Progression-free Survival by Blinded Independent Central Review and Updated Overall Survival of Sunitinib versus Placebo for Patients with Progressive, Unresectable, Well-differentiated Pancreatic Neuroendocrine Tumor

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INTRODUCTION

- Sunitinib malate (SUTENT®) is an inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptors, stem cell factor receptor, and related kinases.
- We conducted a multinational, randomized, double-blind, placebo-controlled, phase III study in patients with advanced, well-differentiated, progressive pancreatic neuroendocrine tumor (NET). The study was closed after the independent data and safety monitoring committee noted a difference in progression-free survival (PFS) in favor of sunitinib and more serious adverse events (AEs) and deaths in the placebo group.[1]
  - The primary endpoint of the study was PFS.
- At the time of study closure there was also an advantage for sunitinib over placebo in the secondary endpoint of overall survival (OS). We performed a retrospective analysis of PFS by blinded independent central review (BICR). This analysis, along with updated OS, is presented here.

OBJECTIVE

- To determine whether BICR confirms the investigator-assessed PFS advantage for sunitinib, and whether sunitinib increases OS despite patient crossover from placebo to sunitinib.

METHODS

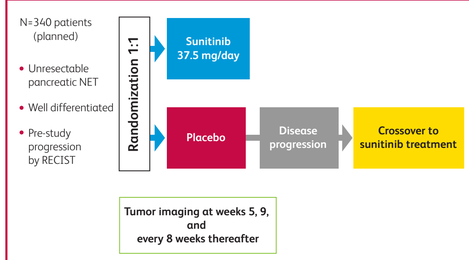
Trial Population

- Key inclusion criteria:
  - histologically or cytologically diagnosed well-differentiated pancreatic islet cell tumor (World Health Organization [WHO] 2000 classification[2])
  - locally advanced, or metastatic disease with disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST], version 1.0[3]) documented radiographically by computed tomography, magnetic resonance imaging, or Octreoscan® in the previous 12 months
  - disease not amenable to treatment with curative intent
  - ≥1 measurable target lesion according to RECIST
  - adequate organ function
  - Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.
- Key exclusion criteria:
  - poorly differentiated pancreatic NET (WHO 2000 classification[2])
  - current cancer treatment other than somatostatin analogs
  - prior treatment with tyrosine kinase inhibitors or anti-vascular endothelial growth factor inhibitors.
- All patients provided written, informed consent.

Trial Design

- Patients were randomized 1:1 to receive either sunitinib at a starting dose of 37.5 mg administered once daily orally on a continuous daily dosing schedule or matching placebo (Figure 1); patients receiving placebo were able to cross over to treatment with sunitinib at disease progression or at study closure.

Figure 1. Study design.



- All patients received best supportive care. Concurrent treatment with somatostatin analogs was permitted.
- Dose interruption and/or dose modification was permitted as necessary.
- Treatment continued until disease progression, unacceptable toxicity, or death.

Trial Endpoints and Assessments

- The primary endpoint of the trial was PFS by investigator-determined objective tumor assessment.
  - Tumor assessments were performed locally at identical, fixed intervals (screening, week 5, week 9, every 8 weeks thereafter, and at the end of treatment/withdrawal); additional assessments were performed if progressive disease (PD) was suspected.
  - Disease progression was determined by investigators according to RECIST based on objective tumor assessments.
- The secondary endpoints included OS and safety.

Blinded Independent Central Review

- Baseline and on-trial scans and radiology data were evaluated retrospectively by independent radiologists according to a two-reader, two-time point lock, followed by a sequential locked read, batch-mode paradigm.
- The reading radiologists were blinded to treatment arm, investigator assessments, and AEs; any discrepancies between their evaluations were adjudicated by a similarly blinded and independent radiologist.

Analysis of Progression-free Survival and Overall Survival

- Analysis of PFS (investigator and BICR assessments) and OS was based on the intent-to-treat (ITT) population, which included all randomized patients (N=171) with drug assignment according to initial treatment groups.
- Identical censoring rules applied to the two PFS analyses.
- PFS was defined as the time from randomization to first objective PD or death due to any cause, whichever occurred first.
  - For patients without PD who did not die during the trial period, PFS data were censored on the date of the last tumor assessment on trial. For patients without baseline scans or lack of any on-study scans, PFS data were censored on day 1.
- PFS and OS were summarized using Kaplan–Meier methods; hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using a Cox proportional hazards model.

RESULTS

Baseline Characteristics and Disposition

- Between June 2007 and April 2009, 171 patients were randomized to treatment (sunitinib, n=86; placebo, n=85; ITT population); all patients were included in the BICR analysis.
- Patient demographics and baseline disease characteristics are presented in Table 1.
  - Although a difference in ECOG PS between study arms was observed, examination of outcome according to baseline characteristics revealed that the benefit of sunitinib extended across all subgroups.

Table 1. Patients' baseline characteristics.

	Sunitinib (n=86)	Placebo (n=85)
Median (range) age, years	56 (25–84)	57 (26–78)
Male/female, n (%)	42/44 (49/51)	40/45 (47/53)
ECOG PS, n (%)		
0	53 (62)	41 (48)
1	33 (38)	43 (51)
2	0	1 (1)
Histology, n (%)		
Non-functioning	42 (49)	44 (52)
Functioning	25 (29)	21 (25)
Unknown/missing	19 (22)	20 (24)
Involved disease sites, n (%)*		
Pancreas	35 (41)	31 (37)
Lymph node	29 (34)	41 (48)
Liver	79 (92)	78 (92)
Lung	9 (11)	15 (18)
Peritoneum	3 (4)	7 (8)
Stomach	0	1 (1)
Other	18 (21)	21 (25)
Prior surgery, n (%)	76 (88)	77 (91)
Pancreatic resection	47 (55)	49 (58)
Hepatic resection	18 (21)	21 (25)
Prior radiation therapy, n (%)	9 (11)	12 (14)
Prior systemic therapy, n (%)†	45 (52)	50 (59)
Concomitant somatostatin analog, n (%)	23 (27)	25 (29)

*Includes both target and non-target sites; sites with multiple lesions were counted once.
†Excluding chemoembolization and regimens with somatostatin analog only.

Progression-free Survival

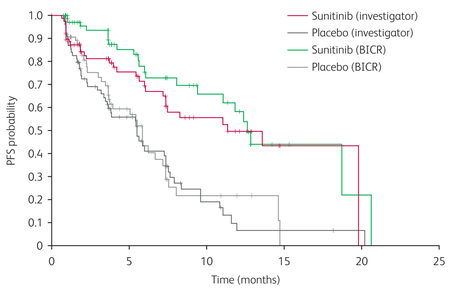
- Investigator assessment:
  - Median PFS was 11.4 months for sunitinib and 5.5 months for placebo (HR=0.418; 95% CI: 0.263–0.662; P=0.000118) using investigator assessments (Table 2; Figure 2).
- BICR assessment:
  - Imaging scans were collected for 170 patients (99.4%). Complete imaging scan sets/timepoints were collected for 160 patients (93.6%).
  - Median PFS using BICR assessments was 12.6 months for sunitinib and 5.8 months for placebo (HR=0.315; 95% CI: 0.181–0.546; P=0.000015), consistent with the investigator assessment (Table 2; Figure 2).

Table 2. Analysis of investigator-assessed and BICR-assessed PFS.

	Investigator assessed		BICR assessed	
	Sunitinib (n=86)	Placebo (n=85)	Sunitinib (n=86)	Placebo (n=85)
Number with event	30	51	22	39
Objective tumor progression	27	48	19	34
Death without objective PD	3	3	3	5
Number censored	56	34	64	46
Median PFS (95% CI), months*	11.4 (7.4–19.8)	5.5 (3.6–7.4)	12.6 (11.1–20.6)	5.8 (3.8–7.2)
Sunitinib vs. placebo				
HR (95% CI)	0.418 (0.263–0.662)		0.315 (0.181–0.546)	
P value	0.000118		0.000015	

*Kaplan–Meier estimate.

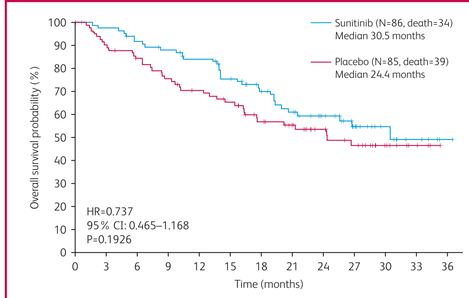
Figure 2. Kaplan–Meier estimates of PFS based on investigator-assessment versus BICR.



Overall Survival

- At study closure, there were 9 deaths in the sunitinib group and 21 deaths in the placebo group (HR=0.409; 95% CI: 0.187–0.894; P=0.0204), and most patients were still in follow-up.
  - After unblinding at study closure, patients were offered open-label sunitinib.
- Fifty-nine placebo patients (69%) crossed over to sunitinib treatment either after disease progression or at study closure.
- As of June 2010, there were 34 deaths in the sunitinib group and 39 deaths in the placebo group.
- Median OS for sunitinib and placebo was 30.5 months (95% CI: 20.6–NR) and 24.4 months (95% CI: 16.3–NR; HR=0.737; 95% CI: 0.465–1.168; P=0.1926; Figure 3), respectively.

Figure 3. Kaplan–Meier estimates of OS.



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Safety

- The most common treatment-emergent (all-causality) grade 3/4 AEs in the sunitinib arm were neutropenia (12%), hypertension (10%), and hand–foot syndrome (6%). In the placebo arm, the most common AEs were abdominal pain (10%), fatigue (9%), and back pain (5%).

CONCLUSIONS

- The BICR analysis of PFS demonstrated a 6.8-month improvement in median PFS with sunitinib, confirming the treatment effect reported with investigator assessment.
- Despite crossover from treatment with placebo to sunitinib, an improvement of 6.1 months in median OS was observed in the sunitinib arm compared with the placebo arm.
- Together, these data support the initial findings of this phase III study, and the clinical benefit of sunitinib in these patients.

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