Table 5 Change from baseline of soluble protein concentrations (cycle 4, day 28) versus tumor response[a]

Soluble protein	Percent change from baseline, median (minimum, maximum)				
	PR (n=4)	SD ≥22 weeks (n=9)	Clinical benefit[b] (n=13)	SD <22 weeks + PD (n=18)	p value[c]
VEGF	365 (142, 473)	449 (49, 889)	385 (49, 889)	351 (52, 814)	0.459
sVEGFR-2	−51 (−65, −32)	−53 (−66, −20)	−53 (−66, −20)	−42 (−69, −4)	0.484
sKIT	−52 (−76, −46)	−12 (−46, 59)	−24 (−76, 59)	2 (−66, 386)	0.238

PR partial response, *PD* progressive disease, *SD* stable disease, *sKIT* soluble KIT, *sVEGFR-2* soluble VEGF receptor-2, *VEGF* vascular endothelial growth factor

[a] Last observation carried forward

[b] Clinical benefit, PR + SD ≥22 weeks

[c] Clinical benefit versus SD <22 weeks + PD, Wilcoxon rank-sum test

mild to moderate in severity; were manageable and reversible through dosing interruption, dose modification, and/or standard medical treatments; and seldom led to treatment withdrawal. Only two patients (6%) discontinued treatment due to an adverse event, consistent with previous reports of low treatment discontinuation rates due to adverse events with sunitinib therapy [14]. On the other hand, serious adverse events were reported in 25% of patients. Although these events did not result in discontinuations, this result suggests that patients should be monitored carefully. Overall, however, the safety profile observed in this study was similar to that reported in the phase III study, with fatigue and skin and gastrointestinal disorders representing the most frequent adverse events [14]. Moreover, no new adverse events were reported in this study compared with previous studies.

The pharmacokinetic results obtained in the present study were also consistent with those obtained in previous studies. In the phase I part of the study, exposure to sunitinib 50 mg on Schedule 4/2 was similar to that reported in a study of sunitinib in Western patients with various types of solid tumors [19] on day 1 (C_{max}: 22.8 versus 27.7 ng/ml; AUC_{0-24}: 374 versus 420 ng·h/ml), and day 28 (C_{max}: 69.3 versus 72.2 ng/ml; AUC_{0-24}: 1,406 versus 1,296 ng·h/ml). On the other hand, SU12662 exposure was somewhat higher in the current study than in the earlier one on day 1 (C_{max}: 4.1 versus 4.1 ng/ml; AUC_{0-24}: 70 versus 64 ng·h/ml) and day 28 (C_{max}: 38.8 versus 33.7 ng/ml; AUC_{0-24}: 772 versus 592 ng·h/ml). However, SU12662 comprised only 23–37% of total drug on day 28, resulting in total-drug exposures calculated to be approximately 15% higher in the current study, which is well within the range of exposures seen in Western patients. Median trough plasma drug concentrations obtained in the 50-mg cohort in the phase II part of the current study were above the preclinically determined effective plasma concentration of 50 ng/ml [10] throughout dosing and similar to those obtained in the phase III GIST study [14] (total drug: 62.4–84.9 versus 64.8–86.3 ng/ml, respectively). As in the phase III study, repeated dosing did not result in accumulation of sunitinib across several cycles of treatment. Taken together, these results suggest that sunitinib pharmacokinetics are comparable in Asian and Western GIST patients, consistent with the results of other analyses [22,23], and that sunitinib may be dosed similarly in both populations. Additionally, as shown in the phase I part of the study, there was a close correlation (r^2=0.80~0.90) between trough concentrations of sunitinib and SU12662 and AUC_{0-24} and C_{max} values at steady state, suggesting that trough concentration may be a useful marker of exposure.

Greater antiangiogenic effects as well as continued sensitivity of some imatinib-resistant KIT mutants have been postulated as possible explanations for sunitinib activity in GISTs resistant to imatinib. In-vitro studies using KIT constructs have demonstrated that sunitinib is capable of inhibiting the kinase activity of KIT mutants resistant to imatinib, including those commonly associated with secondary resistance [24–26]. Although patient numbers were small, a trend towards sustained decreases in plasma sKIT with sunitinib treatment was found in the current study, which correlated with improved outcomes (particularly objective responses). However, how these changes relate to antiangiogenic effects versus direct actions on mutant KIT receptors is not known. That the largest decreases were observed in patients with objective responses suggests that tumor cell loss may contribute to the decreases, although this could result from either antiangiogenic or direct antitumor effects. A correlation between decreased plasma levels of sKIT and sunitinib activity has also been reported among GIST patients who participated in the phase III trial [27], as well as in patients with metastatic breast cancer [28]. Likewise, a correlation between plasma sKIT decreases and response to imatinib in GIST has also been reported [29]. However, more work needs to be done to validate biomarkers that may be used to predict GIST response to sunitinib or other tyrosine kinase inhibitors.

In summary, the results from the present study suggest that Japanese GIST patients obtain comparable benefit from

sunitinib after failure of imatinib as did patients in the international phase III study. In addition, the results indicate that sunitinib may be dosed similarly in Asian and Western patients, and that adverse events can generally be managed by dosing interruptions, dose modifications, and/or the use of standard medical treatments. Although the present study was small and requires verification in larger controlled trials, these results provide guidance to clinicians treating Asian GIST patients after imatinib failure due to disease progression or intolerance.

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