S-1/temozolomide versus S-1/temozolomide plus thalidomide in advanced pancreatic and non-pancreatic neuroendocrine tumours (STEM): A randomised, open-label, multicentre phase 2 trial

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Summary

Background There are currently limited systemic treatment options for patients with advanced neuroendocrine tumours (NETS) and the efficacy of existing treatments is sub-optimal. We evaluated the efficacy and safety of Tegafur/gimeracil/oteracil/potassium capsules (S-1)/Temozolomide with or without thalidomide for the treatment of NETS (STEM trial).

Methods A randomised, controlled, open-label, phase 2 trial conducted at eight hospitals in China. Adults (≥18 years) with unresectable/metastatic, pancreatic or non-pancreatic NETS, with an Eastern Cooperative Oncology Group (ECOG) PS of 0–1, and progression on ≤2 previous therapies were randomised (1:1, using hierarchical block randomization with block length 4, stratified by pancreatic/non-pancreatic disease to receive S-1 40–60 mg orally twice daily on days 1–14 plus temozolomide 200 mg orally daily on days 10–14 in a 21-day cycle OR S-1 and temozolomide plus thalidomide orally nightly (100 mg on days 1–7, 200 mg on days 8–14, and 300 mg from day 15), until disease progression, death, intolerable toxicity, withdrawal of informed consent or at the investigator's discretion. The primary endpoint was objective response rate (ORR) by RECIST 1.1 in an intention-to-treat population. Safety was assessed in all patients who received treatment. The study was registered at ClinicalTrials.gov: NCT03204019 (pancreatic group) and NCT03204032 (non-pancreatic group).

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Findings Between March 23, 2017 and November 16, 2020, 187 patients were screened and 140 were randomly assigned to S-1/temozolomide plus thalidomide (n = 69) or S-1/temozolomide (*n* =71). After a median follow-up of 12·1 months (IQR: 8·4–16·6), the ORR was comparable in the S-1/temozolomide plus thalidomide and S-1/temozolomide groups 26·1% [95% CI 17·2–37·5] versus 25·4% [95% CI 16·7–36·6]; odds ratio: 1·03 [95% CI 0·48–2·22]; *P* = 0·9381). In the S-1/temozolomide plus thalidomide group, the most common grade 3–4 treatment-related adverse event was fatigue (2/68, 3%), and in the control group were thrombocytopenia and diarrhea (both 1/71, 2%). There were no treatment-related deaths in either group.

Interpretation S-1/temozolomide with or without thalidomide leads to a comparable treatment response in patients with advanced/metastatic NETS.

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Keywords: S-1; Temozolomide; Thalidomide; Neuroendocrine tumours

Research in context

Evidence before this study

Neuroendocrine tumours (NETS) are a rare and heterogeneous group of tumours originating from the neuroendocrine system. Temozolomide-based chemotherapy is commonly used for the treatment of NETS. However, prospective clinical trials of these regimens are rare and have largely excluded patients with non-pancreatic NETS. We searched PubMed using the terms "neuroendocrine tumor" AND "RCT" AND "chemotherapy" OR "temozolomide" OR "tegafur" OR "S-1" from Jan 1, 2012, to March 1, 2017, and reviewed all publications of clinical trials, with no language restrictions. We identified only a small number of clinical trials reporting the efficacy and safety of systemic therapies for the treatment of NETS, with an even smaller number including patients with grade 3 or non-pancreatic NETS and investigating temozolomide-based chemotherapy.

Added value of this study

To our knowledge, this phase II STEM trial is the first prospective, randomised, controlled study to evaluate the efficacy and safety of S-1 plus temozolomide, with or without thalidomide, in a patient population including those with grade 3 and non-pancreatic advanced/metastatic NETS. Our study does provide important evidence that S-1 plus temozolomide, with or without thalidomide, has anti-tumour efficacy and is generally well tolerated in patients with advanced/metastatic NETS and also provide the first prospective evaluation of temozolomide-based treatment in patients with non-pancreatic NETS.

Implications of all the available evidence

The results of the phase II STEM trial confirm that S-1 plus temozolomide, with or without thalidomide, is a well-tolerated regimen for patients with pancreatic and non-pancreatic advanced/metastatic NETS, with comparable objective response rate in the S-1/temozolomide plus thalidomide and S-1/temozolomide groups. These findings address an important knowledge gap for the treatment of non-pancreatic NETS and grade 3 NETS and also suggest that MGMT expression is a valuable biomarker for predicting response to temozolomide-based treatment. Given the rare nature of NETS and the limited clinical data available, our results could directly improve clinical practice and broaden treatment options for patients with NETS.

Introduction

Neuroendocrine tumours (NETS) are a relatively rare and heterogeneous group of tumours originating from the neuroendocrine system and are most commonly located in the gastrointestinal tract and lungs.[1,2] There has been a significant increase in the reported annual age-adjusted incidence of NETS over the last 50 years; increasing 6·4 times from 1·09 per 100000 people in 1973 to 6·98 per 100000 people in 2012.[3] In general,

compared with pancreatic NETS, non-pancreatic NETS are characterized by distinct molecular genetics and biological behavior, and systemic therapies often exert significantly different antitumour activity.[4]

Systemic therapies used in the treatment of advanced NETS include somatostatin analogs (octreotide and lanreotide),[5,6] mTOR inhibitors (everolimus),[7] antiangiogenic tyrosine kinase inhibitors (sunitinib, surufatinib), peptide receptor radionuclide therapy (PRRT), and chemotherapy. In general, the objective response rates (ORR) and progression free survival (PFS) times associated with these systemic therapies are relatively low. Among chemotherapy regimens, streptozotocin- and temozolomide-based regimens are the most widely used for the treatment of NETS. In recent years, capecitabine combined with temozolomide (CAPTEM) has shown remarkable activity in the treatment of advanced NETS.[8] However, studies of temozolomide-based regimens have mainly included patients with pancreatic NETS, demonstrating ORRs ranging from 33% to 70%.[9] In contrast, there have been no prospective studies evaluating the efficacy and safety of temozolomide-based chemotherapy in non-pancreatic NETS. Data in this patient population are limited to retrospective analyses, the results of which suggest better activity in pancreatic versus non-pancreatic NETS.[10]

Tegafur/gimeracil/oteracil/potassium capsules (S-1) are a new, oral 5-FU prodrug that combines three drugs with different mechanisms of action: tegafur (a prodrug metabolized to 5-FU in the body), 5-chloro-2,4-dihydroxypyridine (CDHP), and potassium oxonate, in a molar ratio of 1:0.4:1. This combination is designed to enhance the anti-tumour effect and reduce the gastrointestinal toxicity of 5-FU.[11] The safety and efficacy of S-1-based combination regimens in the treatment of multiple cancers has been reported, including gastric and colorectal cancers.[12,13] Compared with capecitabine, S-1 has more controllable cardiotoxicity,[14] with a lower incidence of hand foot reaction, and is more suitable for use in Asian people.[15] We have previously reported that S-1 plus temozolomide has strong anti-tumour efficacy and is well tolerated in patients with locally advanced or metastatic NETS.[16] Thalidomide, an angiogenesis inhibitor that can suppress cell proliferation and tumour angiogenesis, has also shown an anti-tumour effect against NETS.[17] A phase II study demonstrated that temozolomide combined with thalidomide resulted in an overall ORR of 25%, and a 2-year survival rate of 70% in patients with metastatic NETS.[18]

O6-methylguanine-DNA methyltransferase (MGMT) is a specific DNA damage reversal enzyme, which repairs DNA alkylation damage caused by alkylating agents.[19] The cytotoxic activity of temozolomide is related to DNA alkylation/methylation at the O6 and N7 positions of guanine, resulting in DNA mismatch and tumour cell death. The suicide enzyme MGMT repairs DNA by removing the O6-alkylguanine adducts. It has been shown that glioma patients with a methylated MGMT gene had a better response rate when treated with temozolomide compared to those with an unmethylated promoter.[20] The results of retrospective studies suggest that MGMT expression may be associated with response to temozolomide in patients with NETS.[21] However, this association has not been confirmed in a prospective clinical study.

There is an urgent requirement to identify efficacious chemotherapy regimens for the treatment of NETS and to date there has been no prospective study comparing the efficacy of temozolomide-based chemotherapy in both pancreatic and non-pancreatic NETS. In addition, there has been no prospective evaluation of MGMT as a biomarker of response to temozolomide-based therapy in patients with NETS. Given this background, we conducted the phase II STEM trial to assess the efficacy and safety of S-1/temozolomide with or without thalidomide in patients with advanced/metastatic NETS and explore MGMT as a biomarker of treatment response.

Methods

Study design

The STEM trial was a prospective, randomised, controlled, open-label, multi-centre, phase 2 clinical trial conducted at eight hospitals across China. The study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and with the principles of the Declaration of Helsinki. The study protocol and all revisions, and the informed consent form, received master approval from the Ethics Review Board of 8 hospital across China (17-051/1306,17-052/1307) including The Cancer Hospital of The Chinese Academy of Medical Sciences, The First Affiliated Hospital of Zhengzhou University, The First Affiliated Hospital of Zhejiang University, Zhongshan Hospital of Fudan University, The China-Japan Friendship Hospital, Qinghai University Affiliated Hospital, Liaoning Cancer Hospital and The Fifth Medical centre of PLA General Hospital and were approved by independent Ethics Committees at each study centre.

Patients

This study included adults (>18 years) with histopathologically confirmed low or middle grade (G1, G2, or G3, typical carcinoid [TC] and atypical carcinoid [AC]) pancreatic or non-pancreatic well-differentiated NETS with unresectable locally advanced disease or distant metastasis. For gastroenteropancreatic neuroendocrine tumours (GEP-NETS[22]), grading was based on mitotic images and the Ki-67 index (G1: <2 mitotic images per 10 high-power fields (HPF) and Ki-67 proliferation index ≤2%; G2: 2-20 mitotic images per 10 HPF and Ki-67 proliferation index 3% to 20%; G3: >20 mitotic images per 10 HPF and Ki-67

proliferation index >20%). Eligible patients were either systemic treatment naïve or had received ≤2 prior systemic anti-tumour therapies including somatostatin analogues, interferon, PRRT, mTOR inhibitors or chemotherapy (excluding temozolomide, fluorouracil and thalidomide). Patients were also required to have experienced disease progression confirmed by imaging within 12 months before randomization. Further inclusion criteria included the presence of ≥1 measurable lesion based on RECIST 1·1,[23] Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1, and expected survival of >12 weeks. All patients provided written, informed consent before inclusion.

Key exclusion criteria included patients with functional NETS requiring the use of long-acting somatostatin analogues to control symptoms, such as insulinoma, gastrin tumour, glucagon tumour, somatostatin tumour, Adrenocorticotropic Hormone (ACTH) tumour, Vasoactive Intestinal Peptide (VIP) tumour, carcinoid syndrome, Zollinger-Ellison syndrome, or disease-specific active symptoms.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to S-1/temozolomide or S-1/temozolomide plus thalidomide. The randomization sequence was generated by independent statisticians at Xi'an Meta Clinical Technology Co. Ltd (Shanxi Province, China) using hierarchical block randomisation with a block length of 4 and stratified by pancreatic or non-pancreatic cancers. Patients were enrolled and allocated to treatment by the investigators using a randomisation table. The study was open-label and treatment allocation was not masked. This study was an investigator-initiated and funded trial. We did not use a blinded approach for the following two reasons: (1) a blinded approach requires the design of blank drugs, yet as this was an investigator-initiated trial we could not cover the cost of this approach; (2) we strictly followed the random number table in randomisation.

Procedures

All patients received S-1 40-60 mg orally twice daily on days 1-14 plus temozolomide 200 mg orally daily on days 10-14 in a 21-day cycle. Patients assigned to thalidomide also received thalidomide orally nightly; 100 mg on days 1-7, 200 mg on days 8-14, and 300 mg from day 15. Treatment was continued until disease progression[23] or death, intolerable toxicity, withdrawal of informed consent, or at the investigator's discretion. Use of other anti-tumour therapies was not permitted during the study, although patients with obvious functional symptoms of NETS were allowed to receive short-term treatment with somatostatin analogues using time no more than one month to control symptoms. tumours were evaluated by CT or MRI at baseline. Combined chest, abdomen and pelvis contrast-enhanced CT was required during the screening period, although non-contrast CT or MRI could be considered in case of contraindications. For follow-up visits, the imaging sites and methods should be consistent with baseline as far as possible. Imaging evaluations were conducted every 6 weeks (±3 days) from the beginning of treatment, and every 12 weeks (±3 days) after 1 year of treatment. Safety assessments, including evaluation of adverse events (AEs), were performed on each subsequent treatment visit cycle (every 3 weeks ±3 days). AEs were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4·0. Other safety assessments included laboratory indicators, vital signs, physical examinations, electrocardiograms and cardiac ultrasound observations. Patients who terminated treatment within 30 days after the last drug administration underwent an end of treatment safety assessment and then entered a follow-up period. Only serious AEs considered related to the study drugs were recorded beyond 30 days after the last administration. If patients had not experienced disease progression at the time of treatment discontinuation, imaging evaluations should be continued until disease progression or initiation of other anti-tumour therapy. After the end of study treatment, investigators followed up patients by telephone every 12 (±2 days) weeks to record survival status and current anti-tumour treatments until the patient died, was lost to follow-up, or withdrew informed consent.

During treatment, the expression level of MGMT was measured by immunohistochemistry. Pathological tissue samples taken at baseline from 78/140 patients were evaluated at the pathology laboratory of local cancer centres. If there were any difficulties or doubts in diagnosis, a central pathology laboratory reviewed the samples again and provided a pathological revision. Immunohistochemical detection of MGMT was based on the percentage of expression, and immunostained slides were assessed for both extent and intensity of staining. The extent of immunohistochemical staining was expressed semiquantitatively as the percentage of tumour cells with observable staining, followed by the intensity of staining (0, 1+, 2+, 3+). MGMT (2+) and MGMT (3+) were defined as MGMT positive, and MGMT (-) and MGMT (1+) were defined as MGMT negative.

Outcomes

The primary endpoint was ORR, defined as the proportion of patients in the intention-to-treat population achieving a complete response (CR) or partial response (PR) according to RECIST 1·1. The secondary endpoints were: disease control rate (DCR), progression-free survival (PFS, the time from randomization to first disease progression or death from any cause, whichever occurs

first), overall survival (OS, the time from randomization to death from any cause) and safety. The association between MGMT expression level and treatment response was also investigated.

Statistical analysis

The sample size was estimated assuming an ORR of 45% in the S-1/temozolomide group and taking an estimated odds ratio for ORR for the S-1/temozolomide versus S-1/temozolomide plus thalidomide group of 4·3 among patients with non-pancreatic tumours and 5·5 for those with pancreatic tumours. Setting a two-sided alpha of 0·05, a power of 80%, a randomization ratio of 1:1; and assuming a dropout rate of <20%, enrollment was set at 60 patients with pancreatic NETS and 80 with non-pancreatic NETS. No interim analysis was planned in this study, and the final analysis was performed 15 months after the last patient was enrolled.

In the ITT population, ORR comparisons between the two treatment groups were conducted by estimating an odds ratio (OR) and corresponding 95% confidence interval (CI) using a logistic regression model with treatment group and randomization stratification factors as covariates. Treatment differences were evaluated using the Cochran-Mantel-Haenszel test adjusted for the randomization stratification factors as covariates (pancreatic NETS and non-pancreatic NETS). PFS, OS, and duration of response (in patients with a confirmed response) were estimated and compared using the Kaplan-Meier method and log-rank test. The Cox regression model used to estimate the secondary endpoints (PFS, OS, DOR) only included treatment group and were not adjusted for other covariates. Waterfall charts were drawn to assess the best change in target-lesion size from baseline. The proportional hazard assumption was evaluated using the Martingale residual method.

A post-hoc subgroup analysis was performed for ORR and PFS, using univariate logistic regression to estimate OR and 95% CI, and a univariate Cox model to estimate hazard ratio and 95% CI, respectively. Subgroups were determined based on prognostic factors of interest. The covariates included sex, Chromagranin A (CgA) level in baseline, pathological grade, primary tumour sites, Ki-67 level, MGMT expression level, interval from disease diagnosis to randomisation and treatment assignment (Supplemental Table 1 for a complete list).

The intention-to-treat analysis population included all randomly assigned patients, and the safety analysis included all treated patients who received at least one dose of study drug.Data analyses were conducted using SAS, version 9·4. The study was registered at ClinicalTrials.gov: NCT03204019 (pancreatic group) and NCT03204032 (non-pancreatic group).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of this report. H. Z. and Y. C. had access to dataset and all authors had final responsibility for the decision to submit for publication.

Results

187 patients were screened and 140 were randomly assigned to S-1/temozolomide plus thalidomide (n=69) and S-1/temozolomide (n=71) between March 23, 2017 and November 16, 2020 (Figure 1). All randomised patients were included in the intention-to-treat analysis. At the time of data cut off (June 26, 2021), 62 patients had discontinued treatment respectively; the most common reason was disease progression (27 in the S-1/temozolomide plus thalidomide group and 34 in the S-1/temozolomide group). Patient demographics and baseline disease characteristics were generally well balanced between the treatment groups (Table 1).

After a median follow-up of 12·1 months (IQR: 8·4-16·6), the ORR was comparable in the S-1/temozolomide plus thalidomide and S-1/temozolomide groups: 26·1% (95% CI 17·2–37·5) vs. 25·4% (95% CI 16·7–36·6); OR: 1·03 (95% CI 0·48-2·22); P = 0·9381) (Table 2, Supplemental Figure 2 and 3). The DCR was also comparable between the treatment groups (Table 2).

Among the subgroup of patients with pancreatic NETS, the ORR and DCR were comparable in the S-1/temozolomide plus thalidomide group (30·0% and 83·3%, respectively) and the S-1/temozolomide group (36·7% and 76·7%, respectively) (Table 2). Similarly, among patients with non-pancreatic NETS, the ORR and DCR were comparable in the S-1/temozolomide plus thalidomide group (23·1% and 79·5%, respectively) and S-1/temozolomide group (17·1% and 78·0%, respectively) (Table 2). Consistent results were observed in the per-protocol population (Supplemental Table 2).

At the time of data cutoff, the median treatment time was 5·4 months and 6·0 months in the S-1/temozolomide plus thalidomide and S-1/temozolomide groups, respectively, and the longest treatment time was 43·3 months and 43·1 months, respectively. Among all 140 patients in the intention-to-treat population, the median PFS was 11·5 months (95% CI 7·2-16·2) (Supplemental Figure 4). Median PFS was similar among patients in the S-1/temozolomide plus thalidomide and S-1/temozolomide groups: 12·9 months (95% CI 6·6-41·0) and 11·5 months (95% CI 6·4-19·7); HR=1·00 (95% CI 0·61-1·63) (Figure 2A). Median PFS was also comparable among patients with non-pancreatic NETS (6·8 months [95% CI 4·0-14·0] vs. 7·4 months [95% CI 4·8-11·5]; Figure 2B) and pancreatic NETS (16·2 months [95% CI 7·2-not reached (NC)] vs. NC [95% CI 7·1 months-NC]; Figure 2C) assigned to S-1/temozolomide plus thalidomide versus S-1/temozolomide, respectively. The 1-, 2-,

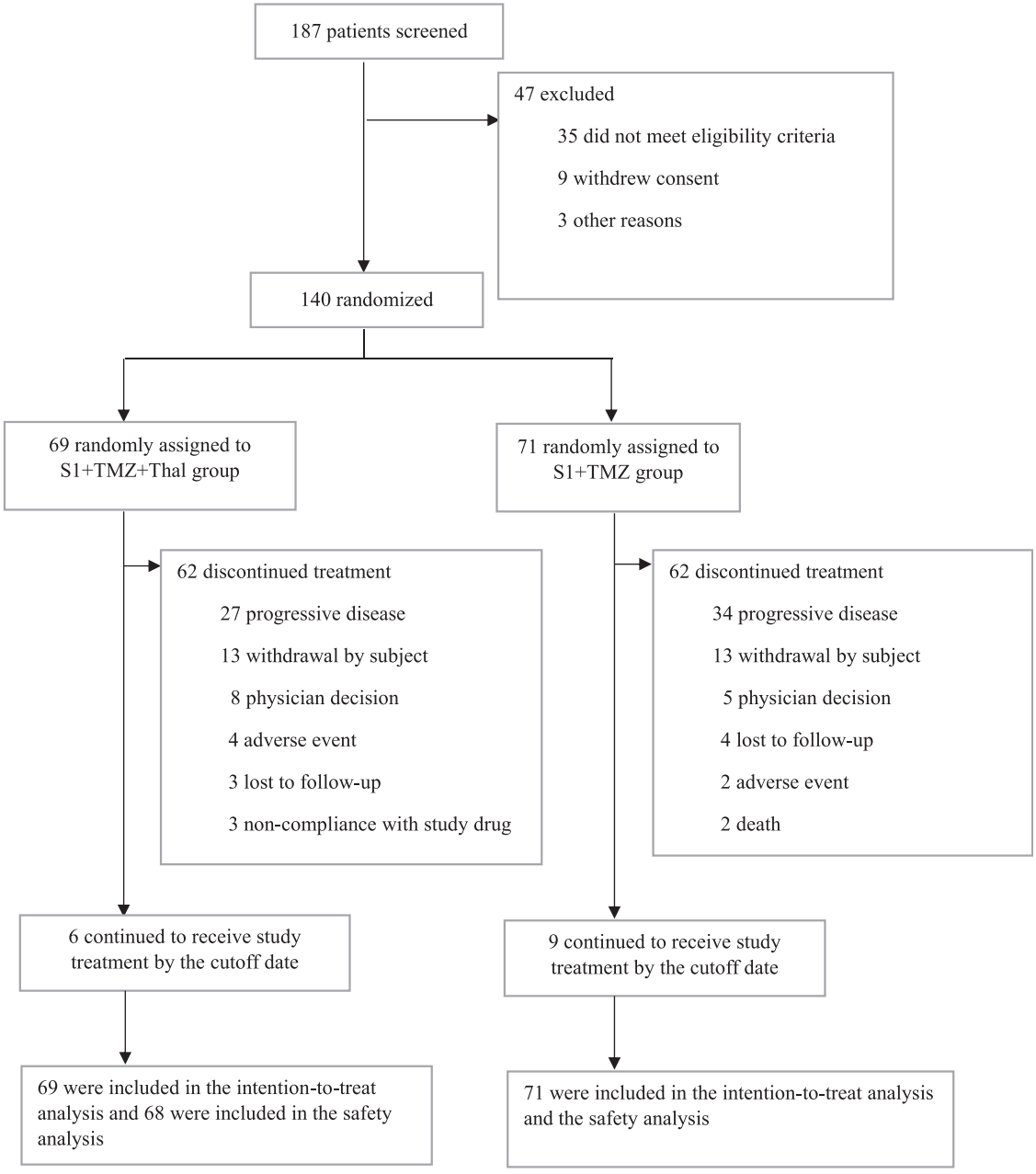

Figure 1. Trial profile.
S1+TMZ, S-1/temozolomide; S1+TMZ+Thal, S-1/temozolomide plus thalidomide.

3-, and 4-year PFS rates in the S-1/temozolomide plus thalidomide group were 50·0%, 36·7%, 36·7%, and 18·4%, respectively, and in the S-1/temozolomide group were 48·2%, 34·0%, 29·8%, and 29·8%, respectively.

Among all 140 patients in the ITT, and in both treatment groups, the median OS was not reached (Supplemental Figure 5 and 6). The 1-, 2-, 3-, and 4-year OS rates in the S-1/temozolomide plus thalidomide group were 88·5%, 70·6%, 62·0%, and 62·0%, respectively, and in the S-1/temozolomide group were 87·1%, 75·0%, 63·1%, and 63·1%, respectively. Among patients with non-pancreatic NETS, median OS was not reached in the S-1/temozolomide plus thalidomide group and was 27·5 months in the S-1/temozolomide group (Supplemental Figure 7). Among patients with pancreatic NETS, median OS was not reached in either treatment group (Supplemental Figure 8).

	Statistics	ITT population		Non-pancreatic NET		Pancreatic NET	
		S1+TMZ+Thal (*n*=69)	S1+TMZ (*n*=71)	S1+TMZ+Thal (*n*=39)	S1+TMZ (*n*=41)	S1+TMZ+Thal (*n*=30)	S1+TMZ (*n*=30)
Age, years	Median (IQR)	51·0 (44·0–60·0)	51·0 (45·0–61·0)	55 (44·0–64·0)	52 (46·0–64·0)	50·5 (43·5–57·25)	50·0 (45·0–59·5)
	Range	19·0–74·0	21·0–80·0	19·0–74·0	21·0–80·0	29·0–69·0	29·0–73·0
Sex, n (%)	Female	30 (43)	31 (44)	18 (46)	20 (49)	12 (40)	11 (37)
	Male	39 (57)	40 (56)	21 (54)	21 (51)	18 (60)	19 (63)
ECOG performance status, n (%)	0	42 (61)	34 (48)	27 (69)	19 (46)	15 (50)	15 (50)
	1	27 (39)	37 (52)	12 (31)	22 (54)	15 (50)	15 (50)
NET pathological grade, n (%)	G1	5 (7)	8 (11)	4 (10)	5 (12)	1 (3)	3 (10)
	G2	43 (62)	40 (65)	20 (51)	18 (44)	23 (77)	22 (73)
	G3	12 (17)	11 (15)	6 (15)	6 (15)	6 (20)	5 (17)
	AC	9 (13)	8 (11)	9 (23)	8 (20)	0	0
	TC	0	1 (1)	0	1 (2)	0	0
	Unknown	0	3 (4)	0	3 (7)	0	0
Chromagranin A(CgA) level, n (%)	≤2 x ULN	13 (19)	6 (8)	12 (31)	5 (12)	1 (3)	1 (3)
	>2 x ULN	15 (22)	10 (14)	8 (20)	6 (15)	7 (23)	4 (13)
	Unknown	41 (59)	55 (77)	19 (49)	30 (73)	22 (74)	25 (84)
Ki-67 level, n (%)	<5%	12 (18)	18 (25)	7 (18)	10 (24)	5 (17)	8 (27)
	5–10%	25 (37)	20 (28)	16 (41)	12 (29)	9 (31)	8 (27)
	>10%	31 (45)	33 (47)	16 (41)	19 (46)	15 (52)	14 (47)
MGMT status, n (%)	MGMT 0 or 1+	30 (43)	23 (32)	19 (49)	13 (32)	11 (37)	10 (33)
	MGMT 2+or 3+	12 (17)	13 (18)	5 (13)	9 (22)	7 (23)	4 (13)
	Unknown	27 (39)	35 (49)	15 (38)	19 (46)	12 (40)	16 (53)
Primary tumour site, n (%)	Pancreas	30 (43)	30 (42)	0	0	30 (100)	30 (100)
	Gastrointestinal	19 (28)	17 (24)	19 (49)	17 (41)	0	0
	Rectum	11 (16)	11 (15)	11 (28)	11 (27)	0	0
	Stomach	4 (6)	4 (6)	4 (10)	4 (10)	0	0
	Colon	2 (3)	1 (1)	2 (5)	1 (2)	0	0
	Duodenum	2 (3)	1 (1)	2 (5)	1 (2)	0	0
	Liver	4 (6)	7 (10)	4 (10)	7 (17)	0	0
	Thymus Gland	5 (7)	7 (10)	5 (13)	7 (17)	0	0
	Lung	4 (6)	4 (6)	4 (10)	4 (10)	0	0
	Others	8 (12)	6 (8)	7 (18)	6 (15)	0	0
Distant metastasis site, n (%)	Liver	54 (78)	51 (72)	28 (72)	24 (59)	26 (87)	27 (90)
	Lymphoglandula	29 (42)	23 (32)	19 (49)	13 (32)	10 (33)	10 (33)
	Bone	11 (16)	16 (23)	9 (23)	13 (32)	2 (7)	3 (10)

Table 1 *(Continued)*

	Statistics	ITT population		Non-pancreatic NET		Pancreatic NET	
		S1+TMZ+Thal (*n*=69)	S1+TMZ (*n*=71)	S1+TMZ+Thal (*n*=39)	S1+TMZ (*n*=41)	S1+TMZ+Thal (*n*=30)	S1+TMZ (*n*=30)
	Lung	5 (7)	6 (8)	5 (13)	5 (12)	0	1 (3)
	Others	17 (25)	20 (28)	10 (26)	15 (37)	7 (23)	5 (17)
Organ metastases, n (%)	≤2 organs	48 (70)	52 (73)	24 (62)	29 (71)	24 (80)	23 (77)
	≥3 organs	18 (26)	16 (23)	12 (31)	10 (24)	6 (20)	6 (20)
	Non-metastases	3 (4)	3 (4)	3 (8)	2 (5)	0	1 (3)
Time from diagnosis to randomization, n (%)	≤12 months	63 (91)	56 (79)	37 (95)	33 (80)	26 (87)	23 (77)
	>12 months	6 (9)	15 (21)	2 (5)	8 (20)	4 (13)	7 (23)
Previous treatment history, n (%)	Previous systemic treatment	14 (20)	24 (34)	8 (21)	15 (37)	6 (20)	9 (30)
	Previous systemic chemotherapy	8 (12)	11 (15)	5 (13)	9 (22)	3 (10)	2 (7)
	Previous treatment with somatostatin	7 (10)	14 (20)	4 (10)	9 (22)	3 (10)	5 (17)
	Previous targeted therapy	4 (6)	7 (10)	2 (5)	3 (7)	2 (7)	4 (13)

***Table 1*: Patient demographics and baseline clinical characteristics.**

ECOG, Eastern Co-operative Oncology Group; ITT, intention-to-treat; IQR, interquartile range; MGMT, O6-methylguanine-DNA methyltransferase; NET, neuroendocrine tumour; S1+TMZ, S-1/temozolomide; S1+TMZ+Thal, S-1/temozolomide plus thalidomide; ULN, upper limit of normal.

	ITT population		Non-pancreatic NET		Pancreatic NET	
	S1+TMZ+Thal (*n*=69)	**S1+TMZ (*n*=71)**	**S1+TMZ+Thal (*n*=39)**	**S1+TMZ (*n*=41)**	**S1+TMZ+Thal (*n*=30)**	**S1+TMZ (*n*=30)**
Best overall response						
Complete response, n (%)	1 (1)	0	1 (3)	0	0	0
Partial response, n (%)	17 (25)	18 (25)	8 (21)	7 (17)	9 (30)	11 (37)
Stable disease, n (%)	38 (55)	37 (52)	22 (56)	25 (61)	16 (53)	12 (40)
Progressive disease, n (%)	6 (9)	6 (8)	4 (10)	4 (10)	2 (7)	2 (7)
Not evaluable, n (%)	7 (10)	10 (14)	4 (10)	5 (12)	3 (10)	5 (17)
Overall response rate (95% CI), %	26·1 (17·2—37·5)	25·4 (16·7—36·6)	23·1 (12·6—38·3)	17.1 (8.5—31.2)	30.0 (16.7—47.9)	36.7 (21.9—54.5)
Odds ratio (95% CI)	1·03 (0·48—2·22)		1·46 (0·48—4·39)		0·74 (0·25—2·17)	
P-Value	0·9381[a]		0·5821[b]		0·7847[b]	
Disease control rate (95% CI), %	81·2 (70·4—88·6)	77·5 (66·5—85·6)	79·5 (64·5—89·2)	78.0 (63.3—88.0)	83.3 (66.4—92.7)	76.7 (59.1—88.2)
Odds ratio (95% CI)	1·25 (0·55—2·85)		1·09 (0·37—3·19)		1·52 (0·42—5·47)	
P-Value	0·5938[a]		1·0000[b]		0·7480[b]	
Median time to response (IQR), months	2·9 (1·6—7·3)	4·6 (1·7—6·9)	2·3 (1·5—5·0)	4.8 (1.7—6.6)	3.6 (1.6—9.3)	4.3 (1.6—8.8)
Median duration of response (95% CI), months	12·7 (5·2-NC)	NC (9·9-NC)	5·5 (3·5-NC)	9.9 (3.0-NC)	NC (5.15-NC)	NC (15.1-NC)
Hazard ratio (95% CI)	1·30 (0·39—4·36)		0·95 (0·20—4·44)		1·98 (0·26—15·07)	
P—Value	0·6740[c]		0·9475[c]		0·5006[c]	

***Table 2*: Summary of efficacy outcomes.**

Tumour response evaluated using RECIST 1·1.

ITT, intention-to-treat; IQR, interquartile range; NC, not reached; NET, neuroendocrine tumour; S1+TMZ, S-1/temozolomide; S1+TMZ+Thal, S-1/temozolomide plus thalidomide.

[a] Comparison between groups uses Cochran-Mantel-Haenszel test (ie, stratified chi-square test).

[b] Comparison between groups uses Fisher's exact probability method;

[c] Duration of Response was compared between groups using Log-rank test; The comparison direction of Odds ratio is: S1+TMZ+Thal vs S1+TMZ (the same below).

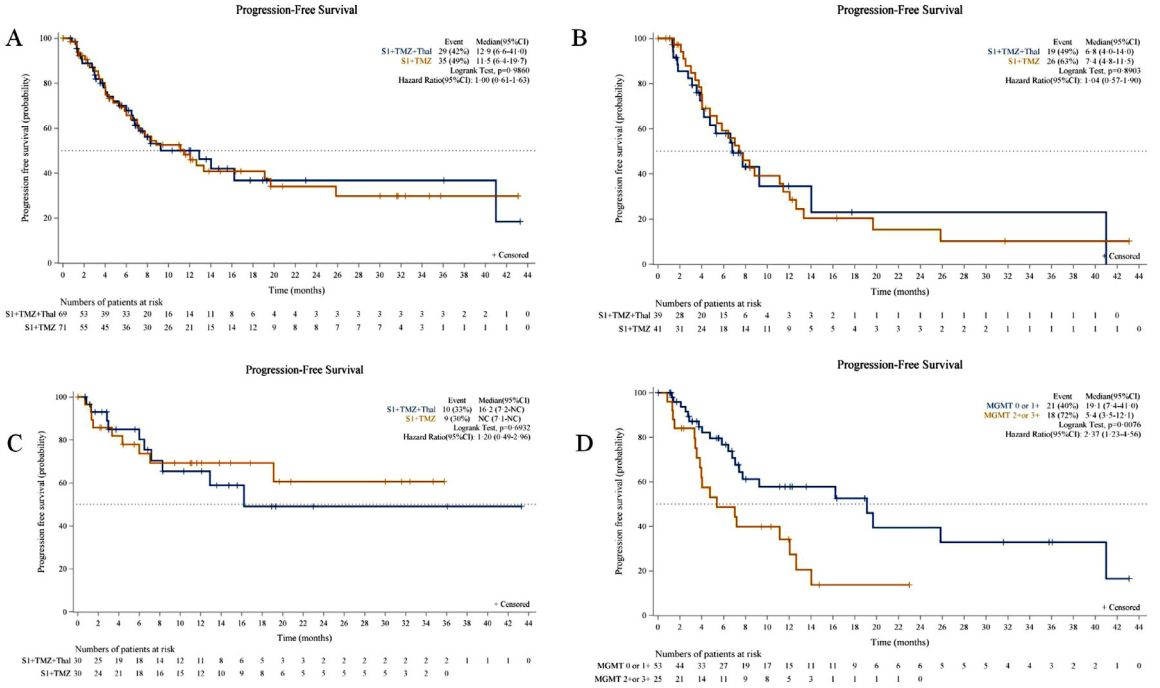

Figure 2. Kaplan-Meier estimates of progression-free survival. A) patients in the intention-to-treat population assigned to S1+TMZ and S1+TMZ+Thal; B) patients with non-pancreatic disease assigned to S1+TMZ and S1+TMZ+Thal; C) patients with pancreatic disease assigned to S1+TMZ and S1+TMZ+Thal and D) patients with MGMT positive or negative status.

S1+TMZ, S-1/temozolomide; S1+TMZ+Thal, S-1/temozolomide plus thalidomide; MGMT, O6-methylguanine-DNA methyltransferase.

Among 78/140 patients who underwent MGMT evaluation, 25 were MGMT positive (MGMT 2+ and 3+) and 53 were MGMT negative (MGMT- and 1+). Among the 25 MGMT positive patients, the most common primary site was the pancreas (11/25, 44·0%), followed by gastrointestinal (7/25, 28·0%) and lung + thymus gland (4/25, 16.0%). Among the 53 MGMT negative patients, the most common primary site was the pancreas (21/53, 39·6%) followed by gastrointestinal (13/53, 24·5%) and lung + thymus gland (8/53, 15.1%) (Supplemental Table 3) .The median PFS among the MGMT positive group was shorter compared with the MGMT negative group (5·4 months vs. 19·1 months; HR=2·37 [95% CI 1·23-4·56]) (Supplemental Table 4 and Figure 2D). In addition, the ORR was higher in the MGMT negative group versus the MGMT positive group (35·9% [19/53] vs. 8·0% [2/25], OR=0·16 [95% CI 0·03–0·73]) (Table 3).

In subgroup analyses, no associations were identified between patient baseline characteristics and treatment outcomes to S-1/temozolomide plus thalidomide versus S-1/temozolomide; both ORR (Supplemental Table 5 and Supplemental Figure 9) and PFS (Supplemental Table 6 and Supplemental Figure 10) were comparable between the subgroups. Among all patients in the intention-to-treat population, an association was observed between age (<65 years and ≥65 years) and median OS (NC vs. 25·6 months [95% CI 8·5-NC]; $P = 0·0018$) (Supplemental Table 7). An association was also observed between pancreatic and non-pancreatic NETS and median PFS (NC [95% CI 12·9-NC] vs. 7·4 months [95% CI 5·3–11·1]; $P = 0·0003$). There was an association between MGMT negative and MGMT positive status and ORR (35·8% [95% CI 24·3–49·3] vs. 8·0% [95% CI 2·2–25·0]; HR=0·16 [95% CI 0·03–0·73]; $P = 0·0127$), median PFS (19·1 months [95% CI 7·4–41·0] vs. 5·4 months [95% CI 3·5–12·1]; HR=2·37 [95% CI 1·23–4·56]; $P = 0·0076$), and median OS (NC [95% CI 27·5-NC] vs. 25·6 [95% CI 12·3-NC] months; HR=2·27 [95% CI 1·00–5·17]; $P = 0·0447$).

In the Cox regression analysis of all patients in the intention-to-treat population, primary tumour site was associated with PFS ($P < 0·05$), and the treatment arm and NET pathological grade were found to have a tendency towards association with PFS ($P < 0·1$) (Supplemental Table 8). In the subsequent logistic regression of ORR, none of the factors was found to be associated with ORR (Supplemental Table 9).

One patient in the S-1/temozolomide plus thalidomide group did not receive treatment and was excluded from the safety analysis. The incidence of any grade AEs was comparable in the S-1/temozolomide plus thalidomide and S-1/temozolomide groups: 65% (44/68 patients) and 70% (50/71 patients). In the S-1/temozolomide plus thalidomide and S-1/temozolomide groups,

	MGMT 0 or 1+	MGMT 2+ or 3+
Best overall response		
N	53	25
Complete response, n (%)	1 (2)	0
Partial response, n (%)	18 (34)	2 (8)
Stable disease, n (%)	27 (51)	19 (76)
Progressive disease, n (%)	5 (9)	4 (16)
Not evaluable, n (%)	2 (4)	0
Overall response rate (95% CI)	35·9 (24·3-49·3)	8.0 (2.2-25.0)
Odds ratio (95% CI)	0·16 (0·03-0·73)	
P-Value	0·0127[a]	

***Table 3*: Comparison of tumour response rates in MGMT negative and positive patients.**
Tumour responses assessed using RECIST 1·1. MGMT, O6-methylguanine-DNA methyltransferase.
Odds ratio direction definition: MGMT 2+ or 3+ vs MGMT 0 or 1+.
[a] Fisher's exact test was used to compare ORR between groups.

AEs led to a dose modification in 10% (7/68 patients) and 4% (3/71 patients), and treatment discontinuation in 1% (1/68 patients) and 1% (1/71 patients) of patients, respectively. The most common AEs in the S-1/temozolomide plus thalidomide group were nausea, leukopenia, elevated blood bilirubin level, and fatigue, and the incidence of grade 3-4 AEs was 9% (6/68 patients), mainly including fatigue, leukopenia, elevated blood bilirubin level, and vomiting. No grade 5 AEs occurred. In the S-1/temozolomide group, the most common AEs were nausea, leukopenia, thrombocytopenia, and fatigue, and the incidence of grade 3-5 AEs was 4% (3/71) and included thrombocytopenia (1/71 patient), diarrhea (1/71 patient), and coma (1/71 patient; grade 5, not considered treatment-related).

Among patients with pancreatic NETS, the incidence of all grade AEs in the S-1/temozolomide plus thalidomide and S-1/temozolomide groups was 63% (19/30) and 67% (20/30), respectively, and the incidence of grade 3-4 AEs was 13% (4/30) and 3% (1/30). Among patients with non-pancreatic NETS, the incidence of all grade AEs in the S-1/temozolomide plus thalidomide and S-1/temozolomide groups was 66% (25/38) and 73% (30/41), respectively, and the incidence of grade 3-4 AEs was 5% (2/38) and 5% (2/41).

Discussion

To our knowledge, this is the first prospective study of temozolomide-based chemotherapy to include patients with pancreatic and non-pancreatic NETS. Furthermore, while previous prospective studies including RADIANT-4[7] and SANET-ep[24] excluded patients with G3 NETS, our study included 23 patients with G3 NETS and provides much needed data in this patient population. Our primary endpoint was not met, and superiority of S-1/temozolomide plus thalidomide versus S-1/temozolomide was not shown. However, our results still show that S-1/temozolomide-based treatment, with or without thalidomide, is an effective and well-tolerated oral regimen for patients with metastatic NETS and was active in both pancreatic and non-pancreatic NETS. Our study also provides the first prospective evidence that expression of MGMT can predict outcomes to S-1/temozolomide-based chemotherapy, with a better ORR, median PFS, and median OS observed in patients with MGMT 0 or 1+ versus those with MGMT 2+ or 3+, strongly supporting the use of MGMT expression as a biomarker for predicting response to temozolomide-based therapy. These results will be of great utility to guide treatment planning and selection for this rare cancer type in clinical practice.

Overall, our study found no significant difference in clinical benefit between S-1/temozolomide with thalidomide and S-1/temozolomide without thalidomide in the treatment of patients with advanced/metastatic NETS. However, our results revealed superior ORR and median PFS in patients with pancreatic NETS compared with non-pancreatic NETS. In addition, we observed no differences in treatment efficacy between patients with G1 NETS and G2 NETS, and in patients who had previously received systemic therapy versus those naive to systemic therapy.

In the present study, the ORR and DCR for patients receiving S-1/temozolomide plus thalidomide and S-1/temozolomide were 26·1% and 25·4% and 81·2% and 77·5%, respectively, which are broadly consistent with the ORR and DCR reported in a meta-analysis of CAPTEM treatment in patients with advanced NETS.[8] However, the ORRs in our study were slightly lower than reported in the meta-analysis, which may be related to the high proportion (17%) of patients with G3 NETS included in the present study, 96% of whom had distant metastasis. Interestingly, our findings show that patients with atypical carcinoids achieved a relatively high ORR. In the long term, the overall prognosis of patients with atypical carcinoids is usually worse than those with typical carcinoids, and the average Ki-67 level is also higher. In addition, for carcinoid types with relatively poor biological behavior and rapid development, combined chemotherapy is associated with higher ORRs than other therapies. Regrettably, according to the analysis of our overall study, among patients with locally advanced unresectable or distant metastases, there was no significant difference in treatment efficacy between patients with different pathological grades and Ki-67 levels.

Previous studies have reported median PFS ranging from 4·7 to not reached for patients with NETS receiving temozolomide-based chemotherapy.[25] The longest median PFS reported in the literature was from a study of patients with metastatic NETS treated with temozolomide and thalidomide, with a median follow-up time of 26 months, and a median PFS of not reached.[18] In our study, the median PFS of patients in the S-1/

temozolomide plus thalidomide and S-1/temozolomide groups was 12·9 months and 11·5 months respectively, and among G3 patients was 6·5 months and 11·5 months, respectively, which are in the same range as previous reports.

Previous studies in which patients with pancreatic NETS received targeted therapy with everolimus, sunitinib or surufatinib, reported ORRs of 5% to 19% and median PFS in the range of 10·9 to 11·4 months.[25,26] In the present study, the ORR and median PFS among patients with pancreatic NETS ranged from 30·0% to 36·7% and 16·2 to NC months, respectively. These results suggest that S-1/temozolomide-based treatment leads to superior outcomes compared with targeted therapy in patients with pancreatic NETS, although cross-trial comparisons should be made with caution. Previous studies in which patients with non-pancreatic NETS patients received everolimus and surufatinib reported ORRs of 2% to 10% and median PFS of 9·2 to 11·0 months.[7,24] In the present study, S-1/temozolomide-based treatment led to ORRs of 23·1% to 17·1% and median PFS of 6·8 to 7·4 months, respectively. The slightly shorter PFS observed among patients with non-pancreatic NETS in the present study compared with previous trials of targeted therapy in this patient population may be related to the characteristics of the ITT population of the present study, which included 23 patients with G3 NETS and 38 patients who had received 1 or 2 prior systemic anti-tumour therapies.

Previous studies have shown that MGMT detection by immunohistochemical staining is a simple and practical biomarker of response to temozolomide-based treatment.[27] However, particularly in patients with pancreatic NETS, conflicting results have been reported so far. For example, a multivariate analysis reported ORRs of 51·8% and 17·7% following temozolomide-based treatment in patients with NETS with and without MGMT promoter methylation, respectively, and the absence of MGMT promoter methylation led to a 2·5 times increase in risk of disease progression.[21] Furthermore, both MGMT promoter methylation and MGMT protein status have been associated with response to alkylating agents in retrospective analyses, as shown by significant differences in PFS and OS after first alkylant use according to MGMT status.[28] Other retrospective studies have reported similar findings.[25] Conversely, a large retrospective study of 144 patients with NETS receiving CAPTEM treatment found that MGMT deficiency (tested with IHC) did not predict treatment response, and therefore cautioned against the use of MGMT expression as the sole predictor of response to CAPTEM.[29] In the context of these conflicting results from retrospective analyses, our study provides the first prospective evidence that MGMT status can predict the efficacy of temozolomide-based chemotherapy in patients with NETS. Our findings support MGMT as a treatment biomarker for temozolomide-based therapy. Interestingly, the E2211 study (presented by P. Kunz at ASCO 2022[30]) investigated capecitabine and temozolomide in patients with advanced pancreatic NETS and also reported that MGMT deficiency was positively associated with ORR, observing a trend for an association between MGMT deficiency, PFS and OS, consistent with our findings and further supporting the conclusions of our STEM trial. In this prior study, capecitabine and temozolomide demonstrated a significant improvement in PFS compared to temozolomide alone (22·7 vs. 14·4 months; HR 0. ·59, P = 0·022) and MGMT deficiency was associated with ORR (MGMT IHC 1-2, H-score low: 52% vs. IHC 3,H-score high: 15%, OR=6.38, P = 0·0004; MGMT promoter methylation positive: 85% vs. negative: 38%, OR=9·79, P = 0·04).

S-1 is a novel oral 5-FU prodrug, designed to enhance the anti-tumour effect and reduce the gastrointestinal toxicity of 5-FU. Multiple Asian studies have compared the efficacy of capecitabine-based regimens and S-1-based treatment in patients with metastatic or recurrent unresectable gastric cancer, and reported consistent efficacy and safety for both regimens.[31,32] In vitro experiments have confirmed that the synergistic effect of 5-FU and temozolomide is related to the time and sequence of drugs administration, and the lethality of temozolomide is strongest when administered 9 days after the administration of 5-FU.[33] The synergistic relationship between S-1 and temozolomide arises because, after S-1 is transformed into 5-FU in tumour tissue, 5-FU further produces fluorodeoxyuridine monophosphate (FdUMP) and fluorodeoxyuridine triphosphate (FdUTP) through different biochemical pathways. 5-FdUTP integrates into DNA, interfering with DNA replication, and 5-FdUMP inhibits thymidylate synthase, thereby reducing the synthesis of dTMP from dUMP, which can further reduce O6-MGMT activity and enhance the inhibitory effect of temozolomide on DNA replication.

In a previous study, we reported that the clinical benefit rate (CR, PR and SD) among patients with metastatic NETS receiving temozolomide plus S-1 was 80%, and that the ORR was higher in patients with pancreatic NETS versus those with non-pancreatic NETS (90% vs. 70%). Similarly, in the present study, patients with pancreatic NETS demonstrated better clinical responses to S-1/temozolomide plus thalidomide and S-1/temozolomide versus those with non-pancreatic disease.

In our study, AEs were mainly of grade 1-2 and most treatment-related adverse events were mild to moderate. The incidence of AEs and the safety profile was generally similar in both treatment groups, although S-1/temozolomide had moderately lower toxicity than S-1/temozolomide plus thalidomide, with a lower incidence of grade 3-4 AEs. In addition, the incidence rates of all grade and grade ≥3 AEs in this study were slightly lower than reported for the CAPTEM regimen in patients with advanced NETS (Table 4).[34]

n (%)	S1+TMZ+Thal (*n*=68)				S1+TMZ (*n*=71)			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Nausea	22 (32)	0	0	0	25 (35)	0	0	0
White blood cell count decreased	12 (18)	1 (2)	0	0	11 (16)	0	0	0
Blood bilirubin increased	6 (9)	1 (2)	0	0	3 (4)	0	0	0
Fatigue	4 (6)	2 (3)	0	0	6 (9)	0	0	0
Rash	4 (6)	1 (2)	0	0	1 (2)	0	0	0
Vomiting	4 (6)	1 (2)	0	0	6 (9)	0	0	0
Thrombocytopenia	3 (4)	0	0	0	8 (12)	1 (2)	0	0
Somnolence	2 (3)	1 (2)	0	0	1 (2)	0	0	0
Lymphocyte count decreased	0	0	1 (2)	0	0	0	0	0
Diarrhea	1 (2)	0	0	0	0	1 (2)	0	0
Deep vein thrombosis	0	1 (2)	0	0	0	0	0	0
Hypotension	0	1 (2)	0	0	0	0	0	0
Gamma-glutamyltransferase increased	0	0	1 (2)	0	0	0	0	0
Syncope	0	1 (2)	0	0	0	0	0	0
Oliguria	0	1 (2)	0	0	0	0	0	0
Coma	0	0	0	0	0	0	0	1 (2)

***Table 4*: Summary of treatment-emergent adverse events (safety population).**
S1+TMZ, S-1/temozolomide; S1+TMZ+Thal, S-1/temozolomide plus thalidomide.

Our study has several limitations that should be mentioned. Firstly, we may have overestimated PFS because the COVID-19 pandemic led to longer review intervals, which may have delayed detection of disease progression. Secondly, this study was initiated by the investigators ourselves, with limited funding. In China, temozolomide and thalidomide are not reimbursable for patients, and patients needed to pay out of pocket for these treatments. Therefore, the economic pressure on patients was relatively large, which may have affected the compliance of patients. Third, not all patients provided tissue samples for IHC analysis, which may have influenced the assessment of MGMT promoter methylation by reducing the sample size. Finally, based on ethical considerations and the intention-to-treat principle, the study was designed so that the control group and treatment group were expected to achieve a therapeutic benefit, and we did not include a placebo group.

In conclusion, this trial did not show a difference in ORR for S-1/temozolomide plus thalidomide versus S-1/temozolomide in patients with advanced NETS. However, both regimens were efficacious and well tolerated in the overall population and in patients with pancreatic NETS and non-pancreatic NETS. Our findings also suggest that expression of MGMT is a potential predictive biomarker of temozolomide-based chemotherapy. Given the promising anti-tumour activity observed with this combination therapy, further studies are warranted to confirm these findings.

Contributors

HZ and YChi conceived, designed the study and verified the underlying data. LS, WL, YZ, YM, WF, HyT, SS, HJ, JX, RJ, BZ, LJ, JZ, RZ, HjT, YW, QC, MY, XG, ZT, ZQ, FZ enrolled patients and collected the data. YChi, LS and WL wrote the first full draft of the article. All authors contributed to the interpretation of data, reviewed the article, had full access to all the data and approved the final version of the article for submission.

Data sharing statement

The original data underlying this paper can be shared, if needed by other researchers. The data can be obtained through the email address of the corresponding author (zhaohong@cicams.ac.cn).

Declaration of interests

The authors have no conflicts of interest to declare.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101667.

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