracil; Doxo: doxorubicin; GEMOX: gemcitabine + oxaliplatin; DTIC: dacarbazine; eve: everolimus; S-1: oral dihydropyrimidine dehydrogenase; TMZ: temozolomide; DTIC: dacarbazine; mPFS: median progression-free survival; mOS: median overall survival; mTTP: median time to progression; mRFS: median relapse free survival; RR: response rate; MGMT: O6-methylguanine–DNA methyltransferase; mo: months; NA: not available; NR: not reached.

[§] first value refers to the retrospective cohort, the second value to the prospective cohort. *No response was a regression of less than 25% or a progression of measurable tumor. Responses lasting less than 1 month were considered as no response. ° RR evaluated in first-line based regimen. ^ RR evaluted on primary tumor

(median OS of 26 months vs. 16.4 months) with STZ-5-FU [10] compared to STZ monotherapy [11]. While encouraging, these results should be considered in a historical context predating the current RECIST criteria, when response definitions incorporated both clinical and biochemical criteria.

Additionally, a non-randomized comparative study by Eriksson and colleagues [18] reported a higher response rate and longer duration of response for STZ-5-FU compared to STZ plus doxorubicin.

A more recent randomized trial found that adding cisplatin to STZ-capecitabine did not result in a significant improvement in ORR or survival in patients with gastro-entero-pancreatic (GEP-NETs) and neuroendocrine tumors of unknown origin [12].

In the phase II BETTER trial [26], the combination of bevacizumab with STZ-5-FU achieved a DCR of 100 % in a homogeneous population of progressive G1-G2 pan-NETs. Although neither median PFS nor median OS were reached, a potential selection bias should be considered, as this population predominantly consisted of patients with very indolent disease (nearly all with a Ki-67 index < 15 %). This observation prompted a comparative phase II trial design to evaluate two chemotherapy regimens (CAPTEM vs. STZ-5-FU) with or without bevacizumab (BETTER II Study, NCT03351296).

The widest experience in clinical practice of the combination STZ plus 5-FU and the toxicity profile of anthracycline, especially dose-limiting cardiotoxicity, and alopecia, may explain the larger use of the combination with 5-FU [18,40].

There is no consensus on the ideal treatment duration for metastatic, progressive NETs, as STZ-based therapy has been administered in varying cycles and durations across trials. Since treatment in metastatic disease often continues until PD or the onset of unacceptable toxicity, careful monitoring is required to avoid and detect drug-related AEs. Although renal impairment is the most common AE during treatment, it should be noted that STZ has not shown dose-limiting toxicity, and renal impairment is generally manageable and rarely severe.

Three studies, of which two prospective [18,24], investigated the interesting issue of maintenance treatment after first-line induction chemotherapy or as part of the stop-and-go policy. In the other study [38], a “maintenance” period was scheduled in case of disease response, demonstrating an advantage in PFS and a more favorable toxicity profile after switching to the extended cycle protocol [38].

Despite limitations in study size and retrospective design, a modulated therapeutic approach that balances quality of life with disease control in cases of indolent disease with long life expectancy presents a promising research avenue.

In the preoperative setting for locally advanced or liver-only metastatic pan-NETs, evidence consistently suggests an average of four cycles before surgical evaluation [13,14].

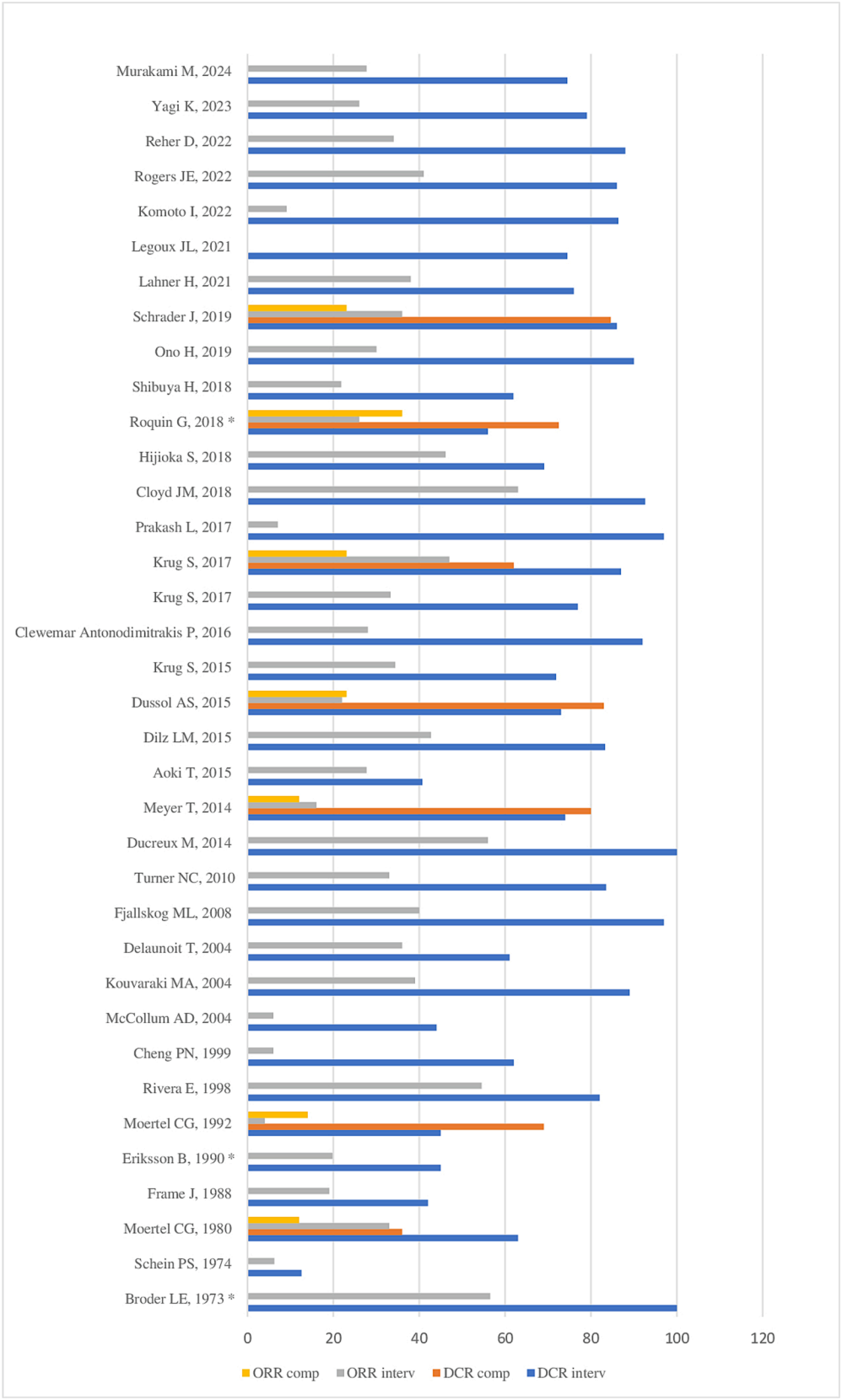

Fig. 2. Efficacy of Streptozotocin-Based Therapies in the Analyzed Studies. Histograms graphic on response rate of the studies included in the review (according to Table 3).

Abbreviations: ORR: overall response rate; DCR: disease control rate; interv: interventional arm; comp: comparator arm

* When two or more DCR/ORRvalues were reported in different population subgroups enrolled in the study, a median value was calculated (Petersen SS 2024 was excluded by this graphic due to RR data not availability).

Is there a role for STZ in preoperative treatment for panNETs unsuitable for upfront surgery?

Curative resection for pan-NETs is associated with 5-year survival rates of 70 %–80 % [66]. While guidelines recommend resection in cases of localized, resectable pan-NETs, its role in locally advanced or metastatic disease remains controversial. Although surgical resection of liver metastases in NENs is known to improve survival, the risk of liver recurrence ranges from 12 % to 18 %, and disease biology may significantly influence prognosis and relapse rates. Given the absence of established adjuvant therapy protocols, the potential role of preoperative treatment for pan-NETs unsuitable for upfront surgery due to factors like vascular invasion or metastases is an intriguing area of exploration.

The preoperative use of PRRT has been investigated in retrospective studies [67] and supported by a recent phase II trial [68], which reported partial responses in nearly 60 % of locally advanced pan-NETs.

A retrospective monocentric study observed similar clinicopathological features among patients with locally advanced G1 to G3 pan-NETs [14]. Following multidisciplinary discussion, these patients were selected for a cytoreductive triplet chemotherapy regimen of STZ-5-FU-doxorubicin, achieving a DCR of 97 %, although without complete response. The study demonstrated a remarkable benefit in survival outcomes in favor of resected patients with a median OS of 112 months and an RFS of 38 months in resected patients, while the OS in non-resected patients was 41 months.

In contrast, conclusions regarding the potential survival benefits of PRRT cannot be definitively drawn [68].

In pan-NETs with liver-only metastases, no significant differences in OS (108.2 months vs. 107.0 months) or PFS (25.1 months vs. 18.0 months) were observed between patients who received preoperative STZ-5-FU-doxorubicin and those who did not. However, when analyzing patients with synchronous liver metastases, survival outcomes clearly favored those who received preoperative chemotherapy (OS 97.3 months vs. 65 months; RFS 24.8 months vs. 12.1 months), suggesting a potential benefit of this approach in this specific subset.

Furthermore, the ORR of 63 % in liver-only advanced pan-NETs, compared to 7 % in locally advanced pan-NETs, underscores the greater efficacy of this strategy for hepatic disease relative to the primary pancreatic tumor.

Temozolomide-based regimens, either as monotherapy or combined with fluoropyrimidines, may also be viable in this setting, given alkylating agents' favorable response and tolerance profile [50,69–72]. After four cycles of CAPTEM, a PR rate exceeding 40 % was observed in patients with locally advanced or liver-metastatic pan-NETs, although this was not significantly correlated with improvements in OS or PFS. Tumor grade was the primary factor influencing survival outcomes [73], suggesting that CAPTEM should be used cautiously in G3 NETs. It should also be noted that most evidence for CAPTEM comes from case reports and retrospective studies.

Multi-tyrosine kinase inhibitors, such as sunitinib and everolimus, have improved median PFS, although response rates remain low at approximately 5–9 % [74,75]. Consequently, these agents are typically reserved for advanced disease settings.

Are there predictive factors for the efficacy of STZ regimens?

The clinical behavior of the disease often guides the use of chemotherapy in NENs; however, there are currently no established prognostic indicators to assist clinicians in selecting therapies. Although findings remain contradictory, likely due to the retrospective nature of many studies, O6-methylguanine-DNA methyltransferase (MGMT) status has been proposed as a potential predictive factor for response to alkylating agents in NETs [76,77]. A recent *meta*-analysis [78] supported the notion that MGMT may predict the responsiveness and efficacy of temozolomide-based chemotherapy in NETs.

In a retrospective cohort of GEP-NETs and lung carcinoids treated with alkylating agents, methylation of the MGMT promoter, assessed through pyrosequencing, was associated with better outcomes than non-methylated cases (ORR 40 % vs. 6 % and median PFS 23.8 months vs. 6.7 months, respectively) [29]. Conversely, another study in a similar population reported no correlation between MGMT status, response rate, and PFS [33].

The impact of MGMT status on predicting outcomes in GEP and lung NETs treated with either alkylating agents or gemcitabine plus oxaliplatin, following MGMT assessment by pyrosequencing or immunohistochemistry (IHC), was evaluated in a randomized 2x2 phase II study presented at the European Society of Oncology (ESMO) congress in 2023 [79]. Although a higher ORR, PFS, and OS were reported for alkylating-based chemotherapy in MGMT-deficient versus MGMT-proficient NETs, the study did not meet its primary endpoint of a 35 % improvement in ORR at 3 months (from 15 % ORR in MGMT-proficient to 50 % ORR in MGMT-deficient cases).

Notably, fewer than 5 % of patients in the alkylating arm received STZ-based chemotherapy; most were treated with temozolomide or dacarbazine. Additionally, the optimal method and cutoff for IHC evaluation of MGMT remain subjects of debate [80], with relatively low concordance rates (approximately 30–60 %) [81–83].

In exploring clinicopathological factors that could predict response to STZ-based chemotherapy, some authors have suggested that a biochemical response—defined as a reduction of more than 30 % from baseline Chromogranin A levels—and positive octreotide scintigraphy may be indicative [32]. Furthermore, certain data support the hypothesis that pan-NETs with a Ki67 index > 5 % may benefit most from STZ-based chemotherapy [36]. Response to STZ-based therapy has correlated with histological grade and Ki67 index [25].

Conclusions

Streptozocin remains an important therapeutic option in managing pan-NETs, particularly for well-differentiated G1-G2 tumors. This review highlights several key insights regarding STZ-based chemotherapy:

- STZ with 5-FU has emerged as the most widely used and effective regimen, offering a better risk/benefit profile than combinations with anthracyclines. The optimal treatment duration remains undefined, though maintenance strategies have improved progression-free survival and reduced toxicity.
- The position in the treatment algorithm is still under investigation. Preliminary data from the SEQTOR trial, the only study to examine the optimal sequencing, did not reveal significant differences between everolimus followed by STZ-5-FU and the reverse sequence. Current guidelines recommend STZ-based therapy as a first-line option for metastatic, progressive, and/or symptomatic non-functioning G1–G2 pan-NETs.
- Preoperative potential of STZ-based chemotherapy shows promise for locally advanced or liver-only metastatic pan-NETs, suggesting possible improvements in resectability and survival outcomes for selected patients.
- Predictive factors for STZ efficacy remain an active area of research. While MGMT status has been proposed as a predictor for response to alkylating agents, results are inconsistent. Other factors, such as the Ki-67 index and tumor grade, may influence response, but further research is required.
- Toxicity profile, particularly renal impairment associated with STZ, is generally manageable with careful monitoring. Future research should optimize treatment schedules, evaluate maintenance strategies, and identify reliable biomarkers to better guide treatment decisions.

As our understanding of pan-NET biology advances, personalized treatment approaches based on tumor characteristics and patient-specific factors will likely play an increasingly important role in

optimizing outcomes for this heterogeneous disease.

CRediT authorship contribution statement

Giulia Arrivi: Writing – original draft, Investigation, Data curation, Formal analysis. **Nicola Fazio:** Visualization, Validation, Writing – review & editing. **Salvatore Tafuto:** Visualization, Validation, Writing – review & editing. **Massimo Falconi:** Visualization, Validation, Writing – review & editing. **Carlo Carnaghi:** Visualization, Validation, Writing – review & editing. **Davide Campana:** Visualization, Validation, Writing – review & editing. **Maria Rinzivillo:** Visualization, Validation, Writing – review & editing. **Francesco Panzuto:** Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Visualization, Writing – review & editing.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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