The Oncologist®

Gastrointestinal Cancer

Sunitinib and Evofosfamide (TH-302) in Systemic Treatment-Naïve Patients with Grade 1/2 Metastatic Pancreatic Neuroendocrine Tumors: The GETNE-1408 Trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Biomarkers • Pancreatic neuroendocrine tumor • Safety • Evofosfamide • Sunitinib

Abstract

Background. Sunitinib (SUN)-induced hypoxia within the tumor could promote the activation of the prodrug evofosfamide (EVO), locally releasing the cytotoxic DNA alkylator bromo-isophosphoramide mustard. SUNEVO, a phase II, open-label, single-arm trial, investigated the potential synergy of SUN plus EVO in advanced progressive pancreatic neuroendocrine tumors (panNETs).

Methods. Systemic treatment-naïve patients with advanced or metastatic, unresectable, grade 1/2 panNETs with a Ki67 ≤20%, received EVO 340 mg/m^2 on days 8, 15, and 22 every 4 weeks and sunitinib 37.5 mg/day continuously. The primary endpoint was objective response rate, measured every 8 weeks by RECIST version 1.1.

Results. From 2015 to 2018, 17 patients were enrolled. The median age was 62.4 years, 47% had a Ki67 >10%, and 70.6% had liver metastasis. Patients received a median of five and four cycles of SUN and EVO, respectively. After a median follow-up of 15.7 months, 17.6% of patients achieved a complete ($n = 1$) or partial response ($n = 2$), and 11 patients had stable disease (64.7%). The median progression-free survival was 10.4 months (95% confidence interval, 2.6–18.0). Treatment-related adverse events (grade ≥3) were observed in 64.7% of the patients, the most frequent being neutropenia (35.3%), fatigue (17.6%), and thrombopenia (11.8%). Treatment discontinuation due to toxicity was reported in 88.2% of the patients. No correlation was found between treatment response and *DAXX*, *ATRX*, *MEN1*, *SETD2*, and *PTEN* gene mutations.

Conclusion. SUN plus EVO had a negative toxicity profile that should be taken into account for further clinical research in advanced panNETs. The combination showed moderate activity in terms of treatment response that did not correlate with somatic mutations. (*Clinical trial identification number*: NCT02402062) ***The Oncologist*** 2021;26:941–949

Implications for Practice: Addition of hypoxia-activated prodrugs has been proposed as a potential mechanism to overcome tumor resistance to antiangiogenic agents. Sunitinib and evofosfamide, which were widely proposed as a potential

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synergistic option, showed modest efficacy in pancreatic neuroendocrine tumors (panNETs), reaching a median objective response rate of 17.6% and median progression-free survival of 10.4 months. Treatment response does not correlate with the biomarkers analyzed. The high systemic toxicity, with 88.2% of patients discontinuing the treatment, makes this therapeutic approach unfeasible and encourages future research to overcome panNETs' resistance to antiangiogenic agents with other therapies with a safer profile.

Introduction

Pancreatic neuroendocrine tumors (panNETs) have complex clinical and biological behaviors, which vary depending on the origin location, hormone production, tumor growth rate, and histological differentiation [1].

Somatostatin analogs (SSAs) are considered the standard systemic approach for those patients with advanced panNETs with a Ki67 of less than 10% [2]. In patients progressing to SSAs or with a higher proliferation index, two targeted therapies, everolimus and sunitinib, with similar median progression-free survival in randomized trials, are approved [3, 4]. Chemotherapy, either orally administered with temozolomide-based regimens or intravenously with streptozotocin or platinum-based schemes, is normally used in progressive panNETs or high-grade neuroendocrine carcinomas [5]. Radionuclides like ^{177}Lu-oxodotreotide have increased available treatment options when tumors progress to standard SSAs [6].

Median overall survival (OS) of approximately 3.6 years and 5-year survival rate of 30.2% in patients with metastatic stage panNETs is expected despite the recent approvals of novel drugs in the field [7]. The major drawback of antiangiogenic therapy (e.g., with sunitinib) is the ability of tumor cells to survive under hypoxic conditions [8]. Hypoxia-activated prodrugs, used in combination with antiangiogenic therapy, have been proposed to potentially overcome this limitation by distributing within the hypoxic regions of the tumor, where they locally exert their cytotoxic effects [9, 10]. Evofosfamide (formerly named TH-302) is a hypoxia-activated prodrug that, upon administration, is expected to distribute into hypoxic tumor regions, where it could be transformed into the DNA alkylator bromo-isophosphoramide mustard, a cytotoxic effector, that selectively and locally would induce tumor cell death [11]. Recent preclinical evidence suggests that TH-302 not only can kill hypoxic pancreatic cancer cells but also has the ability to improve the oxygenation status of residual tumor cells, so it can be used to enhance the effect of radiotherapy and chemotherapy [12, 13]. Results from a phase I clinical trial combining evofosfamide and sunitinib showed preliminary activity in renal cancer [14]. However, there is limited clinical evidence of the safety and efficacy of this combination or equivalent therapeutic approaches in pancreatic cancer. Only two patients with pancreatic adenocarcinoma were included in a phase I trial exploring the combination of pazopanib with evofosfamide [15].

The SUNEVO trial pursued the hypothesis that the hypoxia induced by sunitinib (SUN) might foster the activation of the prodrug evofosfamide (EVO) in patients with locally advanced or metastatic panNETs.

Subjects, Materials, and Methods

Trial Design

GETNE-1408 (SUNEVO) is a multicenter, open-label, single-arm, noncontrolled, and nonrandomized phase II clinical trial assessing the efficacy and safety of the combination of sunitinib and evofosfamide in patients with advanced panNETs. Eligible patients were required to be aged ≥18 years and to have histologically confirmed, well- or moderately differentiated (Ki67 ≤ 20%), unresectable locally advanced, or metastatic panNETs, measurable disease by RECIST version 1.1, no prior systemic treatment other than SSAs, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Exclusion criteria were as follows: previous treatment with chemotherapy, monoclonal antibodies against vascular endothelial growth factor, tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, interferon, immunosuppressants such as cyclosporine, drugs activated by hypoxia, presence of uncontrolled brain metastatic disease, or a second neoplasm in the prior 3 years. This clinical trial was conducted in compliance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, and the Declaration of Helsinki and local laws. The GETNE-1408 trial was granted approval on January 12, 2015, by the Hospital Universitario Ramón y Cajal ethics committee (2014-004072-30) and by the competent authority in Spain (Agencia Española de Medicamentos y Productos Sanitarios). All patients signed the informed consent form prior to their inclusion in the study.

Treatment

Patients received sunitinib treatment at 37.5 mg per day as a single agent, during 1 week, to induce internal tumor hypoxia and increase the release of bromo-isophosphoramide mustard, preferentially inside the tumors, upon treatment with the prodrug evofosfamide.

After the induction phase, patients received the combination of 37.5 mg oral sunitinib daily and 340 mg/m^2 intravenous evofosfamide on days 8, 15, and 22 of every 28-day cycle, until disease progression, unacceptable toxicity, death, investigator decision, patient's noncompliance, or consent withdrawal, whichever occurred first. Continuous safety monitoring by the study scientific committee led to an amendment to the protocol to decrease evofosfamide doses after observation of a high number of treatment-related adverse events (TRAEs). Administration of EVO at the dose of 340 mg/m^2 was changed to days 8 and 22 of every 28-day cycle. Thus, the EVO dose on day 15 of every cycle was omitted.

Objectives and Endpoints

The primary endpoint was to determine the activity of evofosfamide in combination with sunitinib in patients with well- or moderately differentiated panNETs as surrogate of objective response rate (ORR) assessed by the investigators according to RECIST version 1.1 criteria. Secondary endpoints included safety in terms of frequency and severity of adverse events (AEs), progression-free survival (PFS), duration of response (DoR), and OS. Exploratory objectives included the assessment of biomarkers of prognosis and treatment response previously described in panNETs.

Assessments

ORR was measured by computed tomography (CT) scan, according to RECIST version 1.1, every 8 weeks until disease progression, regardless of treatment delays due to AEs. ORR was defined as the percentage of patients with confirmed complete response (CR) or partial response (PR) in relation to the total population analyzed. Confirmed responses were those that persisted in a repeated imaging test ≥4 weeks after the initial documentation of the response. PFS was defined as the time between the start of treatment until the first objective evidence of radiological progression by CT scan or death from any cause. DoR was defined as the time between the start of the first objective response (CR or PR), which was subsequently confirmed, to the first objective evidence of radiological progression by CT scan or death from any cause. OS was defined as the time from the start of treatment to the date of death from any cause. To assess safety, AEs were evaluated throughout the study using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Biomarker Analysis

Somatic mutations in genes frequently altered in panNETs, including the tumor suppressors *MEN1* and *PTEN*, the telomere maintenance genes *DAXX* and *ATRX*, and the chromatin remodeler *SETD2*, were assessed in archival formalin-fixed paraffin embedded (FFPE) tumor samples. These biomarkers were used to study their potential association with response to treatment and clinical outcome. DNA was extracted with the TruXTRAC FFPE DNA microTUBE Kit (Covaris, Woburn, MA) and measured with Quant-iT PicoGreen dsDNA (Thermo Fisher Scientific, Waltham, MA). A hybridization-based target enrichment custom panel was used to sequence the full coding region plus the splice sites of 42 solid tumor–related genes plus the *TERT* promoter region. For library preparation SeqCap EZ Choice Enrichment Kit (Roche-NimbleGen, Madison, WI) was used according to the manufacturer's instructions. After sequencing the DNA libraries in a 100–base-pair paired mode by HiSeq (Illumina, San Diego, CA), bioinformatic data analysis was performed by a Snakemake (version 5.23.0) somatic variant calling in-house pipeline that includes Cutadapt, BWA-mem (version 0.7.17-r1188), Samtools (version 1.9), Picard (version 2.18.7), Mutect2 (tumor-only mode, gatk4-version 4.0.5.1), and Variant Effect Predictor (VEP-*Ensembl* version 94). The median bait coverage obtained in the samples was 792× (min–max, 409–979; interquartile range, 772–830) calculated with the tool Picard *collectHS*. Only loss-of-function and nonsynonymous coding

Table 1. Baseline characteristics in the intention-to-treat population

Baseline characteristics	*n* (%)
Total	17 (100.0)
Gender	
Male	11 (64.7)
Female	6 (35.3)
ECOG PS	
0	11 (64.7)
1	6 (35.3)
Tumor grade	
Grade 2	15 (88.2)
Grade 1	2 (11.8)
Ki67 index	
>2%–5%	5 (29.4)
>5%–10%	4 (23.5)
>10%	8 (47.1)
Mitosis 10 HPF	
Unknown	6 (35.3)
<2	6 (35.3)
2–20	5 (29.4)
Tumor type: Nonfunctioning	17 (100.0)
Primary tumor surgery	
No	11 (64.7)
Yes	6 (35.3)
Stage at diagnosis	
II	3 (17.6)
III	1 (5.9)
IV	13 (76.5)
Metastatic sites (M1)	
Hepatic	12 (70.6)
Unknown	4 (23.5)
Extrahepatic	1 (5.9)
Baseline concomitant medication	
Yes	16 (94.1)
No	1 (5.9)
Prior somatostatin analogs	
No	10 (58.8)
Yes	7 (41.2)
Type of somatostatin analogs	
NA	10 (58.8)
Lanreotide	6 (35.3)
Octreotide	1 (5.9)
Cg A: 13, median (min–max)	197.00 (37.20–2,063.90)
Enolase 1: 10, median (min–max)	15.06 (8.60–92.89)

Percentage calculated with respect to the total number of patients ($n = 17$).
Abbreviations: Cg A, chromogranin A (carcinoid tumor marker); ECOG PS, Eastern Cooperative Oncology Group performance status; HPF, high power field; NA, not applicable.

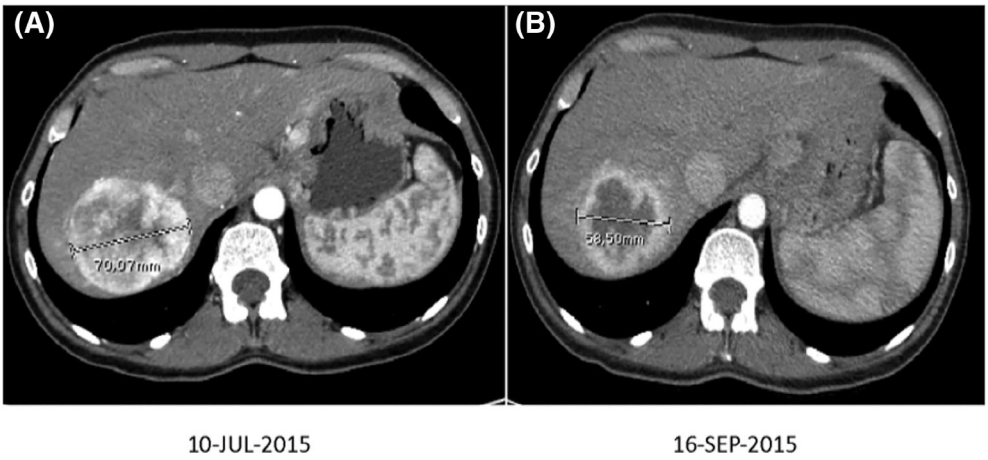

Figure 1. High resolution computed tomography scans from a patient experiencing a partial response at two time points: July 10, 2015 **(A)** and September 16, 2015 **(B)**. From July 2015 to September 2015, the tumor reduced its total size and increased the necrotic areas present inside. Tumor mass is visible as a clear rounded-shape bulk within the pancreas. Darker areas within the tumor are necrotic regions. Dashed line indicates the maximum tumor diameter used to assess clinical response.

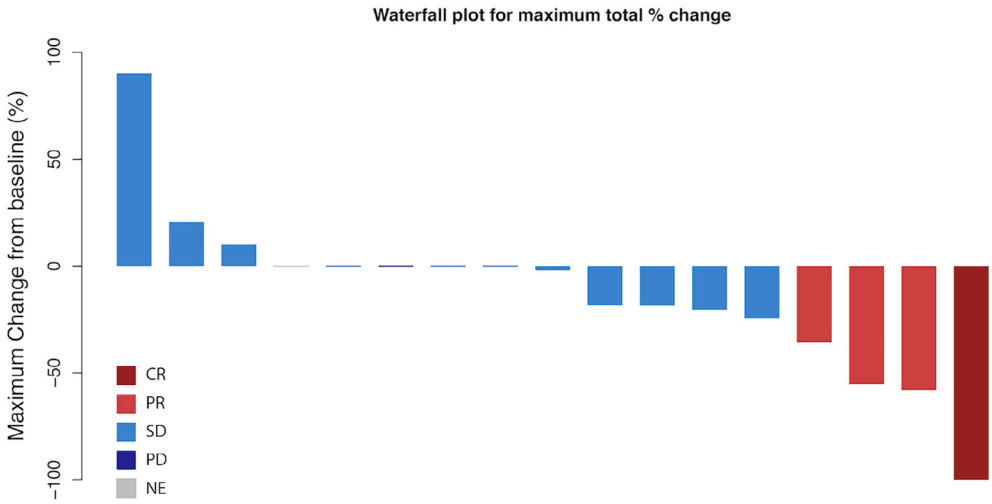

Figure 2. Waterfall plot compiling the best objective responses achieved in the intention-to-treat population ($n = 17$). Data represented as percentage of change in size of the tumor lesions from baseline.
Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; NE, not evaluable; SD, stable disease.

variants with gnomAD minor allele frequency < 0.01% and variant allele fraction ≥15% were retained for the analysis.

Statistical Analysis

Based on previous studies, a Simon two-stage scheme was used. Considering a futility threshold for ORR of 5% and a maximum response of 20%, it was necessary to recruit 18 patients in the first stage and 25 in the second, with a total of 43 patients (power = 0.80; alpha = 0.05). A minimum of three responses were required in the first 18 patients (ORR 16.7%) in order to proceed to the second stage of the study.

Efficacy and safety analyses were performed considering that all patients received at least one dose of sunitinib and evofosfamide. All qualitative data are described as absolute frequencies and the corresponding percentages. Quantitative data are presented using mean ± SD, median, minimum, and maximum values. The response percentages were estimated using 95% confidence intervals (CIs) or full range intervals. Time-to-event endpoints were estimated using the Kaplan-Meier method and Cox regression analysis to obtain hazard ratios and CIs. Patients without documented progression or death at the time of the analysis were censored at the last date of tumor evaluation. All statistical analyses were performed with R (version 3.6.3 [2020-02-29] "Holding the Windsock," The R Foundation for Statistical Computing, Vienna, Austria) and SPSS (IBM SPSS Statistics version 26, Armonk, NY). Figures and tables were generated using RStudio (version 1.2.5033, 2009–2019, RStudio Inc. Boston, MA). All statistical tests were considered two-tailed, and results with $p < .05$ were considered significant.

Results

Patient Demographics and Treatment Duration

Between May 2015 and May 2018, 21 patients were screened, four failed screening (three did not comply with

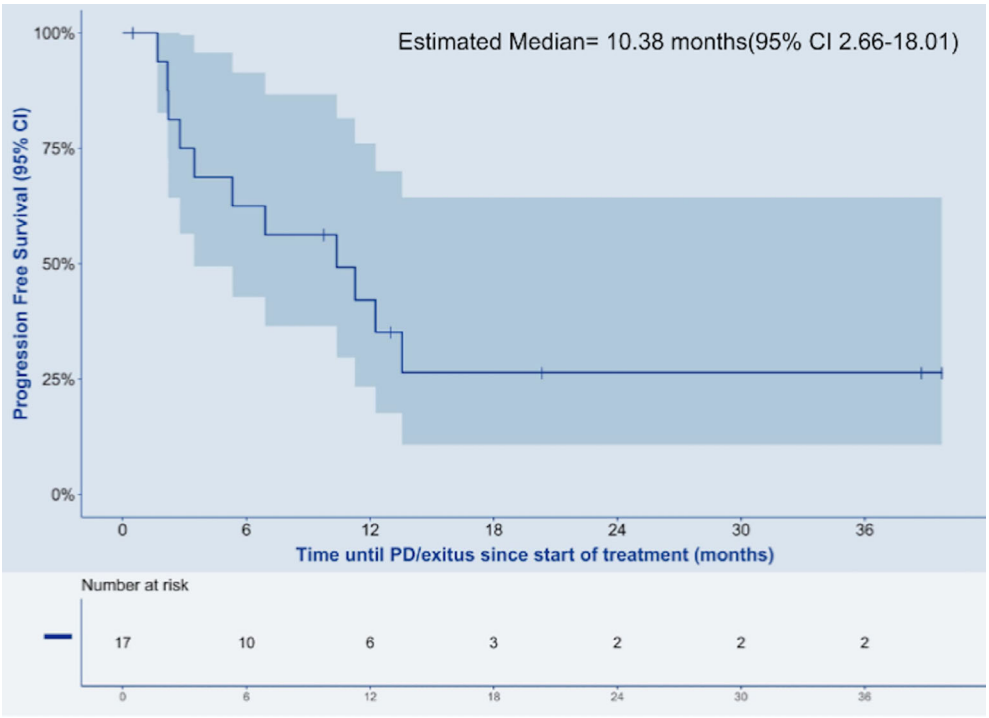

Figure 3. Kaplan-Meier plot of progression-free survival in intention-to-treat population ($n = 17$).
Abbreviations: CI, confidence interval; PD, progressive disease

inclusion criteria and one withdrew consent), and 17 were enrolled in the study. The median age of the patients was 62.4 years (range, 43.4–73.7); most of them were men ($n = 11$; 64.7%), with an overall ECOG performance status of 0 (64.7%) or 1 (35.3%). Baseline characteristics are summarized in Table 1.

At data cutoff (March 15, 2019), all patients had received at least one cycle of the study treatment, with a median of five cycles of sunitinib and four cycles of evofosfamide. Dose reductions of sunitinib and evofosfamide were reported in 35.6% and 100% of patients, respectively. The study treatments were discontinued in 15 patients (88.2%), and only three patients remained on treatment, with one of them receiving sunitinib monotherapy. Reasons for treatment ending included disease progression (50%), toxicity (40%), and death (10%). The study was stopped for safety concerns, before the first pre-established set of enrolled patients completed their participation, because of the elevated number of TRAEs, dose reductions, and discontinuations observed.

Efficacy

Efficacy analysis was performed in the intention-to-treat population, which included all 17 patients enrolled in the study.

Overall, the median ORR (primary endpoint) was 17.6% ($n = 3$) (95% CI, 0.0–35.8), including one confirmed CR and two PR (Figs. 1 and 2). Another patient achieved a PR but was not confirmed in a second radiologic assessment. Stable disease was achieved in 11 patients (64.7%). The median time to treatment response was 1.85 months (95% CI, 1.4–8.8) and the median DoR was 18.48 months (range, 4.2–38.3), with a disease control rate of 82.4% (95% CI, 64.2–100.5).

After a median follow-up time of 15.7 months, the median PFS was 10.4 months (95% CI, 2.7–18.1) (Fig. 3), whereas median OS was not reached.

Safety

The safety analysis comprised the 17 patients enrolled in the study. TRAEs of any grade occurred in 16 patients (94.1%) (Table 2). The most common TRAEs were fatigue, mucositis, neutrophil count decrease, and diarrhea, reported in 82.4%, 58.8%, 52.9%, and 52.9% of patients, respectively (Table 2). Grade ≥ 3 TRAEs occurred in 11 patients (64.7%) (Table 2). Severe or life-threatening TRAEs had a total frequency of 20, more than one per patient. The most common severe TRAEs were neutrophil count decrease (35.3%), fatigue (17.6%), platelet count decrease (11.8%), hypertension, and alanine aminotransferase increase (11.8%) (Table 2). One (5.9%) patient suffered pancreatitis and died as consequence of the TRAE.

Biomarker Substudy

DNA from FFPE tumor samples, available from 10 patients, was used to assess tumor mutations in genes commonly altered in panNETs [16, 17]. Mutations in the telomere maintenance genes *DAXX* and *ATRX* were found in 30% and 20% of patients, respectively, with mutual exclusivity, in agreement with the previously described mutation pattern in panNETs [17] (Fig. 4). The loss of *MEN1* was associated with a greater number of mutations ($p = .019$). However, patients with CR or PR had heterogeneous genetic profiles,

Table 2. Incidence of treatment-related adverse events (>5%) in the safety analysis set ($N = 17$)

Adverse events	***n* (%)**	
Total	17 (100.0)	
Adverse event grade ≥3 (severe, life-threatening, death)		
Yes	11 (64.7)	
No	6 (35.3)	
Related to treatment		
Yes	16 (94.1)	
No	1 (5.9)	
Number of patients reporting serious adverse events		
No	14 (82.4)	
Yes	3 (17.6)	
Adverse reactions (by type)	**All grades, *n* (%)**	**Grade ≥3, *n* (%)**
Fatigue	14 (82.4)	3 (17.6)
Oral mucositis	10 (58.8)	—
Neutropenia	9 (52.9)	6 (35.3)
Diarrhea	9 (52.9)	—
Anorexia	7 (41.2)	—
Hypertension	6 (35.3)	2 (11.8)
Dysgeusia	6 (35.3)	—
Thrombocytopenia	5 (29.4)	2 (11.8)
Palmar-plantar erythrodysesthesia syndrome	5 (29.4)	1 (5.9)
Nausea	5 (29.4)	—
Vomiting	4 (23.5)	—
Acneiform rash	4 (23.5)	—
Headache	4 (23.5)	—
Epigastralgia	3 (17.6)	—
Fever	3 (17.6)	—
Dyspepsia	3 (17.6)	—
Alanine aminotransferase increased	3 (17.6)	2 (11.8)
Venous thrombosis	2 (11.8)	—
Vaginal inflammation	2 (11.8)	—
Skin hypopigmentation	2 (11.8)	—
Skin erythema	2 (11.8)	—
Myalgia	2 (11.8)	—
Gastroesophageal reflux disease	2 (11.8)	—
Epistaxis	2 (11.8)	—
Dysphagia	2 (11.8)	—
Dysesthesia	2 (11.8)	—
Constipation	2 (11.8)	—
Conjunctivitis	2 (11.8)	—
Blood bilirubin increased	2 (11.8)	—
Anemia	2 (11.8)	—
Arthralgia	2 (11.8)	—
Abdominal pain	2 (11.8)	—
Leucopenia	1 (5.9)	—
Skin and subcutaneous tissue toxicity	7 (41.2)	—
Thoracic pain	1 (5.9)	—
Genital dryness	1 (5.9)	—

(continued)

Table 2. (continued)

Adverse reactions (by type)	All grades, *n* (%)	Grade ≥3, *n* (%)
Rectal hemorrhage	1 (5.9)	—
Pharyngitis	1 (5.9)	—
Peripheral motor neuropathy	1 (5.9)	—
Paresthesia	1 (5.9)	—
Pancreatitis	1 (5.9)	1 (5.9)
Nail infection	1 (5.9)	—
Hypocalcemia	1 (5.9)	—
Hemorrhoids	1 (5.9)	—
Hematuria	1 (5.9)	—
Gastrointestinal disorders	4 (23.5)	—
Esophagitis	1 (5.9)	—
Erythroderma	1 (5.9)	—
Dry skin	1 (5.9)	—
Dizziness	1 (5.9)	—
Depression	1 (5.9)	—
Bilirubin increased	1 (5.9)	1 (5.9)
Aspartate aminotransferase increased	1 (5.9)	1 (5.9)
Anal ulcer	1 (5.9)	—
Anal pain	1 (5.9)	—
Alopecia	1 (5.9)	—
Total	163	20

Percentages calculated with respect to the total number of patients ($n = 17$). Toxicity was evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

and no correlation was found between treatment response and somatic mutations (Fig. 4).

Discussion

The SUNEVO trial explored the activity and safety of sunitinib plus evofosfamide in locally advanced or metastatic panNETs. The main concern regarding the combination of sunitinib and evofosfamide in our trial was the unexpected high toxicity, particularly of hematological AEs, that led to reduction and changes in the treatment schedule in a substantial proportion of patients. Toxicity was indeed the main limitation of the SUNEVO trial. During the study, 35.3% and 11.8% of patients reported severe decrease in neutrophil and platelet counts, respectively (Table 2). Previous studies using evofosfamide described similar types and frequencies of toxic events [3, 12–15]. A phase I trial that included patients with recurrent renal and gastrointestinal stromal tumors showed preliminary evidence of a relatively mild toxicity for the drug combination, with pancytopenia being the predominant adverse event, including grade ≥ 3 thrombocytopenia and neutropenia in 40% and 30% of patients, respectively [14]. The toxicity profile makes this therapeutic option not viable in the current setting. Sunitinib dose was reduced in 35.6% of the patients due to toxicity, whereas evofosfamide had to be discontinued in all the patients enrolled in the study. The poor tolerability of the combination, with 64.7% of patients experiencing grade 3 or higher treatment-related adverse events, forced the decrease of drug doses and limited continued administration and subsequently the drugs' potential antitumor activity. Treatment modifications and delays might have masked the efficacy of the combination in patients with panNETs.

The combination treatment showed moderate activity in terms of response. The ORR (17.6%) was somewhat higher than that expected for sunitinib alone according to those clinical trials available by the date of study design, reporting an ORR of 9.3% [3, 18]. However, a recent pooled analysis from the phase III and IV trials in panNETs has reported an ORR of 16.7% for sunitinib monotherapy, which is similar to the ORR observed in our trial for the combination with evofosfamide [19]. Moreover, the addition of evofosfamide did not translate into a prolonged PFS with the treatment combination, with a median of 10.4 months. In fact, patients with panNET treated with sunitinib monotherapy reported a longer median PFS, ranging from 12.6 months in a randomized phase III trial including 171 patients to up to 16.8 months in a phase II trial in a Japanese population [19–21]. These studies found a favorable toxicity profile for sunitinib monotherapy, and quality of life seemed unaffected by this therapeutic approach regardless of diarrhea symptoms [19–22]. Therefore, sunitinib monotherapy is safer and seems equally effective as or even more effective than the combination of evofosfamide and sunitinib.

Despite previous studies demonstrating the efficacy of evofosfamide in combination with antiangiogenic agents [15, 23], we did not observe a clear synergistic effect of the

Figure 4. OncoPrint plot showing the genetic profile of commonly mutated genes in pancreatic neuroendocrine tumors, together with the patients' response. Gray indicates wild-type gene; red indicates loss-of-function mutations; blue indicates missense mutations.
Abbreviations: CR, complete response; PR, partial response.

combination of both drugs in panNETs. Thus, data on the efficacy of evofosfamide in combination with antiangiogenic agents for the treatment of oncology patients remain controversial.

The high systemic toxicity, more similar to conventional chemotherapy than to targeted therapy, may indicate that the hypoxia-induced local release mechanism of the prodrug does not occur as locally as expected.

At the molecular level, previous studies have observed that loss of *DAXX* and *ATRX* genes is a predictor of metastatic disease and poor survival in patients with panNETs [24]. Although the genetic alterations observed in our study are concordant with the previously described mutation frequencies in panNETs [17], no correlation with treatment response or survival was observed. The low number of cases and the high number of sunitinib and evofosfamide dose reductions have nevertheless limited the ability to properly address this potential correlation with clinical response.

First-line panNET is usually an asymptomatic or paucisymptomatic setting, so treatments should be focused on safety and patient's quality of life while achieving control of the disease. The results from this study indicate that the combination of hypoxia-activated prodrugs with antiangiogenic agents might not be viable because of unfavorable toxicity profile and limited efficacy. Consequently, further research should be focused on less toxic therapeutic strategies.

Conclusion

The SUNEVO trial showed that sunitinib plus evofosfamide in locally advanced or metastatic panNET evoked a high systemic toxicity, resulting in a potential unfavorable risk-benefit profile. In spite of the moderate efficacy reported, the safety concerns raised promote future research on safer therapeutic options.

Acknowledgments

This trial was sponsored by Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE). Threshold/MTEM provided evofosfamide and awarded a grant to GETNE to pay the costs of the study. Pfizer provided sunitinib. Medical writing and statistical analyses were performed, respectively, by Pau Doñate, Ph.D., and Jordi Curto, M.Sc., both from MFAR Clinical Research (Barcelona, Spain).

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Disclosures

Enrique Grande: Adacap, AMGEN, Angelini, Astellas, AstraZeneca, Bayer, Blueprint, Bristol-Myers Squibb, Caris Life Sciences, Celgene, Clovis-Oncology, Eisai, Eusa Pharma, Genetracer, Guardant Health, HRA-Pharma, Ipsen, ITM-Radiopharma, Janssen, Lexicon, Eli Lilly & Co., Merck KGaA, Merck Sharp & Dohme, Nanostring Technologies, Natera, Novartis, ONCODNA (Biosequence), Palex, Pharmamar, Pierre Fabre, Pfizer, Roche, Sanofi-Genzyme, Servier, Taiho, Thermo Fisher Scientific (H); **Cristina Rodriguez-Antona:** Pfizer (RF); **Carlos López:** Pfizer, Ipsen, Bristol-Myers Squibb, Roche (C/A), Pfizer, Novartis, AAA, Ipsen, Bristol-Myers Squibb, Roche (H), Ipsen, Bristol-Myers Squibb, Roche (RF); **Teresa Alonso-Gordoa:** Ipsen, Pfizer, Roche, Bayer, Sanofi-Genzyme, Adacap, Janssen, Eisai, Bristol-Myers Squibb (H); **Marta Benavent:** Ipsen, Novartis, Pfizer, Roche (H); **Jaume Capdevila:** Novartis, Pfizer, Ipsen, Exelixis, Bayer, Eisai, Amgen, Sanofi, Merck Serono, Advanced AcceleratorApp, Eli Lilly & Co. (C/A, H), Novartis, Ipsen, AstraZeneca, Eisai, Advanced AcceleratorApp (RF); **Jorge Hernando:** Adacap, Angelini, Bayer, Eisai, Ipsen, Pfizer, Roche, Novartis (H); **Javier Molina-Cerrillo:** Ipsen, Roche, Pfizer, Sanofi, Janssen, Bristol-Myers Squibb (C/A), Ipsen, Pfizer (RF); **Juan José Díez:** Ipsen, Novartis, Pfizer, Adacap, Bayer (H); **Rocío García-Carbonero:** AAA, Advanz Pharma, Bayer, HMP, Ipsen, Merck, Midatech Pharma, Merck Sharp & Dohme, Novartis, PharmaMar, Pfizer, Pierre Fabre, Roche, Servier, Sanofi (C/A), Bristol-Myers Squibb, Merck Sharp & Dohme, Pfizer (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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