Abstract **1490P**

Continued Sunitinib Treatment after Progressive Disease in a Worldwide Treatment-use Trial of Patients with Gastrointestinal Stromal Tumor

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INTRODUCTION

- Sunitinib malate (SUTENT®), an oral multitargeted tyrosine kinase inhibitor (TKI), is approved multinationally for the treatment of gastrointestinal stromal tumor (GIST) after failure of imatinib due to resistance or intolerance, for advanced renal cell carcinoma, and for unresectable or metastatic, well-differentiated pancreatic neuroendocrine tumor.
- A worldwide, open-label, treatment-use study (NCT00094029; enrollment: September 2004 – December 2007) provided access to sunitinib to patients with advanced imatinib-resistant/-intolerant GIST who may have benefited from it, but were ineligible for sunitinib clinical studies, or were in a country in which regulatory approval had not yet been granted and in which no sunitinib GIST studies were available.
  - An earlier report from this study concluded that sunitinib was effective and well tolerated in this broad population of patients with advanced GIST.[1]
- Continuous kinase inhibition has been posited as important for optimizing outcomes of patients with kinase-mutant-driven cancers such as GIST.

OBJECTIVE

- An ad-hoc analysis was performed to compare the outcomes of patients who continued on sunitinib treatment after progressive disease (PD) versus those who stopped after PD using data from the treatment-use study of sunitinib in GIST.

METHODS

Study Population

- Key inclusion criteria included:
  - age ≥18 years (country-specific protocol amendments also allowed younger patients to enroll)
  - histologically confirmed, advanced and/or recurrent GIST not amenable to standard therapy with curative intent
  - failure of prior treatment with imatinib (PD or significant toxicity that precluded further treatment)
  - ineligibility for participation in ongoing sunitinib clinical studies
  - potential to derive clinical benefit from treatment with sunitinib (investigator's judgment)
  - resolution of all acute toxic effects of any prior therapy/surgery to grade ≤1
  - adequate organ function.
- Exclusion criteria included:
  - participation in any other concurrent therapeutic clinical trial
  - symptomatic central nervous system metastases
  - cardiovascular disease in the previous 6 months.

Study Design and Assessments

- All patients received sunitinib at a starting dose of 50 mg/day in 6-week cycles (4 weeks on treatment/2 weeks off treatment [Schedule 4/2]); a protocol amendment ultimately allowed patients to switch to 37.5 mg on a continuous daily dosing schedule as an alternative.
- Treatment continued for as long as there was evidence of disease control in the judgment of the investigator.
- Survival was monitored for up to 2 years after the last dose of sunitinib or until July 2008, whichever came first.
- Tumor measurements/assessments were performed by investigators using local standards of care.
- Safety and tolerability were assessed by monitoring adverse events (AEs) and laboratory values, and by physical examination.
- Toxicities were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistical Methods

- Due to the nature of the study, a sample size was not predetermined and no inferential analyses were planned.
- All continuous data were summarized using descriptive statistics (mean, standard deviation, median, minimum and maximum values) and all categorical data were summarized using frequencies and percentages.
- The study population included all patients enrolled who received at least one dose of sunitinib (intent-to-treat [ITT] population).
- Overall survival (OS) was estimated using Kaplan–Meier methods.
- In this post-hoc analysis, patients were dichotomized based on whether sunitinib treatment was continued or stopped after objective assessment of PD.

RESULTS

Patients

- At final data cut-off (October 2011), 1,124 of 1,131 patients enrolled had received at least one dose of sunitinib on study (ITT population).
- Of these patients, 380 continued and 324 stopped sunitinib treatment after PD.
- The two subgroups were generally well balanced for baseline demographics (Table 1).
  - There was a higher proportion of men (67% vs. 59%) and patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (44% vs. 35%) among patients who continued treatment after PD.

Drug Exposure

- Exposure to sunitinib treatment is summarized in Table 2.
- Patients who continued on sunitinib after PD did so for a median of 4.7 months after PD.
  - These patients generally received sunitinib longer than those who did not continue post-PD (median 9 vs. 4 cycles started in total).
  - They also had a longer median time on drug and a higher median total dose administered overall than those who discontinued treatment after PD.

Table 1. Baseline patient characteristics.

Characteristic	All patients (N=1,124)	Sunitinib continued after PD (n=380)	Sunitinib stopped after PD (n=324)
Age, years			
Median	59	58	59
Range	10–92	10–84	11–89
Sex, n (%)			
Male	672 (60)	253 (67)	192 (59)
Female	452 (40)	127 (33)	132 (41)
Race/ethnicity, n (%)			
White	858 (76)	292 (77)	239 (74)
Black	38 (3)	15 (4)	8 (2)
Asian	201 (18)	63 (17)	69 (21)
Unknown	27 (2)	10 (3)	8 (2)
ECOG PS, n (%)			
0	420 (37)	166 (44)	115 (35)
1	521 (46)	165 (43)	164 (51)
2	135 (12)	38 (10)	40 (12)
3	33 (3)	10 (3)	2 (1)
4	5 (<1)	0	0
Unknown	10 (1)	1 (<1)	3 (1)

Table 2. Sunitinib exposure (from start of treatment).

	All patients (N=1,124)	Sunitinib continued after PD (n=380)	Sunitinib stopped after PD (n=324)
No. of treatment cycles started			
Median	5	9	4
Range	1–62	1–62	1–35
Time drug was administered, months			
Median	4.6	8.1	3.7
Range	<0.1–56.9	0.4–56.9	<0.1–31.9
Time on treatment, months[a]			
Median	7.0	12.5	5.5
Range	<0.1–75.4	0.7–74.2	<0.1–52.0
Patients with dosing interruptions, n (%)	592 (53)	231 (61)	141 (44)
AE-related[b]	470 (42)	179 (47)	113 (35)
Other[b]	248 (22)	115 (30)	52 (16)
Days with interruption, %			
Median	5	3	6
Range	0–96	0–49	0–96
Patients with dose reductions,[c] n (%)	484 (43)	213 (56)	122 (38)
Total dose, mg			
Median	6,075	10,112	5,238
Range	38–69,950	450–65,962	50–42,000
Daily dose, mg			
Median	50	46	50
Range	15–53	15–53	27–50

[a]For Schedule 4/2, time on treatment was the time period starting from date of first dose and ending at earlier of termination date or last dose date plus planned off-treatment period (2 weeks) for a cycle. For the continuous daily dosing schedule, time on treatment was the time period starting from date of first dose and ending at last dose date.
[b]Dosing could be interrupted for more than one reason.
[c]Patients who had their daily dose prescribed below the assigned dose for any reason at any time during the study.

Table 3. Most common treatment-related AEs.[a]

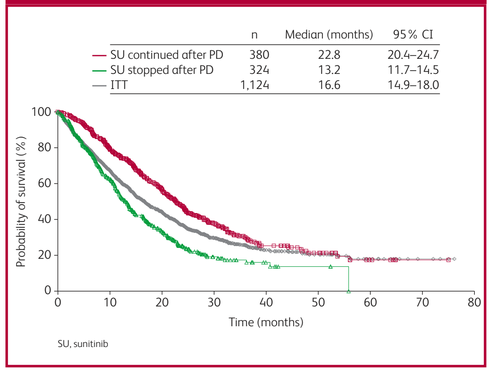
	n (%)					
	All patients (N=1,124)		Sunitinib continued after PD (n=380)		Sunitinib stopped after PD (n=324)	
AE	Any grade[b]	Grade 3/4	Any grade[c]	Grade 3/4	Any grade[d]	Grade 3/4
Any AE	1,030 (92)	580 (52)	363 (96)	214 (56)	300 (93)	152 (47)
Diarrhea	454 (40)	60 (5)	186 (49)	25 (7)	114 (35)	11 (3)
Fatigue	477 (42)	97 (9)	182 (48)	38 (10)	132 (41)	18 (6)
Hand–foot syndrome	363 (32)	123 (11)	150 (40)	54 (14)	102 (31)	37 (11)
Hypertension	288 (26)	74 (7)	140 (37)	34 (9)	77 (24)	25 (8)
Nausea	327 (29)	23 (2)	138 (36)	6 (2)	76 (23)	6 (2)
Decreased appetite	302 (27)	25 (2)	114 (30)	5 (1)	83 (26)	7 (2)
Stomatitis	258 (23)	22 (2)	101 (27)	11 (3)	83 (26)	9 (3)
Neutropenia	212 (19)	90 (8)	99 (26)	46 (12)	54 (17)	17 (5)
Vomiting	247 (22)	28 (2)	89 (23)	6 (2)	76 (23)	11 (3)
Thrombocytopenia	223 (20)	63 (6)	87 (23)	24 (6)	57 (18)	17 (5)
Dysgeusia	180 (16)	0	84 (22)	0	43 (13)	0
Mucosal inflammation	258 (23)	23 (2)	77 (20)	5 (1)	63 (19)	6 (2)
Anemia	181 (16)	61 (5)	75 (20)	23 (6)	47 (15)	13 (4)
Skin discoloration	173 (15)	1 (<1)	74 (19)	0	46 (14)	1 (<1)

[a]Occurring in ≥20% of patients in either subgroup; listed in descending order of overall frequency in the continuation-after-PD subgroup.
[b]Seventeen grade 5 events considered to be treatment-related occurred in the study.
[c]One grade 5 event deemed related to treatment occurred in this subgroup.
[d]Two grade 5 events deemed related to treatment occurred in this subgroup.

Overall Survival

- Median OS (from start of treatment) among patients who remained on treatment after PD was 22.8 months (95% confidence interval [CI]: 20.4–24.7) and 13.2 months (95% CI: 11.7–14.5) among those who did not continue sunitinib after PD (Figure 1).

Figure 1. OS from start of treatment in patients who continued or stopped sunitinib treatment after PD and in the overall ITT population.



Safety

- The rate of treatment-related AEs was numerically higher among patients who continued sunitinib treatment after PD (96%) compared with those who stopped treatment after PD (93%; Table 3).
- The most common treatment-related AEs in both subgroups were diarrhea, fatigue, and hand–foot syndrome.
  - These were mainly grade 1/2 and occurred at a numerically higher rate among patients who continued sunitinib after PD than among those who stopped treatment after PD.

CONCLUSIONS

- Results of this analysis suggest that patients with GIST who continued on sunitinib after PD exhibited a better clinical outcome (longer OS) than those who stopped treatment after PD.
  - However, the potential impact of differing patient characteristics and selection bias cannot be ruled out in this retrospective analysis.
- While these results must be interpreted with caution and would require validation in prospective trials for confirmation, they suggest the benefits of continuing sunitinib treatment despite disease progression, depending on alternatives available for individual patients.
  - This agrees with findings with imatinib suggesting that continued treatment or rechallenge with a TKI in patients with GIST is beneficial.[2,3]

REFERENCES

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