

ORIGINAL ARTICLE

Sunitinib in pancreatic neuroendocrine tumors: updated progression-free survival and final overall survival from a phase III randomized study

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Background: In a phase III trial in patients with advanced, well-differentiated, progressive pancreatic neuroendocrine tumors, sunitinib 37.5 mg/day improved investigator-assessed progression-free survival (PFS) versus placebo (11.4 versus 5.5 months; HR, 0.42; $P < 0.001$). Here, we present PFS using retrospective blinded independent central review (BICR) and final median overall survival (OS), including an assessment highlighting the impact of patient crossover from placebo to sunitinib.

Patients and methods: In this randomized, double-blind, placebo-controlled study, cross-sectional imaging from patients was evaluated retrospectively by blinded third-party radiologists using a two-reader, two-time-point lock, followed by a sequential locked-read, batch-mode paradigm. OS was summarized using the Kaplan–Meier method and Cox proportional hazards model. Crossover-adjusted OS effect was derived using rank-preserving structural failure time (RPSFT) analyses.

Results: Of 171 randomized patients (sunitinib, $n = 86$; placebo, $n = 85$), 160 (94%) had complete scan sets/time points. By BICR, median (95% confidence interval [CI]) PFS was 12.6 (11.1–20.6) months for sunitinib and 5.8 (3.8–7.2) months for placebo (HR, 0.32; 95% CI 0.18–0.55; $P = 0.000015$). Five years after study closure, median (95% CI) OS was 38.6 (25.6–56.4) months for sunitinib and 29.1 (16.4–36.8) months for placebo (HR, 0.73; 95% CI 0.50–1.06; $P = 0.094$), with 69% of placebo patients having crossed over to sunitinib. RPSFT analysis confirmed an OS benefit for sunitinib.

Conclusions: BICR confirmed the doubling of PFS with sunitinib compared with placebo. Although the observed median OS improved by nearly 10 months, the effect estimate did not reach statistical significance, potentially due to crossover from placebo to sunitinib.

Trial registration number: NCT00428597.

Key words: VEGFR inhibitor, antiangiogenics, crossover, rank-preserving structural failure time (RPSFT), blinded independent central review

Introduction

Pancreatic neuroendocrine tumors (NETs), although uncommon, are increasing in incidence [1]. NETs are highly angiogenic and dependent on VEGF receptor (VEGFR activation) [2,3]. Sunitinib malate (SUTENT, Pfizer, Inc, New York, NY) is an oral small-molecule tyrosine kinase inhibitor that targets VEGFRs, PDGFRs, and KIT [4–6]. After a phase I trial showed sunitinib activity in NETs [7], an open-label phase II study demonstrated promising evidence of sunitinib clinical benefit in 66 patients with advanced pancreatic NET [8]. Consequently, a randomized double-blind placebo-controlled, phase III trial (NCT00428597) was conducted to assess the efficacy and safety of continuous daily dosing of sunitinib 37.5 mg in 171 patients with advanced, well-differentiated pancreatic NET [9]. The primary endpoint was progression-free survival (PFS) based on investigator assessment. The study was closed after an independent data and safety monitoring committee noted a PFS difference in favor of sunitinib and more serious adverse events (AEs) and deaths in the placebo group. Median PFS among patients who received sunitinib was higher than that in patients who received placebo (11.4 versus 5.5 months; hazard ratio [HR] 0.42; 95% confidence interval [CI] 0.26–0.66; $P=0.0001$). Two years after study closure, OS data was updated with median OS equal to 33.0 months for sunitinib and 26.7 months for placebo (HR 0.71; 95% CI 0.47–1.09; $P=0.115$) [10].

Here, we present updated efficacy data from this phase III study: PFS as determined through a retrospective analysis of tumor imaging scans using blinded independent central review (BICR), final OS at 5 years after study closure, and the effect of sunitinib on OS with and without adjustment for treatment crossover in the placebo arm.

Patients and methods

Patients and trial design

As described previously [9], patients had pathologically confirmed, well-differentiated pancreatic NETs (World Health Organization 2000 classification [11]) that were advanced, metastatic, or both and were not candidates for surgery. Additional eligibility criteria are provided in the [Supplementary Methods](#), available at *Annals of Oncology* online.

This was a multinational, randomized, double-blind, placebo-controlled phase III trial. Patients were randomly assigned 1:1 to receive sunitinib 37.5 mg or matching placebo on a continuous daily dosing schedule until documented RECIST-defined progression, unacceptable AEs occurred, or the patient died. Patients receiving placebo could cross over to sunitinib at disease progression or study closure. Trial end points and assessments are described in the [Supplementary Material](#), available at *Annals of Oncology* online.

BICR of PFS

Retrospective BICR, requested by the US Food and Drug Administration (FDA) Oncology Drugs Advisory Committee and the European Medicines Agency, was conducted by an independent third-party central radiology contractor (CoreLab Partners, Princeton NJ). Scans and imaging data were evaluated by third-party radiologists using a two-reader, two-time-point lock, followed by a sequential locked-read, batch-mode paradigm. The two reading radiologists were blinded to treatment arm, investigator assessments, and AEs. Any discrepancies between their

evaluations were adjudicated by a third, similarly blinded, independent radiologist.

PFS and OS analysis

PFS and OS were summarized using Kaplan–Meier methods. HR and 95% CI were estimated using a Cox proportional hazards model. Two-sided log-rank tests were used to compare the results obtained in the two treatment arms.

PFS was defined as the time from randomization to the first evidence of PD or death from 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 who lacked baseline or on-study scans (13%), PFS data were censored on day 1. Both analyses of PFS (investigator- and BICR-assessed) were based on the intent-to-treat (ITT) population, which included all randomized patients with drug assignment based on initial treatment groups. Identical censoring rules applied to both analyses.

OS was defined as the time from date of randomization to date of death due to any cause. In addition to the ITT analysis, OS data were analyzed to adjust for the impact of crossover using the rank-preserving structural failure time (RPSFT) approach, defined as a nonparametric model that produces a randomization-based treatment-effect estimator and assumes that treatment with the investigational drug affects survival time uniformly in all patients [12, 13]. For patients who crossed over to sunitinib, the time on treatment after crossover was adjusted to reflect what would have happened if they had stayed on placebo. A Cox regression analysis was used to estimate HR based on observed event times in the sunitinib arm and estimated event times for crossover patients or observed event times for other patients in the placebo arm. More details about the RPSFT method are provided in the [Supplementary Methods](#), available at *Annals of Oncology* online. OS data were also analyzed using two other approaches for exploratory purpose: (i) survival times for patients in the placebo arm were censored at time of crossover and (ii) data were analyzed using a Cox model in which treatment was a time-dependent covariate. In this analysis, crossover patients were counted both in the placebo arm before crossover and in the sunitinib arm after crossover as a means of eliminating the crossover effect from the placebo arm.

Results

As previously reported, between June 2007 and April 2009, 171 patients were randomized to treatment ($n=86$ and 85 , sunitinib and placebo, respectively, in the ITT population; [supplementary Figure S1](#), available at *Annals of Oncology* online) [9]. Patient demographics and baseline disease characteristics are presented in [supplementary Table S1](#), available at *Annals of Oncology* online. Patients received sunitinib for a median duration of 4.6 months (range: 0.4–17.5 months) or placebo for a median duration of 3.7 months (range: <0.1–20.2 months).

BICR of PFS

Complete imaging scan sets/time points for BICR analysis were collected for the majority of patients ($n=160$; 94%). The primary reason for scans not being included for 11 patients (sunitinib $n=7$; placebo $n=4$) was an inability to retrieve scans from sites/patients. Median PFS by BICR was 12.6 months with sunitinib and 5.8 months with placebo treatment (HR 0.32; 95% CI 0.18–0.55; $P=0.000015$; [Table 1](#) and [Figure 1](#)). The overall discordance rate, including both event and timing discordance, between BICR- and investigator-assessed PFS was 45%. Analysis of

Table 1. Analysis of investigator-assessed and BICR-assessed PFS

	Investigator assessed		BICR assessed ^a	
	Sunitinib	Placebo	Sunitinib	Placebo
	(n = 86)	(n = 85)	(n = 86)	(n = 85)
Number of events, n	30	51	22	39
Objective PD	27	48	19	34
Deaths without objective PD	3	3	3	5
Censored patients, n	56	34	64	46
Mean PFS, months (95% CI)	11.4 (7.4–19.8)	5.5 (3.6–7.4)	12.6 (11.1–20.6)	5.8 (3.8–7.2)
HR (95% CI)		0.42 (0.26–0.66)		0.32 (0.18–0.55)
P value ^b		0.000118		0.000015

^aAbout 11 (sunitinib, n = 7; placebo, n = 4) of 171 patients did not have tumor scans available for BICR assessment.

^bSunitinib versus placebo.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; PD, progressive disease; PFS, progression-free survival.

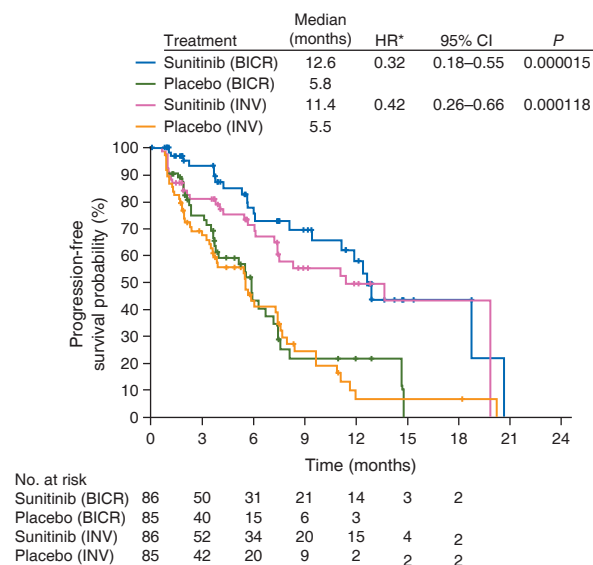


Figure 1 Kaplan–Meier estimates of progression-free survival based on investigator-assessment (INV) versus blinded independence central review (BICR). Asterisk indicates sunitinib versus placebo. CI, confidence interval; HR, hazard ratio.

PFS by BICR based on baseline and tumor characteristics favored sunitinib for all subgroups evaluated (supplementary Figure S2, available at *Annals of Oncology* online).

OS analyses

As of April 2014 (with 5 years of follow-up since study closure), there were 55 (64%) and 58 (68%) deaths in the sunitinib and placebo groups, respectively; median (95% CI) OS was 38.6 months (range: 25.6–56.4 months) and 29.1 months (range: 16.4–36.8 months; HR 0.73, 95% CI 0.50–1.06, $P=0.094$), respectively (Table 2 and Figure 2A). Median duration of follow-up was 67.4 months. In total, 59 (69%) patients randomized to placebo crossed over to sunitinib: 38 at disease progression before study termination and 21 after study closure. Among the patients who crossed over from placebo to sunitinib, 31% and 52% of patients crossed over by 3 and 6 months, respectively.

OS results obtained after applying methods to adjust for crossover are shown in Table 2 and Figure 2B. Using the RPSFT method, median OS in the placebo arm was calculated to be 13.2 months (HR 0.34; 95% CI 9.2–38.5). When data for each of the 59 patients randomized to placebo were censored at the time of crossover, median OS in the placebo arm was calculated to be 16.3 months (HR 0.40; 95% CI 0.23–0.71), 22.3 months less than that of sunitinib. The Cox model in which treatment was a time-dependent covariate yielded a HR of 0.46 (95% CI 0.27–0.78).

Discussion

BICR analysis of PFS showed a 6.8-month improvement in median PFS with sunitinib compared with placebo, respectively, in patients with progressive, well-differentiated pancreatic NET in this phase III study (12.6 versus 5.8 months), confirming the treatment effect reported previously with investigator assessment (11.4 versus 5.5 months) [9]. This benefit was also confirmed across all patient subgroups evaluated, including those based on prior treatment history. Additionally, at 5 years after study closure, final OS based on the ITT population continued to favor sunitinib, although this result was not statistically significant due to the relatively small size of the study population and the likely effect of crossover on OS in the placebo arm. However, an improvement of 9.5 months in median OS was observed in the sunitinib arm compared with the placebo arm without adjustment for crossover is clinically meaningful. Several exploratory methods of adjusting for the crossover effect suggested the improvement observed might have been more pronounced had no crossover occurred.

Retrospective BICR by an expert radiologist blinded to treatment assignment is a strategy recommended by regulatory guidance in an attempt to correct for potential bias introduced by the investigators. The FDA advocates BICR of radiographic examinations for oncology registration studies when the primary endpoint is based on tumor measurements [14]. In a retrospective analysis of tumor data in the present study, PFS by BICR was consistent with PFS assessed by the study investigators, confirming the magnitude of the treatment effect reported previously [9]. In

Table 2. Analysis of final overall survival

OS analysis/treatment group	n	Deaths	Median OS, months (95% CI)	HR ^a (95% CI)	P value
ITT, no adjustment for crossover					
Sunitinib	86	55	38.6 (25.6–56.4)		
Placebo	85	58	29.1 (16.4–36.8)	0.73 (0.50–1.06)	0.094
Adjustment for crossover (placebo)					
RPSFT model	85	54 ^b	13.2 (9.2–38.5)	0.34 (0.14–1.28) ^c	0.094 ^d
Additional OS analysis					
Censoring at crossover	85	21	16.3 (12.5–24.3)	0.40 (0.23–0.71)	0.001
Time-dependent Cox model	85	NA	NA	0.46 (0.27–0.78)	0.004

^aSunitinib versus placebo.

^bDeaths occurring after crossover may become censored at an earlier time after adjustment for the impact of crossover in RPSFT.

^cFrom 20 000 bootstrap samples.

^dThe RPSFT method does not alter the P value obtained using the ITT method.

CI, confidence interval; HR, hazard ratio; ITT, intent to treat; NA, not applicable; OS, overall survival; RPSFT, rank-preserving structural failure time.

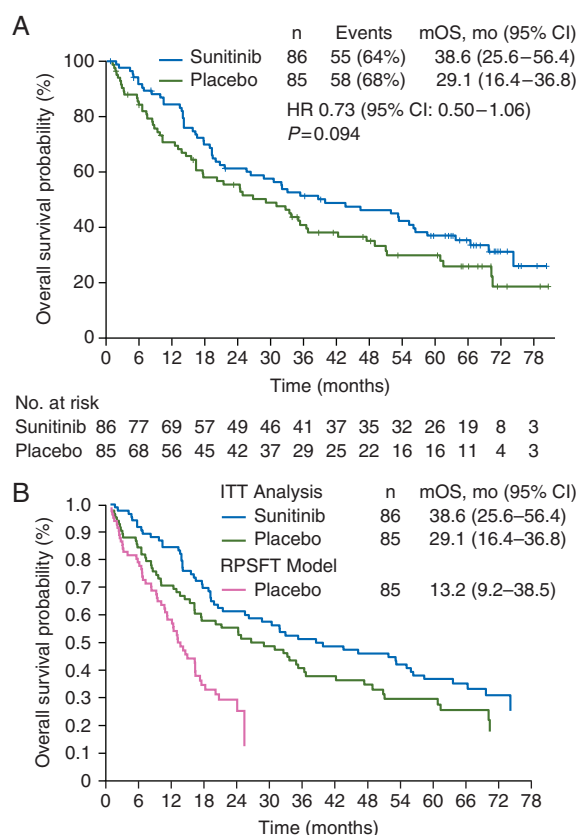


Figure 2 Kaplan–Meier estimates of overall survival in the intent-to-treat (ITT) population (A) without adjustment for crossover and (B) both with and without adjustment for crossover in the placebo arm. CI, confidence interval; HR, hazard ratio; mOS, median overall survival; RPSFT, rank-preserving structural failure time.

pivotal oncology trials, discordance rates between investigator- and BICR assessed PFS are ~35–55% [15]. The 45% discordance observed in this trial was consistent with these historical data.

When the current phase III study was terminated, more deaths had occurred in the placebo arm ($n=21$ versus 9 in the sunitinib arm), suggestive of an early survival advantage with sunitinib (HR 0.41; 95%

CI 0.19–0.89) [9]. Kaplan–Meier analysis suggests that in patients with advanced metastatic disease, sunitinib acts by reducing the risk of early death (Figure 2A). Median OS, 5 years after study closure, was 38.6 months in the sunitinib arm and 29.1 months in the placebo arm (HR 0.73; 95% CI 0.50–1.06). The results obtained with sunitinib compared favorably with—and those obtained with placebo were similar to—data from the National Cancer Institute Surveillance Epidemiology and End Results (SEER) registry that estimated a median OS of 24 months in patients with pancreatic NET with distant metastases [1]. Though, survival based on SEER was defined as the time from date of diagnosis (as opposed to date of randomization in the current study) to date of death due to any cause. In addition, the OS results in this trial compared favorably with those from a phase III placebo-controlled study of the mTOR inhibitor everolimus in patients with advanced pancreatic NET. In that trial, no early separation of the OS curves could be detected, the ITT analysis showed a nonsignificant improvement in median OS of 6.3 months (HR 0.94; 95% CI 0.73–1.20), and the RPSFT analysis showed a reduction in risk of death equal to 40% (HR 0.60; 95% CI 0.09–3.35) [16].

Interpreting OS data from the present phase III study is confounded by the number of patients who were randomized to placebo arm and crossed over to receive sunitinib at disease progression or after the study was closed (69%) and by the treatments received after study ended. Allowing patients access to sunitinib was a decision based on the lack of proven treatment options for patients with pancreatic NET. Since there is no single optimal statistical method of adjusting for crossover in clinical trials, several methods were explored with acknowledgement of the advantages and flaws of each method. Censoring at crossover can result in censoring bias because the event being censored (e.g. PD) is associated with outcome (e.g. death), ultimately resulting in overestimation of OS in the placebo arm. The power of the study can also be reduced using this method as a consequence of the reduction in the number of observed events in the control arm. In general, this approach does not produce valid inferences about the distribution of survival time that would have occurred had crossover not happened. Outcomes derived using this method are not representative of what would be expected from the originally randomized group.

An alternative approach is to use the Cox proportional hazards model with actual treatment as a time-dependent covariate for crossover placebo patients. The difficulties of this approach are well known, since this method compares patient groups based on the treatment actually received rather than comparing all patients as randomized, thereby incurring the risk of selection bias. Statistical methods that respect the randomization are therefore of great importance. The RPSFT method compares treatment groups as randomized, with results that have the same significance level as those of the ITT analysis [12]. No assumption is required as to how actual treatment relates to prognosis, but it assumes that patients randomized to sunitinib and those who received it after crossover derive the same benefit. It is possible, however, that patients failing standard treatment may derive less improvement in mortality. Thus, the OS HR derived from the analyses reflects a mixture of these two effects. Correcting for crossover has been employed in several other phase III studies [17–19], and the RPSFT model has been recognized by health technology assessment bodies, e.g. the National Institute of Clinical Excellence in UK [20] and Tandvårds-och läkemedelsförmånsverket in Sweden [21].

In summary, our current results confirm the benefit of sunitinib and show that the efficacy findings are robust after longer term analysis. BICR confirmed the PFS results obtained using investigator assessments. Long-term OS results continued to favor sunitinib, although this result was not statistically significant.

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