Sunitinib for Treatment of Pancreatic Neuroendocrine Tumors: Patient-reported Outcomes and Efficacy Across Patient Subgroups in a Phase III Trial

A Vinik,[1] Y-J Bang,[2] J-L Raoul,[3] J Valle,[4] P Metrakos,[5] D Hörsch,[6] B Korytowsky,[7] R Mundayat,[7] R Chao,[8] E Raymond[9]

[1]EVMS Strelitz Diabetes Research Center and Neuroendocrine Unit, Norfolk, VA, USA; [2]Seoul National University Hospital, Seoul, Korea; [3]Eugène Marquis Centre and European University in Brittany, Rennes, France; [4]Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [5]McGill University Hospital Center, Montreal, Canada; [6]Clinic for Internal Medicine, Gastroenterology, Oncology and Endocrinology, Center for Neuroendocrine Tumors, Bad Berka Central Clinic, Bad Berka, Germany; [7]Pfizer Oncology, New York, NY, USA; [8]Pfizer Oncology, La Jolla, CA, USA; [9]Service Inter-Hospitalier de Cancerologie et Service de Gastroenteropancréatologie, Hôpital Beaujon, Clichy, France

INTRODUCTION

- Sunitinib is an oral, multitargeted tyrosine kinase inhibitor approved for use in advanced renal cell carcinoma and imatinib-resistant/-intolerant gastrointestinal stromal tumors. Activity against pancreatic neuroendocrine tumors (NET) has been demonstrated in preclinical and phase I and II clinical trials.[1–4]
- In a phase III, randomized, double-blind trial (NCT00428597) in patients with well-differentiated, advanced, progressive pancreatic NET, median progression-free survival (PFS) was significantly prolonged with sunitinib (n=86), compared with placebo (n=85): 11.4 months (95% confidence interval [CI]: 7.4, 19.8) vs. 5.5 months (95% CI: 3.6, 7.4), respectively (hazard ratio [HR]=0.418; 95% CI: 0.263, 0.662; P=0.0001) (Figure 1).[5]
  - The HR for overall survival was 0.409 favoring sunitinib (95% CI: 0.187, 0.894; P=0.0204).
- Treatment was generally well tolerated, with most adverse events being manageable by dose interruption, dose reduction, and/or standard medical therapy.[5]
- Here we present exploratory subgroup analyses, evaluating the impact of baseline characteristics on treatment efficacy, and patient-reported outcomes (PROs).

METHODS

- Patients with well-differentiated advanced pancreatic NET and disease progression in the past 12 months were randomized (1:1) to once-daily treatment with oral sunitinib 37.5 mg/day, continuous daily dosing, or matching placebo, each with best supportive care. Treatment was continued until Response Evaluation Criteria in Solid Tumors-defined progression, unacceptable adverse events, or death.
- Somatostatin analogs (SSAs) were allowed before and/or during the study.
- The primary endpoint was PFS, defined as the time from randomization to the first evidence of progression or death.
- Efficacy was assessed in the intent-to-treat (ITT) population based on investigator assessments of tumor response. Kaplan–Meier methods were used to obtain estimates of median PFS, with corresponding two-sided 95% CI.
- Exploratory regression analyses using the Cox proportional hazards model were performed to test the influence of baseline characteristics on PFS.
- The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) was used to assess health-related quality of life (HRQoL), specifically evaluating global health status/QoL, functioning (physical, role, cognitive, emotional, and social), symptoms (fatigue, nausea/vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation, diarrhea) and financial impact. It was self-administered at baseline (cycle 1, day 1) and day 1 of every cycle thereafter (cycle = 4 weeks) and at the end of treatment or withdrawal.
- A minimal important difference (MID) approach was used, with clinical significance defined as ≥10-point in mean change from baseline and statistical significance at the 0.05 level based on a two-sided test. Repeated measures mixed-effects models were used as the primary model for between-treatment comparison.
- For global HRQoL and functioning scales, time to deterioration was evaluated as a composite endpoint, defined as time from randomization to death, first progression, or two consecutive cycles of clinically significant changes.
- Time to deterioration was evaluated as a post-hoc analysis and was repeated controlling for death and tumor progression. Treatment groups were compared using survival analysis techniques: unstratified log-rank test and Cox proportional hazards model.

RESULTS

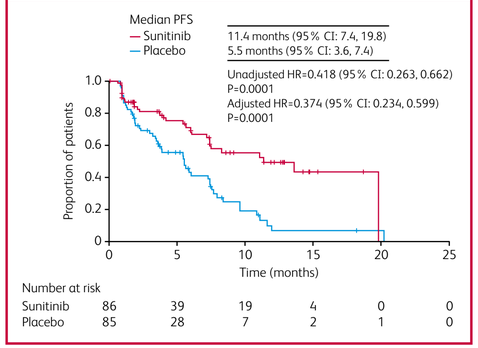
- Patient demographics and baseline characteristics were generally similar in the two treatment arms (Table 1).

Table 1. Patient demographic and baseline characteristics.

	Sunitinib (n=86)	Placebo (n=85)
Age		
Median (range), years	56 (25–84)	57 (26–78)
≥65 years, n (%)	22 (25.6)	23 (27.1)
Gender, n (%)		
Male	42 (48.8)	40 (47.1)
Female	44 (51.2)	45 (52.9)
Race, n (%)		
White	48 (55.8)	53 (62.4)
Asian	13 (15.1)	10 (11.8)
Other/unspecified*	25 (29.1)	22 (25.9)
ECOG performance status, n (%)		
0	53 (61.6)	41 (48.2)
1	33 (38.4)	43 (50.6)
2	0	1 (1.2)†
Tumor functionality, n (%)‡		
Non-functioning	42 (48.8)	44 (51.8)
Functioning		
Gastrinoma	9 (10.5)	10 (11.8)
Glucagonoma	3 (3.5)	2 (2.4)
Insulinoma	2 (2.3)	2 (2.4)
VIPoma	0	2 (2.4)
Other/multisecretory/unknown	11 (12.8)	5 (5.9)
Not specified	19 (22.1)	20 (23.5)
Ki-67 index		
Patients with Ki-67 index reported, n (%)	36 (41.9)	36 (42.3)
≤2%	7 (19.4)	6 (16.7)
>2–5%	16 (44.4)	14 (38.9)
>5–10%	5 (13.9)	10 (27.8)
>10%	8 (22.2)	6 (16.7)
Median (range) time from diagnosis, years§	2.4 (0.1–25.6)	3.2 (0.1–21.3)
No. of involved sites, n (%)		
1 site	30 (34.9)	23 (27.1)
2 sites	31 (36.0)	26 (30.6)
≥3 sites	24 (27.9)	35 (41.2)
Not reported	1 (1.2)	1 (1.2)
Presence of distant metastases, n (%)		
Any (including hepatic)	82 (95.3)	80 (94.1)
Extrahepatic	21 (24.4)	34 (40.0)
Prior treatments, n (%)		
Surgery	76 (88.4)	77 (90.6)
Radiation therapy	9 (10.5)	12 (14.1)
Chemoembolization	7 (8.1)	14 (16.5)
Radiofrequency ablation	3 (3.5)	6 (7.1)
Percutaneous ethanol injection	1 (1.2)	2 (2.4)
SSA¶	30 (34.9)	32 (37.6)
Prior systemic treatment, n (%)		
Any	57 (66.3)	61 (71.8)
Streptozocin	24 (27.9)	28 (32.9)
Anthracyclines	27 (31.4)	35 (41.2)
Fluoropyrimidines	20 (23.3)	25 (29.4)
Concomitant SSA treatment, n (%)	23 (26.7)	25 (29.4)
Started prior to study and continued	22 (25.6)	20 (23.5)
Started during study	1 (1.2)	5 (5.9)

*Per local regulations, race was not routinely reported in one participating country.
†Protocol violation.
‡Tumor functionality was as reported by investigators. Unknown = clinical symptoms but no identified corresponding neuropeptide secretion.
§n=85 per arm.
¶Includes patients who received SSAs prior to first dose of trial medication, regardless of whether or not they continued to receive these concomitantly during the study.

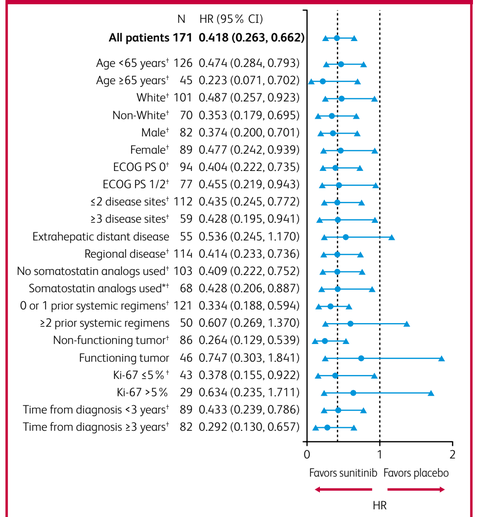
Figure 1. PFS in total patient cohort.



Subgroup Analysis According to Baseline Patient Characteristics

- In all subgroups analyzed, the HR for PFS favored sunitinib (Figure 2).
- The treatment effect of sunitinib was statistically significant regardless of the following demographic and baseline patient characteristics:
  - age (<65 vs. ≥65 years)
  - race (White vs. non-White)
  - gender
  - Eastern Cooperative Oncology Group performance status (0 vs. 1/2)
  - number of disease sites (≤2 vs. ≥3)
  - use of SSAs prior to or during the study vs. no use
  - time from diagnosis to study enrollment (<3 vs. ≥3 years).

Figure 2. Cox proportional hazard analysis of PFS of selected subgroups, according to baseline patient characteristics (ITT population).



*Includes all patients receiving somatostatin analogs at any time before and/or concomitant with study treatment.
†Statistically significant.
ECOG PS = Eastern Cooperative Oncology Group performance status.

- The treatment effect of sunitinib was also significant in patients with regional disease, those who had received 0 or 1 prior systemic regimens, and those with non-functioning tumors.

Influence of Baseline Factors on Treatment Effects

- Overall treatment effect HR (using the Cox proportional hazard model) when controlling for each individual baseline factor was similar to the overall HR (0.418).
- Only time from diagnosis (≥3 vs. <3 years) was found to be a potential independent prognostic variable using univariate and multivariate analyses (P=0.03 in both cases). The PFS advantage with sunitinib vs. placebo was greater when adjusting for time from diagnosis (Table 2).

Table 2. Multivariate Cox proportional hazard analysis of PFS (ITT population)

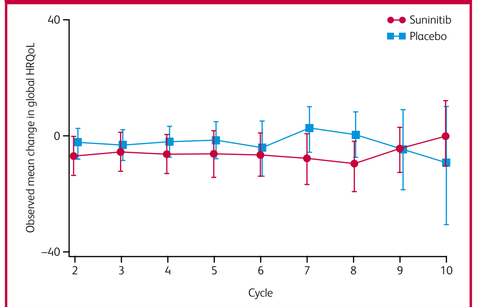
Model	HR	95% CI	P value
Treatment effect (sunitinib vs. placebo), unadjusted	0.418	0.263, 0.662	0.0002
Treatment effect (sunitinib vs. placebo), adjusted*	0.374	0.234, 0.599	<0.0001
+ Time from diagnosis (≥3 vs. <3 years)	0.603	0.382, 0.952	0.03

*Adjusted for time from diagnosis.

HRQoL and Other PROs

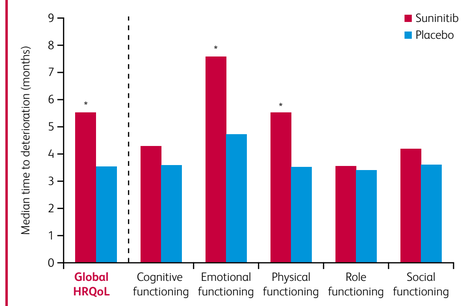
- The completion rate through 10 cycles was >80% at most time points.
- Sunitinib and placebo did not differ clinically or statistically in terms of global HRQoL (Figure 3) or in the cognitive, emotional, physical, role, and social functioning domains.

Figure 3. Global HRQoL is comparable between sunitinib and placebo treatment arms.



- Patients receiving sunitinib experienced a clinically and statistically significant worsening of diarrhea (difference = 21.38; P<0.001) and a small but statistically significant worsening of insomnia (difference = 7.753; P=0.0372), compared with placebo.
- Sunitinib delayed deterioration in emotional and physical functioning and global HRQoL (Figure 4). When this analysis was repeated, controlling for PFS and death, the difference between the two treatment arms was not statistically significant. Thus, the prolonged time to deterioration was dependent on the effects of sunitinib on PFS and overall survival.

Figure 4. Time to deterioration in Global HRQoL and functional scales by treatment arm.



*P<0.05 vs. placebo; log-rank test.
Symptom scales were also assessed and did not show a significant delay in deterioration with the exception of constipation.

CONCLUSIONS

- In this randomized trial of patients with advanced, progressive, well-differentiated pancreatic NET, there was an approximately 6-month improvement in median PFS in the sunitinib arm (11.4 months) compared with the placebo arm (5.5 months; P=0.0001).
- PFS favored the sunitinib arm in all subgroups studied, supporting its use in patients with pancreatic NET regardless of their baseline characteristics, including the number of prior treatments or previous exposure to SSAs.
- Patients treated with sunitinib exhibited comparable scores in global HRQoL and all functional domains (using EORTC QLQ-C30), compared with placebo. Sunitinib's tolerability profile had no adverse impact on QoL.
- Additionally, treatment with sunitinib delayed deterioration as defined by the composite endpoint (PFS/death/MID) in emotional and physical functioning, as well as in global HRQoL.

REFERENCES

1. Pietras K, Hanahan D. *J Clin Oncol* 2005;23:939–952.
2. Yao VJ, Sennino B, Davis RB. Presentation at EORTC-NCI-AACR, Prague, Czech Republic, 2007 (Abstract 78).
3. Faivre S, Delbaldo C, Vera K, et al. *J Clin Oncol* 2006;24:25–35.
4. Kulke MH, Lenz HJ, Meropol NJ, et al. *J Clin Oncol* 2008;26:3403–3410.
5. Raymond E, Niccoli P, Raoul J-L, et al. Presentation at the ASCO Annual Meeting, Chicago IL, USA, June 4–6, 2010 (Abstract 4031).

ACKNOWLEDGMENTS

We would like to thank all of the participating patients and their families, as well as the global network of investigators, research nurses, study coordinators, and operations staff.

This trial (ClinicalTrials.gov ID: NCT00428597) was funded by Pfizer Inc. Medical writing assistance was provided by Susanne Gilbert of ACUMED® (Tytherington, UK) with funding from Pfizer, Inc.

Presented at the 2010 NANETS Neuroendocrine Tumor Symposium, Santa Fe, New Mexico, USA, October 29 and 30, 2010.