Evaluation of Progression-free Survival by Blinded Independent Central Review in Patients with Progressive, Well-differentiated Pancreatic Neuroendocrine Tumors Treated with Sunitinib or Placebo

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INTRODUCTION

- Sunitinib (SU) is an oral, multitargeted receptor tyrosine kinase inhibitor with antiangiogenic activity.
- A phase II, open-label study demonstrated promising evidence of clinical benefit with SU in patients with advanced pancreatic neuroendocrine tumors (NET).[1]
- In a phase III, double-blind, placebo-controlled, randomized trial in patients with advanced, well-differentiated, progressive pancreatic NET, SU 37.5 mg/day on a continuous daily dosing (CDD) regimen resulted in a clinically significant improvement in investigator-assessed progression-free survival (PFS) compared with placebo.
  - Median PFS 11.4 months versus 5.5 months, respectively; hazard ratio (HR)=0.418; 95% confidence interval (CI): 0.263, 0.662; P=0.0001.[2]
  - An advantage for SU was also observed in the secondary endpoints of objective response rate and overall survival.
- Unintentional unblinding of investigators due to known treatment-related adverse events (AEs) may confound estimates of PFS when based on investigator assessments only.[3,4]
- In this phase III trial, a retrospective, blinded independent central review (BICR) of imaging studies was conducted in a large subset of patients with available and adequate magnetic resonance imaging (MRI)/computed tomography (CT) scan image sets.

METHODS

Trial Population

- Key inclusion criteria:
  - histologically or cytologically diagnosed well-differentiated pancreatic islet cell tumor (World Health Organization [WHO] 2000 classification[5])
  - local, locally advanced, or metastatic disease with disease progression (per Response Evaluation Criteria in Solid Tumors [RECIST], version 1.0[6]) documented radiographically by CT, MRI, 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
  - life expectancy ≥3 months.
- Key exclusion criteria:
  - poorly differentiated pancreatic NET (WHO 2000 classification[5])
  - current cancer treatment other than somatostatin analogs
  - prior treatment with tyrosine kinase inhibitors or vascular endothelial growth factor angiogenic inhibitors.
- All patients provided written informed consent.

Trial Design

- Patients were randomized 1:1 on a double-blind basis to receive either SU at a starting dose of 37.5 mg administered once daily orally on a CDD schedule or matching placebo; all patients received best supportive care. Concurrent treatment with somatostatin analogs was permitted.
- Dose interruption and/or modification of SU was permitted for toxicity.
- Treatment continued until disease progression, unacceptable toxicity, or death.

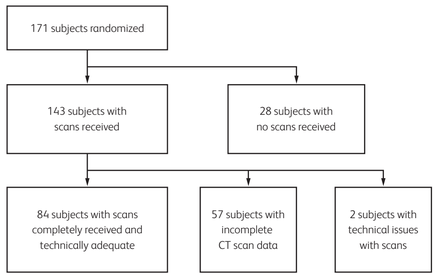
Trial Endpoints and Assessments

- The primary endpoint of the trial was PFS by investigator 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.
- Tumor response and disease progression were determined by investigators according to RECIST, based on objective tumor assessments.
- Confirmatory scans were required ≥4 weeks after an initial response.

Blinded Independent Central Review

- BICR was conducted for 84 patients whose MRI/CT scan image sets were fully collected and available as of February 15, 2010 (Figure 1).
  - Subjects were not pre-selected for the BICR.
  - Subjects represented a subset whose radiographic image sets were fully collected by a third party and passed an image assessment demonstrating acceptable quality.
  - Fifty-seven subjects, with incomplete CT scan data, were not included in the BICR.
  - Imaging data from two subjects failed image quality assessment for technical reasons.

Figure 1. Patient disposition for BICR analysis.



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

Analysis of Progression-free Survival

- Primary analyses of PFS were based on the intent-to-treat (ITT) population, which included all randomized patients (N=171), with drug assignment according to initial randomization.
- The secondary BICR analyses of PFS reported here were based on the subset of 84 patients.
- 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.
- PFS was summarized using Kaplan–Meier methods; HRs and 95% CIs were estimated using a Cox proportional hazards model.

RESULTS

Baseline Characteristics and Disposition

- In total, 171 patients were randomized to treatment (SU, n=86; placebo, n=85; ITT population); 84 patients (49%) were included in the BICR subset (SU, n=41; placebo, n=43).
- The BICR subset was representative of the ITT population with respect to demographics, baseline disease characteristics, and prior treatment (Table 1). However, a higher proportion of patients in the SU arm had an ECOG PS of 0 in both data sets.

Table 1. Patient demographic and baseline disease characteristics.

	ITT population		BICR subset population	
	SU n=86	Placebo n=85	SU n=41	Placebo n=43
Median (range) age, years	56 (25–84)	57 (26–78)	53 (27–77)	57 (26–78)
Male/female, n (%)	42/44 (49/51)	40/45 (47/53)	17/24 (41/59)	20/23 (47/53)
ECOG PS, n (%)				
0	53 (62)	41 (48)	24 (59)	19 (44)
1	33 (38)	43 (51)	17 (41)	23 (53)
2	0	1 (1)	0	1 (2)
Tumor secretion, n (%)				
Non-functioning	42 (49)	44 (52)	19 (46)	20 (47)
Functioning	25 (29)	21 (25)	13 (32)	11 (26)
Unknown/missing	19 (22)	20 (24)	9 (22)	12 (28)
Involved disease sites, n (%)*				
Pancreas	35 (41)	31 (36)	19 (46)	20 (47)
Lymph nodes	29 (34)	41 (48)	13 (32)	21 (49)
Liver	79 (92)	78 (92)	38 (93)	38 (88)
Lung	9 (10)	15 (18)	3 (7)	5 (12)
Peritoneum	3 (3)	7 (8)	0	5 (12)
Stomach	0	1 (1)	0	0
Other†	18 (21)	21 (25)	5 (12)	11 (26)
Prior surgery, n (%)	76 (88)	77 (91)	35 (85)	38 (88)
Pancreatic tumor resection	47 (55)	49 (58)	21 (51)	22 (51)
Liver metastasis resection	18 (21)	21 (25)	5 (12)	10 (23)
Prior radiation therapy, n (%)	9 (10)	12 (14)	3 (7)	5 (12)
Prior systemic therapy, n (%)‡	45 (52)	50 (59)	23 (56)	24 (56)

*Includes both target and non-target sites; sites with multiple lesions were counted once.

†Other sites included kidney, adrenal gland, bone, bilateral pleural effusion, vena lienalis, pleura, ascites, spleen, left pedicle, pelvis, breast, buttock, thorax, costa, mesentery, epiploon, uterus, and heterogenous mediastinal mass.

‡Excluding chemoembolization and regimens with somatostatin analogs only.

- All patients in the BICR subset population had a primary diagnosis of malignant neoplasm of islets of Langerhans (MedDRA, version 12.0 preferred term); median duration since diagnosis was 2.4 years (range: 0.1–25.6) in the SU arm and 2.5 years (range: 0.1–15.0) in the placebo arm.

Progression-free Survival

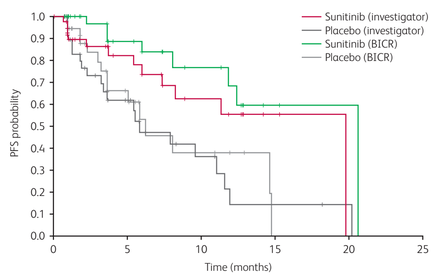
- Median PFS in the BICR subset population (n=84):
  - BICR assessment of the BICR subset population: 20.6 months for SU and 6.2 months for placebo (HR=0.289; 95% CI: 0.117, 0.716; P=0.0042; Table 2; Figure 2).
  - Investigator assessment of the BICR subset population: 19.8 months for SU and 5.8 months for placebo (HR=0.449; 95% CI: 0.218, 0.924; P=0.0249; Table 2; Figure 2).
  - Findings in the BICR subset population are consistent with the overall ITT population for investigator assessment of treatment effect.
  - Preliminary findings from the ongoing full BICR population (N=171) appear to align closely with investigator assessment in the overall ITT population.

Table 2. Analysis of PFS.

	ITT population		BICR subset population			
	Investigator-assessed		Investigator-assessed		BICR-assessed	
	SU n=86	Placebo n=85	SU n=41	Placebo n=43	SU n=41	Placebo n=43
Number with event	30	51	12	21	8	15
Objective tumor progression	27	48	10	19	6	12
Death without objective PD	3	3	2	2	2	3
Number censored	56	34	29	22	33	28
Median PFS (95% CI), months*	11.4 (7.4, 19.8)	5.5 (3.6, 7.4)	19.8 (8.3, 19.8)	5.8 (3.4, 11.1)	20.6 (11.9, 20.6)	6.2 (3.6, 14.6)
SU versus placebo						
HR (95% CI)	0.418 (0.263, 0.662)		0.449 (0.218, 0.924)		0.289 (0.117, 0.716)	
P-value	0.0001		0.0249		0.0042	

*Kaplan–Meier estimate.

Figure 2. PFS (Kaplan–Meier plots) in the BICR subset population based on investigator and BICR assessment of tumor response.



- Discordance rates for evaluation of disease progression between BICR and investigator assessments demonstrated no evidence of effective unblinding leading to systematic bias favoring SU.

Safety

- The AE profile in the BICR subset reflected that in the ITT population (Table 3).

Table 3. All grades and grade 3/4, all-causality, treatment-emergent AEs in ≥20% of patients in either arm.*

	ITT population				BICR subset population			
	SU n=83†		Placebo n=82†		SU n=41†		Placebo n=41†	
AE, n (%)	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Diarrhea	49 (59)	4 (5)	32 (39)	2 (2)	28 (68)	3 (7)	16 (39)	2 (5)
Nausea	37 (45)	1 (1)	24 (29)	1 (1)	16 (39)	0	16 (39)	0
Asthenia	28 (34)	4 (5)	22 (27)	2 (2)	15 (37)	3 (7)	8 (20)	1 (2)
Vomiting	28 (34)	0	25 (30)	2 (2)	11 (27)	0	15 (37)	1 (2)
Fatigue	27 (33)	4 (5)	22 (27)	7 (9)	16 (39)	4 (10)	13 (32)	3 (7)
Neutropenia	24 (29)	10 (12)	3 (4)	0	12 (29)	5 (12)	2 (5)	0
Hair color changes	24 (29)	1 (1)	1 (1)	0	11 (27)	1 (2)	1 (2)	0
Abdominal pain	23 (28)	4 (5)	26 (32)	8 (10)	12 (29)	3 (7)	13 (32)	5 (12)
Hypertension	22 (27)	8 (10)	4 (5)	1 (1)	10 (24)	3 (7)	2 (5)	1 (2)
Hand–foot syndrome	19 (23)	5 (6)	2 (2)	0	13 (32)	4 (10)	1 (2)	0
Stomatitis	18 (22)	3 (4)	2 (2)	0	14 (34)	3 (7)	2 (5)	0
Anorexia	18 (22)	2 (2)	17 (21)	0	11 (27)	1 (2)	11 (27)	0
Leukopenia	9 (11)	5 (6)	1 (1)	0	3 (7)	1 (2)	0	0

*In order of incidence in SU arm of ITT population.

†Patients receiving ≥1 dose of trial medication.

- In the ITT population, the most common treatment-emergent, grade 3/4 AEs in the SU arm were neutropenia (12%), hypertension (10%), hand–foot syndrome (6%), and leukopenia (6%).
- In the BICR subset, the most common treatment-emergent, grade 3/4 AEs in the SU arm were neutropenia (12%), fatigue (10%), and hand–foot syndrome (10%).

CONCLUSIONS

- The BICR subset was representative of the ITT population given similarities in demographics, baseline disease characteristics, prior treatment, and AE profiles.
- The BICR analyses support the overall findings of the investigator-assessed PFS (ITT population), demonstrating a clinical benefit of SU in patients with progressive, well-differentiated pancreatic NET, and argue against the presence of any bias favoring SU.
- A BICR of PFS for the full population (N=171) is ongoing.

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