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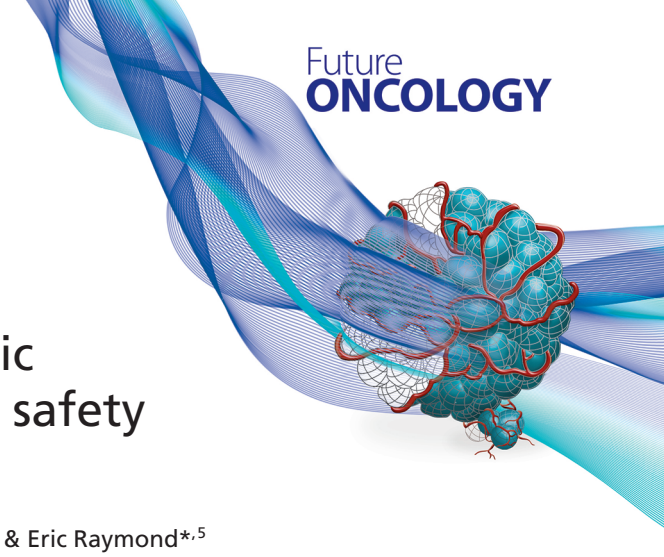

Sunitinib in patients with pancreatic neuroendocrine tumors: update of safety data

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Aim: To describe the long-term safety of sunitinib in patients with progressive, well-differentiated, advanced/metastatic pancreatic neuroendocrine tumors. **Patients & methods:** Sunitinib- and placebo-treated patients from the Phase III study continued to receive sunitinib (37.5 mg on a continuous daily-dosing regimen) in two open-label extension studies. **Results:** Median (range) treatment exposure: 30.2 (0.7–269.4) and 87.1 (3.9–319.4) weeks for medium-term (n = 41) and long-term-treated (n = 61) populations, respectively. All patients experienced ≥1 adverse event (AE); 47 (45.6%) reported serious AEs. Common all-causality AEs: diarrhea (63.1%); neutropenia (43.7%); abdominal pain (40.8%). Fifteen (14.6%) patients discontinued treatment due to treatment-related AEs. **Conclusion:** The safety of extended sunitinib treatment was consistent with the known safety profile of sunitinib in pancreatic neuroendocrine tumors.

First draft submitted: 26 November 2018; Accepted for publication: 10 January 2019; Published online: 31 January 2019

Keywords: long-term • pancreatic neuroendocrine tumor • safety • sunitinib

Of an estimated 53,070 new cases of pancreatic cancers expected in the USA in 2016, well-differentiated pancreatic neuroendocrine tumors (panNETs) accounted for less than 5% [1]. Traditional pharmacologic treatment options for unresectable disease have included somatostatin analogs (SSA) for symptomatic control of some functioning tumors and IFN-α or streptozocin, with or without doxorubicin, as antiproliferatives. However, modest treatment benefit and significant side effects have limited their use [2]. More recent treatment options include temozolomide with or without capecitabine chemotherapy, the mammalian target of rapamycin inhibitor everolimus, as well as lanreotide for somatostatin receptor-positive (on radionuclide imaging) NETs [2–5].

Overexpression of VEGF, PDGF and their receptors has been implicated in tumor angiogenesis in panNETs [6–10]. Sunitinib is a multitargeted tyrosine kinase inhibitor of angiogenesis [11,12]. In a Phase III study, sunitinib demonstrated an improvement in progression-free survival, overall survival and objective response rate versus placebo in patients with well-differentiated, advanced and/or metastatic panNETs [13]. The difference in progression-free survival (primary end point) favored sunitinib (hazard ratio [HR]: 0.42; 95% CI: 0.26–0.66; $p < 0.001$; median: 11.4 vs 5.5 months) [13]. Due to a high number of serious adverse events (SAEs) and deaths in the placebo arm, the study was terminated early. Five years after study closure (from a preplanned updated analysis), median overall survival was 38.6 (95% CI: 25.6–56.4) months for sunitinib and 29.1 (95% CI: 16.4–36.8) months for placebo (HR: 0.73; 95% CI: 0.50–1.06; $p = 0.094$), with 69% of placebo-treated patients having crossed over to sunitinib treatment [14].

At study termination, placebo-treated patients crossed over to sunitinib into one of two open-label extension studies (NCT00428220 and NCT00443534), and received sunitinib per the Phase III regimen, along with patients in the sunitinib treatment arm, allowing for long-term safety evaluation. Here, we present safety data from patients

with advanced and/or metastatic, well-differentiated, unresectable panNETs who were treated with sunitinib for medium- and long-term duration. This is the first clinical trial reporting safety after long-term sunitinib use in patients with panNETS. We also report the relationship between baseline characteristics/clinical variables and time to AE occurrence.

Patients & methods

Patients & study design

The Phase III study was a multinational, randomized, double-blind, placebo-controlled study (NCT00428597; Pfizer study A6181111) [13]. Eligibility criteria have been reported previously [13]. Briefly, patients were aged ≥18 years and had pathologically confirmed, well-differentiated panNETs (by WHO 2000 classification) that were advanced, metastatic, or both. Additional inclusion criteria were: documented disease progression within the previous 12 months, according to Response Evaluation Criteria in Solid Tumors v1.0 (RECIST); at least one measurable target lesion; and Eastern Cooperative Oncology Group performance status (ECOG PS) ≤1. Patients with poorly differentiated tumors or previous tyrosine kinase inhibitor or VEGF inhibitor treatment were excluded.

Patients were randomized 1:1 to receive oral sunitinib 37.5 mg once daily on a continuous daily-dosing (CDD) regimen or matching placebo [13]. Treatment interruptions and dose reductions to 25 mg/day were permitted, to manage adverse events (AEs), with a subsequent increase in dose if toxicity grade ≥2 did not recur. The dose could be increased to 50 mg/day in patients without an objective tumor response who had grade ≤1 nonhematologic or grade ≤2 hematologic treatment-related AEs during the first 8 weeks. SSA for symptomatic control was permitted [13].

In the Phase III study, patients were treated until death, RECIST-defined progression or occurrence of unacceptable AEs [13]. Upon Phase III study closure, those patients still receiving study treatment (sunitinib or placebo) could roll over into one of two open-label sunitinib extension studies (NCT00428220 and NCT00443534; Pfizer studies A6181114 and A6181078), wherein patients receiving placebo began sunitinib treatment [13]. Patients in the sunitinib treatment arm were to continue on open-label treatment if judged by the investigator to have been receiving clinical benefit.

Patients were enrolled in one of the two open-label extension studies, across 35 sites, within 8 weeks and 28 days, depending on the study, from the last dose of placebo or sunitinib in the Phase III study. Sunitinib-treated patients continued to receive sunitinib per the Phase III study regimen. Patients previously treated with placebo were switched to the 37.5 mg sunitinib starting dose once-daily CDD regimen. Dose escalations, de-escalations and dose schedule options were similar to the Phase III study [13].

The protocols, amendments and informed consent forms were reviewed and approved by institutional review boards or independent ethics committees at each study center. The studies were conducted in accordance with the protocol, International Conference on Harmonisation Good Clinical Practice guidelines and applicable local regulatory requirements and laws. All patients provided written informed consent.

Assessments

For the purposes of these analyses, baseline was the last measurement taken prior to starting the first dose of sunitinib in the parent study for long-term patients, and in the extension study for medium-term patients. Safety assessments included a description of AEs and their type, incidence, severity, seriousness and relatedness to study drug. AEs were coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA); severity was graded by the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. AEs were reported from time of first dose of sunitinib to the start of new anticancer treatment or 28 days after the last dose of sunitinib. Any SAEs possibly related to sunitinib were reported indefinitely.

Other safety assessments included physical examination, vital signs and laboratory evaluations (hematology and blood chemistry). These were monitored at day 1 of each sunitinib treatment visit, at end of treatment/withdrawal and at post-treatment follow-up (28 days after the last dose of sunitinib), if applicable.

Early occurrence AEs were those experienced by 12 weeks (all cause), in other words, patient's first start date for the AE is ≤12 weeks from the first dose of sunitinib. Late occurrence AEs were those experienced by 12–36 weeks or more than 36 weeks from the first dose of sunitinib. AE clusters of special interest included stomatitis, hypertension, hand–foot syndrome, bleeding and cardiac AEs (Supplementary Material).

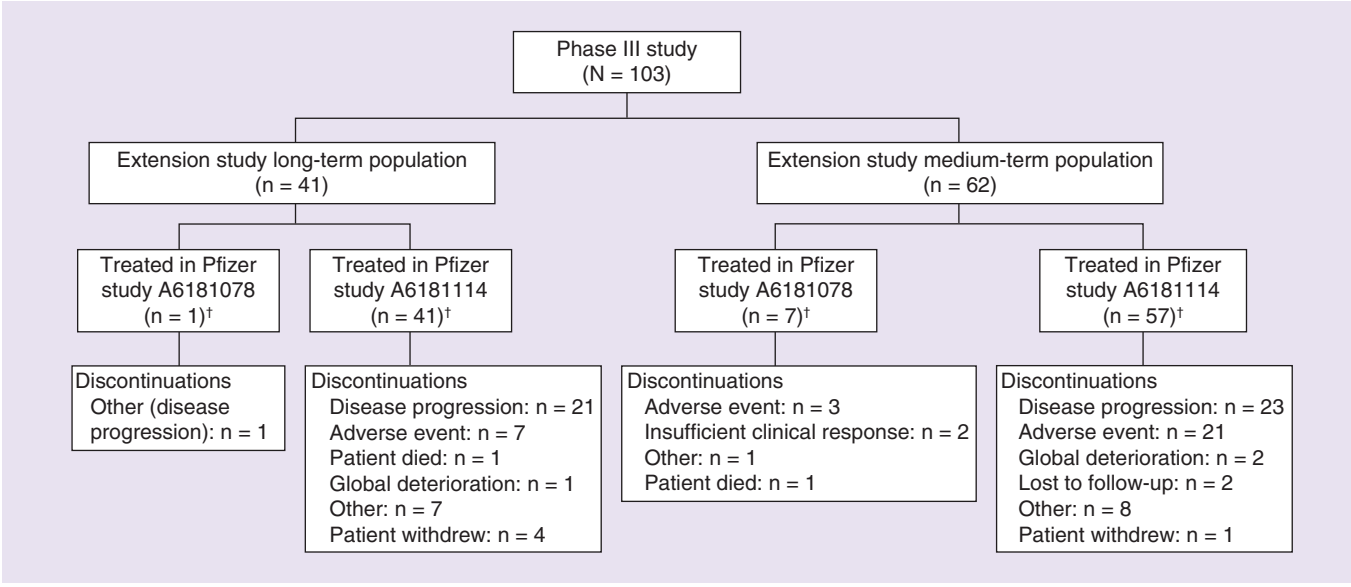

Figure 1. Patient disposition/analyses populations.
†Three patients discontinued from both the Pfizer A6181078 and A6181114 studies. One patient discontinued from study A6181078 due to 'Other (disease progression)', then rolled over to study A6181114 and discontinued that study due to 'Other' (in long-term follow-up only). One patient discontinued from study A6181078 due to 'adverse event', then rolled over to study A6181114 and discontinued that study due to 'Other' (in long-term follow-up only). One patient discontinued from study A6181078 due to 'Other', then rolled over to study A6181114 and discontinued that study due to 'Other' (rolled over to another sponsor program to continue sunitinib treatment).

Statistical analyses

Statistical analyses were based on the last-patient/last-visit date of 12 September 2014, using SAS version 9.2 (SAS Institute Inc., NC, USA). Due to the nature of these studies, the number of patients to be enrolled was not predetermined.

Three subpopulations were evaluated. The long-term population comprised patients who had received sunitinib in the Phase III study and continued sunitinib treatment in the extension studies. The medium-term population comprised patients who were receiving sunitinib for the first time in the extension studies after blind was broken. Lastly, the total population included both the long-term and medium-term populations.

Safety assessments were summarized descriptively. Mean change from baseline through cycle 10 (one cycle = 4 weeks) was reported for absolute neutrophil count, diastolic blood pressure (BP) and systolic BP.

Regression analyses for AE clusters of special interest were conducted *post hoc*. The Cox proportional hazards regression model was used to assess time to first on-treatment occurrence of an AE in the cluster with covariates: age, sex, race, distant extrahepatic metastases at baseline, baseline ECOG PS, prior systemic therapy, prior anthracyclines, history of hypertension, history of cardiovascular disease, history of diabetes, prior/concomitant use of somatostatin analog and functioning tumor. For this analysis, only treatment-emergent AEs (start date from day 1 of treatment through 28 days after the last dose) are used as events. Censorship for patients still on treatment without an AE event occurs at the last follow-up. Censorship for patients off treatment without an event during treatment or within 28 days after the last dose occurs at 29 days after the last dose. A logistic regression model was used to assess any occurrence of an AE in the cluster with the same covariates described above.

Results

Patients

A total of 103 (long-term, n = 41; medium-term, n = 62) patients received sunitinib in the extension studies and became part of this updated safety analysis. Forty-eight patients discontinued due to disease progression or health deterioration (Figure 1).

The majority of patients were male (52.4%) and white (64.1%), and mean age was 55.3 years. Median (range) time from diagnosis to treatment was 2.7 (0.1–24.1) years. Most patients did not have a functioning tumor (54.4%) and had not received prior systemic therapy (75.7%), prior/concomitant SSA (59.2%) or prior anthracyclines

Table 1. Patient demographics and baseline characteristics.

Characteristic	Long-term (n = 41)	Medium-term (n = 62)	Total (N = 103)
Males, n (%)	24 (58.5)	30 (48.4)	54 (52.4)
Mean (SD) age, years	56.4 (13.2)	54.5 (12.7)	55.3 (12.9)
Race, n (%):			
– White	24 (58.5)	42 (67.7)	66 (64.1)
– Asian	5 (12.2)	10 (16.1)	15 (14.6)
– Other	12 (29.3)	10 (16.1)	22 (21.4)
ECOG PS, n (%):			
– 0	30 (73.2)	22 (35.5)	52 (50.5)
– ≥1[†]	11 (26.8)	40 (64.5)	51 (49.5)
Median (range) time from date of diagnosis to treatment start date, years	2.32 (0.1–24.1)	3.08 (0.4–21.3)	2.71 (0.1–24.1)
Distant extrahepatic metastasis, n (%)	10 (24.4)	25 (40.3)	35 (34.0)
Tumor functionality, n (%)	19 (46.3)	28 (45.2)	47 (45.6)
Prior systemic therapy, n (%)	11 (26.8)	14 (22.6)	25 (24.3)
Prior and concomitant SSAs, n (%)	19 (46.3)	23 (37.1)	42 (40.8)
Prior anthracyclines, n (%)	12 (29.3)	21 (33.9)	33 (32.0)
History of diabetes, n (%)	12 (29.3)	13 (21.0)	25 (24.3)
History of hyperglycemia, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
History of impaired glucose tolerance, n (%)	1 (2.4)	1 (1.6)	2 (1.9)
History of hypertension, n (%)	13 (31.7)	16 (25.8)	29 (28.2)
History of CV disease other than hypertension, n (%)	6 (14.6)	6 (9.7)	12 (11.7)
History of GI disorders, n (%)	25 (61.0)	35 (56.5)	60 (58.3)
History of mucositis, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
History of stomatitis, n (%)	0 (0.0)	1 (1.6)	1 (1.0)
History of skin disorders, n (%)	1 (2.4)	3 (4.8)	4 (3.9)
History of hand–foot syndrome, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
ALT, U/l:			
– Mean (SD)	41.1 (38.3)	41.2 (25.0)	41.2 (31.0)
– Median (range)	30.0 (12.0–221)	34.0 (13.0–129)	32.0 (12.0–221)
AST, U/l:			
– Mean (SD)	34.7 (20.5)	46.9 (47.5)	41.8 (38.9)
– Median (range)	28.0 (14.0–125)	35.0 (14.0–334)	31.5 (14.0–334)
Bilirubin, mg/dl:			
– Mean (SD)	0.7 (0.3)	0.8 (0.5)	0.7 (0.4)
– Median (range)	0.55 (0.1–1.5)	0.60 (0.2–2.3)	0.58 (0.1–2.3)
Creatinine, mg/dl:			
– Mean (SD)	1.1 (1.3)	0.9 (0.2)	1.0 (0.9)
– Median (range)	0.90 (0.5–9.2)	0.90 (0.5–1.6)	0.90 (0.5–9.2)
Glucose, mg/dl:			
– Mean (SD)	126 (57.5)	170 (341)	151 (261)
– Median (range)	104.5 (64.9–357)	102.7 (45.1–2590)	103.8 (45.1–2590)
TSH:			
– Median (range)	1.19 (0.3–7.2)	1.68 (0.2–11.8)	1.49 (0.2–11.8)

[†]One patient had an ECOG PS score of 2, which was a protocol deviation.
Patients were enrolled in one of the two open-label extension studies within 8 weeks and 28 days, depending on the study, from the last dose of placebo or sunitinib in the Phase III study. Baseline was the last measurement taken prior to starting the first dose of sunitinib in the extension studies.
CV: Cardiovascular; ECOG PS: Eastern Cooperative Oncology Group performance status; GI: Gastrointestinal; SD: Standard deviation; SSA: Somatostatin analog; TSH: Thyroid-stimulating hormone.

(68.0%) (Table 1). The symptoms of the functioning PanNETs were not specified in the majority of patients in

Table 2. Summary of treatment-related adverse events, including adverse events experienced by ≥15% of patients in the total population.

AEs, by MedDRA preferred term	Long-term (n = 41), n (%)			Medium-term (n = 62), n (%)			Total (N = 103), n (%)		
	Grades 1–2	Grades 3–4	All grades	Grades 1–2	Grades 3–4	All grades	Grades 1–2	Grades 3–4	All grades
Diarrhea	24 (58.5)	6 (14.6)	30 (73.2)	28 (45.2)	3 (4.8)	31 (50.0)	52 (50.5)	9 (8.7)	61 (59.2)
Neutropenia	9 (22.0)	10 (24.4)	19 (46.3)	8 (12.9)	18 (29.0)	26 (41.9)	17 (16.5)	28 (27.2)	45 (43.7)
Hair color changes	19 (46.3)	1 (2.4)	20 (48.8)	21 (33.9)	0	21 (33.9)	40 (38.8)	1 (1.0)	41 (39.8)
Asthenia	15 (36.6)	3 (7.3)	18 (43.9)	11 (17.7)	7 (11.3)	18 (29.0)	26 (25.2)	10 (9.7)	36 (35.0)
Decreased appetite	15 (36.6)	0	15 (36.6)	20 (32.3)	0	20 (32.3)	35 (34.0)	0	35 (34.0)
Nausea	20 (48.8)	2 (4.9)	22 (53.7)	11 (17.7)	0	11 (17.7)	31 (30.1)	2 (1.9)	33 (32.0)
Hand–foot syndrome	9 (22.0)	4 (9.8)	13 (31.7)	16 (25.8)	4 (6.5)	20 (32.3)	25 (24.3)	8 (7.8)	33 (32.0)
Thrombocytopenia	13 (31.7)	0	13 (31.7)	12 (19.4)	7 (11.3)	19 (30.6)	25 (24.3)	7 (6.8)	32 (31.1)
Fatigue	11 (26.8)	2 (4.9)	13 (31.7)	11 (17.7)	4 (6.5)	15 (24.2)	22 (21.4)	6 (5.8)	28 (27.2)
Dysgeusia	14 (34.1)	0	14 (34.1)	12 (19.4)	0	12 (19.4)	26 (25.2)	0	26 (25.2)
Stomatitis	11 (26.8)	2 (4.9)	13 (31.7)	11 (17.7)	2 (3.2)	13 (21.0)	22 (21.4)	4 (3.9)	26 (25.2)
Epistaxis	14 (34.1)	2 (4.9)	16 (39.0)	7 (11.3)	1 (1.6)	8 (12.9)	21 (20.4)	3 (2.9)	24 (23.3)
Mucosal inflammation	8 (19.5)	0	8 (19.5)	12 (19.4)	4 (6.5)	16 (25.8)	20 (19.4)	4 (3.9)	24 (23.3)
Hypertension	9 (22.0)	6 (14.6)	15 (36.6)	4 (6.5)	3 (4.8)	7 (11.3)	13 (12.6)	9 (8.7)	22 (21.4)
Leukopenia	6 (14.6)	6 (14.6)	12 (29.3)	5 (8.1)	3 (4.8)	8 (12.9)	11 (10.7)	9 (8.7)	20 (19.4)
Vomiting	9 (22.0)	1 (2.4)	10 (24.4)	8 (12.9)	0	8 (12.9)	17 (16.5)	1 (1.0)	18 (17.5)
Abdominal pain	9 (22.0)	0	9 (22.0)	6 (9.7)	2 (3.2)	8 (12.9)	15 (14.6)	2 (1.9)	17 (16.5)
Dyspepsia	10 (24.4)	0	10 (24.4)	7 (11.3)	0	7 (11.3)	17 (16.5)	0	17 (16.5)
Dry skin	8 (19.5)	0	8 (19.5)	8 (12.9)	0	8 (12.9)	16 (15.5)	0	16 (15.5)
Headache	8 (19.5)	0	8 (19.5)	7 (11.3)	1 (1.6)	8 (12.9)	15 (14.6)	1 (1.0)	16 (15.5)

AE: Adverse event; MedDRA: Medical Dictionary of Regulatory Activities.

this study. In the patients with identified symptoms, most had gastrinoma, others had glucagonoma, insulinoma, VIPoma and mixed types. Patient baseline demographics, disease characteristics and medical history were generally consistent across medium-term and long-term populations, with the exception of ECOG PS, distant extrahepatic metastasis, prior/concomitant SSA, aspartate aminotransferase, glucose and thyroid-stimulating hormone (Table 1). The median (range) duration of treatment exposure in the total, medium-term and long-term populations was 51.6 (0.7–319.4) weeks, 30.2 (0.7–269.4) weeks and 87.1 (3.9–319.4) weeks, respectively.

Safety

In all, 102 (99.0%) patients experienced at least one treatment-related AE, and 76 (73.8%) experienced at least one grade 3–4 AEs. The number of AEs occurring in at least 15% of patients was higher in the long-term (n = 27) versus the medium-term (n = 13) population. In the total population, the most common treatment-related AEs were diarrhea (n = 61; 59.2%), neutropenia (n = 45; 43.7%) and hair color changes (n = 41; 39.8%). The most common grade 3–4 AEs were neutropenia (n = 28; 27.2%) and asthenia (n = 10; 9.7%; Table 2). Treatment-related cases of thyroid dysfunction and venous thromboembolic events were hypothyroidism (n = 10; 9.7%), increase in thyroid-stimulating hormone (n = 5; 4.9%), tri-iodothyronine decrease (n = 1; 1.0%), portal vein thrombosis (n = 1; 1.0%) and thrombosis (n = 1; 1.0%). There were no cases of keratoacanthoma. The most common, all-causality AEs among all patients are reported in Supplementary Table 1.

Thirty-four (33.0%) patients (long-term, n = 9; 22.0%; medium-term, n = 25; 40.3%) discontinued treatment due to AEs. The most common AEs leading to discontinuation were health deterioration (3.9%) and disease progression (2.9%). Discontinuations due to treatment-related AEs occurred in 15 (14.6%) patients: three (7.3%) long-term and 12 (19.4%) medium-term patients. Dose reductions (37.5 to 25 mg or 50 to 37.5 mg) or temporary discontinuations due to AEs occurred in 74 (71.8%), 30 (73.2%) and 44 (71.0%) patients in the total, long-term and medium-term populations, respectively.

The most common AEs first occurring ≤12 weeks after the first sunitinib dose were diarrhea (n = 33; 32%), neutropenia (n = 29; 28%) and thrombocytopenia (n = 23; 22%; Supplementary Figure 1). The most common

AEs first occurring more than 36 weeks from the first sunitinib dose were abdominal pain (n = 11; 17%), nausea (n = 10; 15%) and vomiting (n = 8; 12%; Supplementary Figure 1).

Forty-seven (45.6%) patients reported SAEs: 20 (48.8%) and 27 (43.5%) in the long-term and medium-term populations, respectively. Overall, the most common SAEs were abdominal pain (n = 6; 5.8%), general health deterioration (n = 5; 4.9%), disease progression (n = 4; 3.9%) and gastrointestinal hemorrhage, hematemesis and vomiting (n = 3 each; 2.9%). Nineteen (18.4%) patients had treatment-related SAEs: ten (24.4%) long-term and nine (14.5%) medium-term patients. No treatment-related SAE by MedDRA preferred term was reported by more than two patients in any treatment group. Twelve patients died during the extension studies: four long-term patients (disease progression [n = 2], hepatic failure [n = 1], sudden death [n = 1]) and eight medium-term patients (health deterioration [n = 2], disease progression [n = 2], acidosis, acute kidney injury, dyspnea and hepatic encephalopathy [n = 1 each]). None of these deaths was considered to be related to study treatment.

Overall, the following grade 3–4 hematologic AEs were reported: neutropenia (n = 28; 27.5%); anemia (n = 10; 9.8%); leukopenia (n = 10; 9.8%); thrombocytopenia (n = 8; 7.8%); lymphopenia (n = 7; 6.9%). The most common grade 3–4 biochemistry AEs were: hyperglycemia (n = 19; 19.8%); hypophosphatemia (n = 16; 15.7%); elevated alkaline phosphatase (n = 12; 11.8%; Supplementary Table 2).

Mean changes from baseline through cycle 10 in absolute neutrophil count, systolic BP and diastolic BP were variable, although there was a general trend toward a slight decrease in mean change from baseline over time (Figure 2).

Relationship between baseline characteristics/clinical variables & time to AE occurrence

Based on the univariate analysis, baseline ECOG PS ≥1 was associated with time to first occurrence of stomatitis (HR: 1.751; p = 0.0489) and hypertension (HR: 0.260; p = 0.0035). Prior/concomitant SSA use (HR: 0.530; p = 0.0421) and history of hypertension (HR: 3.273; p = 0.0047) were also associated with time to first occurrence of stomatitis and hypertension, respectively. Race (white vs non-white; HR: 0.305; p = 0.0011) and history of diabetes (HR: 0.328; p = 0.0247) were associated with time to first occurrence of hand–foot syndrome. Age (<65 vs ≥65 years; HR: 0.222; p = 0.0120) was associated with time to first occurrence of cardiac AEs (Table 3).

Based on the multivariate analysis, a baseline ECOG PS ≥1 (odds ratio [OR]: 0.200; p = 0.0050) and history of prior hypertension (OR: 4.074; p = 0.0157) were associated with hypertension while on treatment. Race (white vs non-white; OR: 0.236; p = 0.0034) and history of diabetes (OR: 0.215; p = 0.0161) were associated with hand–foot syndrome. Treatment group (long-term vs medium-term; OR: 4.941; p = 0.0354) was associated with bleeding AEs, whereas age (<65 vs ≥65 years; OR: 0.207; p = 0.0308) was associated with cardiac AEs (Table 4).

Discussion

This is the first report on the safety of continued sunitinib treatment in patients with advanced and/or metastatic, well-differentiated, unresectable panNETs from the pivotal Phase III study. In all, 103 (long-term, n = 41; medium-term, n = 62) patients continued to receive sunitinib after the end of the Phase III study, with a median treatment duration approaching 1 year, thus allowing for longer term safety evaluation. Results showed that the safety profile of sunitinib in patients who continued on longer treatment intervals was consistent with the original Phase III study, with a median treatment duration of 4.6 months [13]. Furthermore, these updated safety data demonstrate that sunitinib, with dose reductions, temporary dose holds or AE management strategies over the longer term, was well tolerated in both medium-term and long-term patients. In addition, the type, frequency and grade of AEs and SAEs were generally comparable between the two populations. AEs that occurred in ≥15% of patients were higher in the long-term versus the medium-term population, possibly reflecting a time-on-treatment effect. However, more medium-term patients permanently discontinued treatment versus long-term patients. In the medium-term population, 19.4% discontinued due to treatment-related AEs – mostly due to disease progression/global deterioration. The delayed sunitinib treatment for these patients, who were primarily from the placebo group in the pivotal trial, may explain the higher rate of permanent discontinuations compared with the long-term group.

The safety profile of sunitinib 37.5 mg on a CDD regimen based on the updated data for the pivotal Phase III population was consistent with the known safety profile of sunitinib 50 mg once daily dosed on the 4-weeks-on/2-weeks-off schedule used in other indications [15,16]. Although there were fewer grade 3–4 hematologic AEs, the frequency and grade of common AEs and hematologic AEs were similar to those of the Phase I and II studies in patients with panNETs, as well as to those reported in recent Phase IV trial, and studies in real-world setting [11,17–20]. The safety profile was also similar to the global expanded-access study in metastatic renal cell carcinoma (mRCC)

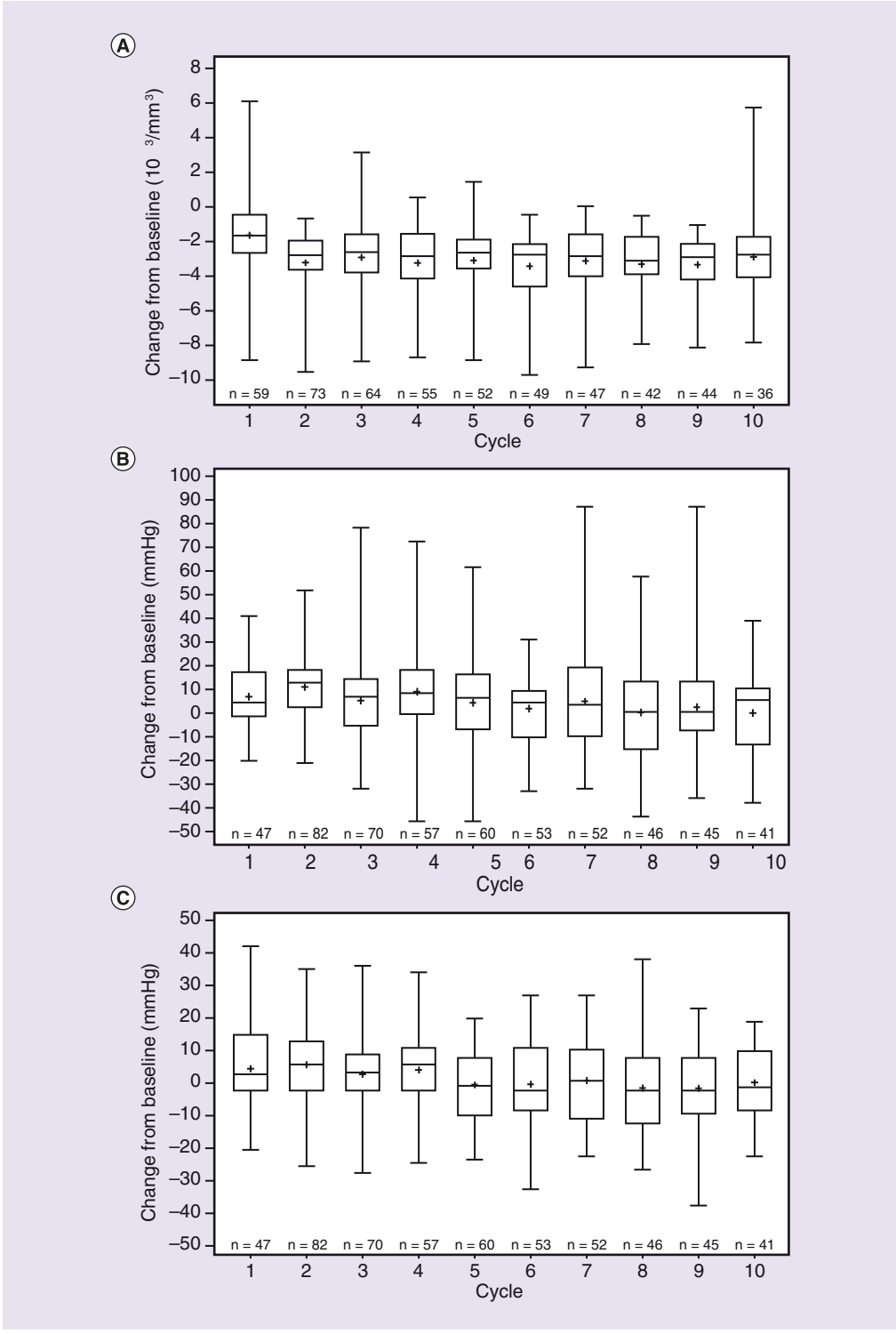

Figure 2. Change in absolute neutrophil count and blood pressure from baseline through cycle 10 in the total population. Box plot of change from baseline and mean change from baseline through cycle 10 in the total population for: **(A)** absolute neutrophil count, **(B)** systolic blood pressure and **(C)** diastolic blood pressure.

Table 3. Cox proportional hazards regression model of time to first occurrence of an adverse event.

Parameter	Time to first occurrence of AE		
	HR	95% CI	p-value
Stomatitis and related AEs:			
– ECOG PS†	1.751	1.00–3.06	0.0489
– Use of SSA	0.530	0.29–0.98	0.0421
– Functioning tumor	1.765	0.99–3.15	0.0541
Hypertension:			
– Age‡	2.167	0.76–6.21	0.1495
– Race§	0.585	0.28–1.24	0.1635
– ECOG PS†	0.260	0.11–0.64	0.0035
– History of hypertension	3.273	1.44–7.45	0.0047
Hand–foot syndrome and related AEs:			
– Race§	0.305	0.15–0.62	0.0011
– History of hypertension	0.413	0.16–1.08	0.0712
– History of diabetes	0.328	0.12–0.87	0.0247
Bleeding and related AEs:			
– Treatment group¶	3.423	0.91–12.9	0.0684
– Gender	0.328	0.08–1.32	0.1172
– ECOG PS†	3.334	0.82–13.6	0.0924
Cardiac AEs:			
– Age‡	0.222	0.07–0.72	0.0120
– History of diabetes	0.165	0.02–1.31	0.0884

†≥1 vs 0.
‡<65 vs ≥65 years.
§White vs non-white.
¶Sunitinib-treated vs sunitinib-naive.
AE: Adverse event; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: Hazard ratio; SSA: Somatostatin analog.

and the long-term safety analysis across nine studies in patients with mRCC [15,16]. These results further support the practical management of AEs with sunitinib treatment in patients with panNETs based on prior experience in other indications [21]. Therapy management for sunitinib treatment in panNETs includes AE monitoring, patient education and proactive AE prevention, as well as dose interruptions and reductions [21].

Despite differing mechanisms of action, the incidence and grade of AEs and SAEs reported during long-term sunitinib treatment were comparable with those reported for other agents, for example, everolimus and lanreotide, for treatment of panNETs [4,5,22–25]. Diarrhea appears to be one of the most commonly reported AEs across all three treatments. Patients treated with sunitinib reported higher rates of neutropenia and hair color changes versus those treated with lanreotide or everolimus. Compared with sunitinib-treated patients, those receiving lanreotide reported higher rates of abdominal pain and cholelithiasis [4,25], and those receiving everolimus reported higher rates of stomatitis, rash, infections and hyperglycemia [5,22–24]; these were in line with the known safety profiles of these agents.

Regression analyses identified that certain baseline characteristics/clinical variables had an impact on time to AE occurrence. Time to first occurrence of hypertension and stomatitis was associated with an ECOG PS ≥1; this was as expected, since higher ECOG PS is associated with certain toxicities [26]. Patient's history of hypertension was also associated with hypertension AEs. Similarly, and unsurprisingly, since older age has been linked to increased cardiovascular risk [27], time to first occurrence of cardiac AEs was associated with age ≥65 versus <65 years. Race and history of diabetes were associated with time to first occurrence of hand–foot syndrome. The association between race and hand–foot syndrome is consistent with an analysis of sunitinib in patients with mRCC that demonstrated Asian patients had a higher incidence of hand–foot syndrome compared with white patients [28]. It is hypothesized that genetic differences between Asian and white patients may result in differences in sunitinib plasma exposure, resulting in a higher incidence of hand–foot syndrome among other AEs [28].

There was no predetermined sample size and not all patients rolled over from the Phase III study (N = 171); thus, the number of patients (n = 103) included in these open-label extension studies is low. However, these numbers

Table 4. Logistic regression model of any occurrence of an adverse event.

Parameter	Occurrence of AE		
	OR	95% CI	p-value
Stomatitis and related AEs:			
– Gender	0.582	0.261–1.298	0.1861
– Use of SSA	0.477	0.195–1.169	0.1057
– Functioning tumor	2.360	0.973–5.726	0.0575
Hypertension:			
– Treatment group†	2.519	0.912–6.958	0.0747
– Age‡	2.496	0.631–9.868	0.1921
– ECOG PS§	0.200	0.065–0.616	0.0050
– History of hypertension	4.074	1.303–12.739	0.0157
Hand–foot syndrome and related AEs:			
– Race¶	0.236	0.090–0.620	0.0034
– Distant extrahepatic metastases	0.446	0.160–1.242	0.1225
– History of hypertension	0.350	0.110–1.115	0.0758
– History of diabetes	0.215	0.062–0.752	0.0161
Bleeding and related AEs:			
– Treatment group†	4.941	1.115–21.892	0.0354
– Gender	0.351	0.080–1.542	0.1654
– ECOG PS§	2.911	0.647–13.102	0.1640
– Prior anthracyclines	0.218	0.025–1.891	0.1671
Cardiac AEs:			
– Age‡	0.207	0.050–0.864	0.0308
– Race¶	0.417	0.110–1.588	0.2000
– History of CV disease	3.473	0.705–17.102	0.1259
– History of diabetes	0.106	0.010–1.076	0.0577

†Sunitinib-treated vs sunitinib-naive.
‡<65 vs ≥65 years.
§ECOG score: ≥1 vs 0.
¶White vs non-white.
AE: Adverse event; CV: Cardiovascular; ECOG PS: Eastern Cooperative Oncology Group performance status; OR: Odds ratio; SSA: Somatostatin analog.

are reflective of the rarity of advanced and/or metastatic, well-differentiated, unresectable panNETs. Furthermore, limitations of the statistical analyses included the *post hoc* nature of the regression analyses. Extension studies consist of a patient population in whom the drug is known to be efficacious and well tolerated, as only those patients who were eligible and completed the prior clinical trials were enrolled. Although there are limitations to fully characterizing the benefit–risk profile of sunitinib in this setting, this analysis details important information on the safety profile of sunitinib in the absence of long-term real-world evidence.

Conclusion

This updated safety analysis of sunitinib confirms the safety of the 37.5-mg CDD schedule in patients with advanced and/or metastatic, well-differentiated, unresectable panNETs from open-label extension studies. Furthermore, sunitinib was well tolerated in the longer term in patients who were either on medium-term (median duration: 30.2 weeks) or long-term treatment (median duration: 87.1 weeks). Additionally, certain baseline characteristics and clinical variables had an impact on time to AE occurrence. In this analysis, the safety profile of sunitinib in patients who continued on treatment in the open-label extension studies was consistent with the original results from the pivotal Phase III study and the known safety profile of sunitinib in patients with panNETs.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2018-0882

Acknowledgements

The authors thank the participating patients and their families, as well as the global network of research nurses, study coordinators and operations staff for their contributions, and investigators who participated in these studies.

Authors' contributions

B Rosbrook and K Fernandez conceived study concepts and performed study design. JW Valle, I Borbath and E Raymond contributed to the data acquisition. B Rosbrook and K Fernandez maintained the quality control of data and algorithms. All the authors reviewed the data analysis and interpretation. B Rosbrook examined the statistical analysis. All the authors reviewed the manuscript preparation, editing and review.

Financial & competing interests disclosure

The study was funded and conducted by Pfizer Inc. JW Valle has been a consultant and advisor for Pfizer Inc, Novartis and Ipsen; on the Speakers' Bureau for Pfizer Inc and Novartis; and has received research funding and travel/accommodation expenses from Novartis. I Borbath has been a consultant and advisor for Pfizer Inc, Novartis and Ipsen; and has received research funding from Novartis, Ipsen, Bayer and Celgene. B Rosbrook and K Fernandez are employees of Pfizer Inc. E Raymond has been a consultant for and has received trial support from Ipsen, Novartis, Eli Lilly and Pfizer Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support was provided by Anne Marie McGonigal and Vardit Dror of Engage Scientific Solutions and was funded by Pfizer Inc.

Ethical conduct of research

The protocols, amendments and informed consent forms were reviewed and approved by institutional review boards or independent ethics committees at each study center. The studies were conducted in accordance with the protocol, International Conference on Harmonisation Good Clinical Practice guidelines and applicable local regulatory requirements and laws. All patients provided written informed consent.

Data sharing statement

Upon request, and subject to certain criteria, conditions and exceptions (see www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices: for indications that have been approved in the USA and/or EU or in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.Trial registration numbers: ClinicalTrials.gov identifiers: extension studies NCT00428220 and NCT00443534 of Phase III NCT00428597.

Summary points

- This is the first report of the long-term safety of continuous sunitinib 37.5-mg once daily in patients with pancreatic neuroendocrine tumors.
- After continued treatment from the original Phase III study, sunitinib was well tolerated in the longer term.
- Certain characteristics (ECOG PS $\geq$1, race and age) and clinical variables (history of prior hypertension or diabetes) had an impact on time to adverse event occurrence.
- There were no unexpected long-term safety findings, and the safety profile of sunitinib in patients who continued on treatment (median treatment duration: $\sim$1 year) was consistent with the original Phase III study (median treatment duration: 4.6 months) and the known safety profile of sunitinib in patients with pancreatic neuroendocrine tumors.

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