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

INTRODUCTION

Sunitinib malate (SUFTEN™), an oral multikinase tyrrosine kinase inhibitor (TKI), is approved marketed worldwide 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 2006 – December 2007) provided access to sunitinib to patients with advanced imatinib-resistant/intolerant GIST who may have benefited from it, but were ineligible for advanced clinical studies, or were in a country in which regulatory approval had not yet been granted and in which no sunitinib clinical 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.

Continuous kinase inhibition has been postulated as being 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 therapy 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)
- historically 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
- eligibility for participation in ongoing sunitinib clinical studies
- potential to derive clinical benefit from treatment with sunitinib (investigator’s judgment)
- resolution of all grade 1 effects of any prior therapy/surgery to grade 1
- adequate organ function.

Exclusion criteria included:

- participation in any other concurrent therapeutic 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 daily 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 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 analysis were planned.

All continuous data were summarized using descriptive statistics (mean, standard deviation, median, minimum, 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 data cut-off (October 2011), 1124 of 1131 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 those who continued sunitinib treatment after PD.
  - Patients generally received sunitinib longer than those who stopped treatment after PD.

Drug Exposure

- Exposure to sunitinib is summarized in Table 2.
  - Patients who continued on sunitinib after PD did so for a median of 4.7 months after PD.

Study Table 1: Baseline patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N=1,124)</th>
<th>Sunitinib continued after PD (n=380)</th>
<th>Sunitinib stopped after PD (n=324)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>65 (33, 89)</td>
<td>65 (33, 89)</td>
<td>65 (33, 89)</td>
</tr>
<tr>
<td>Sex, %</td>
<td>59 (52, 65)</td>
<td>59 (52, 65)</td>
<td>59 (52, 65)</td>
</tr>
<tr>
<td>Median</td>
<td>59</td>
<td>59</td>
<td>59</td>
</tr>
<tr>
<td>Female</td>
<td>57 (26, 80)</td>
<td>57 (26, 80)</td>
<td>57 (26, 80)</td>
</tr>
<tr>
<td>Male</td>
<td>65 (35, 65)</td>
<td>65 (35, 65)</td>
<td>65 (35, 65)</td>
</tr>
<tr>
<td>Time on treatment, months</td>
<td>22.8</td>
<td>22.8</td>
<td>13.2</td>
</tr>
<tr>
<td>Overall Survival</td>
<td>14.5</td>
<td>14.5</td>
<td>14.5</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>No. of treatment cycles started</th>
<th>Median</th>
<th>Range</th>
<th>No. of treatment cycles started</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>0–50</td>
<td></td>
<td>1</td>
<td>0–50</td>
</tr>
<tr>
<td>Time on sunitinib, months</td>
<td>22.8</td>
<td>11.7–24.7</td>
<td>13.2</td>
<td>13.2</td>
<td>11.7–14.5</td>
</tr>
</tbody>
</table>

- 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 treatment after PD than among those who stopped treatment after PD.

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).

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 available alternatives for individual patients.
- This agrees with findings with imatinib suggesting that continued treatment or rechallenge with a TKI in patients with GIST is beneficial.

REFERENCES