Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial

George D Demetri, Allan T van Oosterom, Christopher R Garrett, Martin E Blackstein, Manisha H Shah, Jaap Verweij, Grant McArthur, Ian R Judson, Michael C Heinrich, Jeffrey A Morgan, Jayesh Desai, Christopher D Fletcher, Suzanne George, Carlo L Bello, Xin Huang, Charles M Baum, Paolo G Casali

Summary

Background **No effective therapeutic options for patients with unresectable imatinib-resistant gastrointestinal stromal tumour are available. We did a randomised, double-blind, placebo-controlled, multicentre, international trial to assess tolerability and anticancer efficacy of sunitinib, a multitargeted tyrosine kinase inhibitor, in patients with advanced gastrointestinal stromal tumour who were resistant to or intolerant of previous treatment with imatinib.**

Methods **Blinded sunitinib or placebo was given orally once daily at a 50-mg starting dose in 6-week cycles with 4 weeks on and 2 weeks off treatment. The primary endpoint was time to tumour progression. Intention-to-treat, modified intention-to-treat, and per-protocol analyses were done. This study is registered at ClinicalTrials.gov, number NCT00075218.**

Findings **312 patients were randomised in a 2:1 ratio to receive sunitinib (n=207) or placebo (n=105); the trial was unblinded early when a planned interim analysis showed significantly longer time to tumour progression with sunitinib. Median time to tumour progression was 27·3 weeks (95% CI 16·0–32·1) in patients receiving sunitinib and 6·4 weeks (4·4–10·0) in those on placebo (hazard ratio 0·33; p<0·0001). Therapy was reasonably well tolerated; the most common treatment-related adverse events were fatigue, diarrhoea, skin discolouration, and nausea.**

Interpretation **We noted significant clinical benefit, including disease control and superior survival, with sunitinib compared with placebo in patients with advanced gastrointestinal stromal tumour after failure and discontinuation of imatinab. Tolerability was acceptable.**

Introduction

Gastrointestinal stromal tumours are a form of sarcoma and the most common mesenchymal tumour of the gastrointestinal tract, distinguishable from other soft-tissue neoplasms by histology and immunohistochemistry.[1] The tumour probably arises from mutations in precursor cells that normally give rise to the interstitial cells of Cajal. Like these cells, most gastrointestinal stromal tumours express the protein product of the *KIT* proto-oncogene, a transmembrane receptor tyrosine kinase for which activity would normally be regulated by binding of its ligand. A subset of these tumours are overtly malignant, and greater than 40% are thought to be metastatic.[1–4] About 85–90% of gastrointestinal stromal tumours are associated with gain-of-function *KIT* gene mutations that lead to constitutive activation of KIT kinase activity.[5–7] A much smaller proportion (5%) are associated with analogous gain-of-function mutations in *PDGFRA*, the gene encoding platelet-derived growth factor receptor α (PDGFRα); less than 10% contain no identified receptor tyrosine kinase mutations.[5–7] Activating mutations of *KIT* and *PDGFRA* have been defined as the driving force behind development and maintenance of the malignant phenotype in most cases of gastrointestinal stromal tumours.

Understanding the molecular pathophysiology of this condition has allowed rational development of agents that target these signalling aberrations in the cancer cell. Traditional cytotoxic treatment is ineffective.[8,9] Imatinib mesylate, a selective inhibitor of the kinase activities of KIT and PDGFR, has substantially improved clinical outcomes for patients with advanced disease.[10–12] However, in a pivotal study of imatinib in advanced gastrointestinal stromal tumour, 5% of patients showed primary resistance to imatinib and another 14% developed early resistance.[11] Secondary or acquired resistance develops after a median of about 2 years of treatment with the drug.[12] Such resistance can develop through various mechanisms, the most common being secondary KIT mutations in clonally expanded cancer cells.[13–15] Since its approval in 2002, imatinib has been the only effective treatment for advanced gastrointestinal stromal tumour. Effective alternative treatments for use after failure of imatinib therapy were therefore an important unmet medical need justifying the development of alternative agents.

Sunitinib malate (SUTENT, previously known as SU11248; Pfizer, New York, USA) is an oral multitargeted receptor tyrosine kinase inhibitor that has shown antiangiogenic and antitumour activities in several in-vitro and in-vivo tumour models.[16–21] These effects were associated with the blockade of receptor tyrosine kinase

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Ludwig Center at Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA 02115, USA (G D Demetri MD, J A Morgan MD, J Desai MD, S George MD); **Department of General Medical Oncology, Leuven Cancer Institute, University Hospital Gasthuisberg, Catholic University Leuven, Leuven, Belgium** (Prof A T van Oosterom MD); **H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA** (C R Garrett MD); **Mount Sinai and Princess Margaret Hospitals and the University of Toronto, Toronto, ON, Canada** (M E Blackstein MD); **Ohio State University Comprehensive Cancer Center, Columbus, OH, USA** (M H Shah MD); **Erasmus University Medical Center, Rotterdam, The Netherlands** (Prof J Verweij MD); **Peter MacCallum Cancer Centre and Department of Medicine, St Vincent's Hospital, University of Melbourne, Australia** (G McArthur MD); **Royal Marsden Hospital, Sutton, UK** (Prof I R Judson MD); **Oregon Health and Science University Cancer Institute and Portland VA Medical Center, Portland, OR, USA** (Prof M C Heinrich MD); **Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA** (Prof C D Fletcher MD); **Pfizer Global Research and Development, La Jolla, CA, USA** (C L Bello MSc, X Huang PhD, C M Baum MD); **and Istituto Nazionale Tumori, Milan, Italy** (P G Casali MD)

Correspondence to: Dr George D Demetri **gdemetri@partners.org**

signalling by KIT, PDGFRs, all three isoforms of the vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2, VEGFR-3), Fms-like tyrosine kinase-3 receptor (FLT3), and the receptor encoded by the ret proto-oncogene (RET;[16–21] and unpublished data, Pfizer, 2006). Although both sunitinib and imatinib bind within the ATP-binding domain of both KIT and PDGFRs, they are members of different chemical classes and presumably have different binding characteristics and affinities. Additionally, sunitinib inhibits the VEGFR kinases, which are important in tumour-related angiogenesis, a property not shared by imatinib. Because of these differences, we postulated that sunitinib might yield clinical benefit in patients with gastrointestinal stromal tumour who were resistant to imatinib. Results from a phase I/II study[22] showed that sunitinib induced promising clinical activity in patients with imatinib-resistant disease, although rates of tumour regression (and therefore, the rates of objective anti-tumour response) were low, despite a clinically significant rate of stable disease. Additionally, no second-line treatments have proven efficacy after failure of imatinib therapy. Therefore, a prospective, placebo-controlled, randomised clinical trial, with a crossover option available for patients assigned initially to placebo, was designed to test the clinical worth of sunitinib. The objectives were to assess the efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure and withdrawal of imatinib because of resistance or intolerance.

Methods

Patients and study design

Patients were eligible if they had histologically proven malignant gastrointestinal stromal tumour that was not amenable to surgery, radiation, or a combination of different approaches with curative intent, and confirmed objective failure of previous imatinib therapy. Criteria for inclusion were evidence of disease that was unidimensionally measurable with CT or MRI; failure of treatment with imatinib—based either on progression of disease (according to Response Evaluation Criteria in Solid Tumours [RECIST][23] or WHO criteria[24]) or on unacceptably severe toxic effects during imatinib therapy that precluded further treatment; imatinib last administered at least 2 weeks before randomisation; resolution of all toxic effects of imatinib or other therapy to grade 1 or less; adequate hepatic, renal, and cardiac function; absolute neutrophil count of at least 1500 per µL; platelet count of at least 100 000 per µL; haemoglobin concentration of 90 g/L or greater; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The study was approved by the institutional review board of each participating institution, and written informed consent was obtained from all participants.

This study was a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase III clinical trial. Patients were randomised in a 2:1 ratio to receive blinded study drug (sunitinib or placebo) daily for 4 consecutive weeks followed by a 2-week period without treatment, comprising a 6-week cycle. Sunitinib was given at a starting daily dose of 50 mg. Study drugs were given orally in the morning with water and without regard to meals beginning on day 1 of the study. All patients received best supportive care in addition to blinded study drug.

Randomisation was done centrally with an interactive voice response system. The clinical site staff provided patient identifiers, demographic information, and stratification variables. The centralised randomisation system assigned unique numbers to each patient and provided treatment group information. Patients were stratified by best outcome of previous imatinib treatment (disease progression within 6 months *vs* disease progression beyond 6 months of treatment initiation or intolerance to imatinib) and baseline McGill Pain Questionnaire score (0 *vs* 1 or more).[25]

At the time of documented RECIST-defined disease progression during trial participation, treatment assignments were unblinded, and patients found to be receiving sunitinib were given the opportunity to continue treatment at the investigator's discretion. Patients who were receiving placebo were given the opportunity to cross over to open-label sunitinib treatment, provided they met eligibility criteria (evidence of RECIST-defined disease progression and ECOG performance status 0–2). Dose reductions of sunitinib were required in the case of clinically relevant grade 3 or 4 toxic effects (to 37·5 mg per day and, if additional reduction was warranted, to 25 mg per day), provided criteria for withdrawal from study drug were not met. Available daily doses of sunitinib consisted of one 50-mg capsule (starting dose), three 12·5-mg capsules (37·5-mg dose), or one 25-mg capsule. Doses of placebo were matched for capsule size, number, and colour. Intrapatient dose escalation to a previous dose level was permitted at the discretion of the investigator.

Procedures

Measurement of efficacy was based on objective tumour assessments made using RECIST,[23] with a minor modification to allow use of standard radiographic protocols for spiral CT. Tumour imaging was done at least at baseline screening, on day 28 of all treatment cycles, and at the end of treatment, but could be done more frequently. An independent third-party radiology laboratory reviewed selected imaging studies to verify entry criteria and all imaging assessments done during the period of treatment with study medication plus 28 days after the last dose of study medication, to ensure consistent unbiased application of RECIST principles. The central radiology laboratory was blinded to treatment assignment when reviewing scans.

The primary endpoint was time to tumour progression as defined using RECIST. Secondary endpoints included

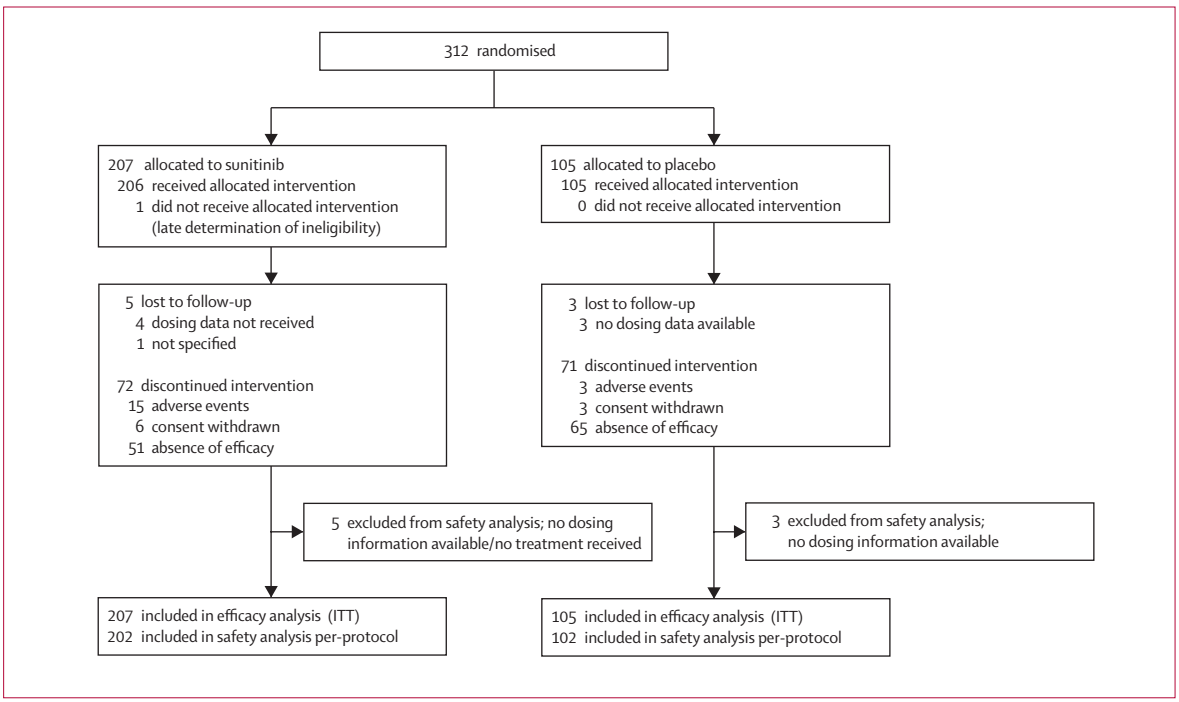


Figure 1: **Trial profile**

progression-free survival, overall survival, overall confirmed objective response rate, time to tumour response, duration of response, and duration of performance status maintenance (time from date of randomisation to the last time the performance status was no worse than at baseline or to death from cancer).

Safety and tolerability were assessed by analysis of adverse events, physical examinations, vital signs, ECOG performance status, and laboratory-abnormality assessments (eg, complete blood count with differential count, serum electrolyte measurements, and electrocardiogram). Cardiac function was assessed at screening, day 28 of all treatment cycles, and treatment end with 12-lead electrocardiogram and multigated acquisition scans. Severity of adverse events was rated by investigators by use of the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.[27]

Blood samples for measurement of trough concentrations of sunitinib, its active metabolite (SU12662), and total drug (sunitinib plus SU12662) were obtained predose on days 1, 14, and 28 of treatment cycle 1; on days 1 and 28 of subsequent cycles; and at end of treatment. Concentrations were measured using a validated, sensitive, and specific isocratic liquid-chromatographic tandem-mass-spectrometric method in positive-ionisation mode.[28]

Statistical design and data analysis

When the study was designed (2002–03), little objective data had been published about the expected clinical course of patients with disease progression despite the introduction of the only effective available therapy, imatinib, into routine clinical practice in 2002. Therefore, an informal survey was done among approximately 25 experts worldwide who regularly used imatinib to treat advanced gastrointestinal stromal tumour. The time to tumour progression after imatinib failure was generally reported to be less than 4 months. A 50% improvement (hazard ratio [HR] 0·67) in median time to tumour progression from 4 months to 6 months in patients randomised to receive sunitinib was judged to be clinically meaningful by the investigators designing the study. 281 patients with disease progression were estimated to be needed to detect such an improvement using a two-sided, unstratified log-rank test with an overall significance level of 0·05 and power of 0·90. We estimated that 357 patients (238 sunitinib, 119 placebo) would need to be enrolled to observe 281 patients with progressive disease by the end of the minimum follow-up period. Analysed study populations included intention-to-treat (ITT; all patients randomised to treatment), modified ITT (all ITT patients with disease progression on imatinib confirmed by central radiology laboratory), and per-protocol (all patients who received at least one dose of assigned study treatment). ITT data are presented for efficacy and per-protocol data for safety; modified ITT data are discussed where relevant. Protocol-defined interim analyses of efficacy and safety were planned after 141 and 211 patients had documented progressive disease. The nominal levels of significance for the interim analyses were determined using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary.[28]

Time to tumour progression in each group was assessed using Kaplan-Meier methods and compared with the log-rank test (primary efficacy analysis). A stratified log-rank test and Cox regression models were used to explore the potential effects of the stratification factors and patients' baseline characteristics on the primary endpoint (primary efficacy sub-analyses). Other time-to-event data, including progression-free survival and overall survival, were assessed with Kaplan-Meier methods and log-rank tests. The proportion of patients who achieved an objective tumour response was calculated for each arm and compared by means of a χ^2 test.

	Sunitinib (n=207)	Placebo (n=105)
Age (years)		
Median	58·0	55·0
Range	23–84	23–81
Sex		
Male	132 (63·8%)	64 (61·0%)
Female	75 (36·2%)	41 (39·0%)
ECOG status		
0	92 (44·4%)	48 (45·7%)
1	113 (54·6%)	55 (52·4%)
2*	2 (1·0%)	2 (1·9%)
GIST histology		
Spindle cell	125 (60·4%)	74 (70·5%)
Mixed spindle+epithelioid	33 (15·9%)	13 (12·4%)
Epithelioid	17 (8·2%)	7 (6·7%)
Other	31 (15·0%)	10 (9·5%)
Missing	1 (0·5%)	1 (1·0%)
Tumour burden at baseline (mm)		
Median	233	239
Range	26–722	29–749
Maximum dose of imatinib therapy (mg)		
Median	800	800
Range	300–1600	400–1600
Duration of imatinib therapy (weeks)		
Median	105·3	106·9
Range	0·3–205·1†	11·4–187·7
Imatinib therapy outcome		
Progression within 6 months	36 (17·4%)	17 (16·2%)
Progression after >6 months	162 (78·3%)	84 (80·0%)
Intolerance‡	9 (4·3%)	4 (3·8%)
Best response to imatinib		
Complete response	6 (2·9%)	1 (1·0%)
Partial response	51 (24·6%)	36 (34·3%)
Stable disease	87 (42·0%)	36 (34·3%)
Progressive disease	58 (28·0%)	30 (28·6%)
Not applicable or missing	5 (2·4%)	2 (1·9%)

Data are number (%) unless otherwise stated. *Patients with ECOG performance status 2 at baseline were eligible for study with status <2 at earlier screening assessment. †Lower limit represents incomplete dosing information for one patient. ‡In the event of both disease progression and drug intolerance during imatinib therapy, disease progression was regarded as the dominant entry criterion.

Table 1: **Baseline characteristics and disease and treatment history (ITT population)**

This study was registered with ClinicalTrials.gov with the identifier NCT00075218.

Role of the funding source

The study was designed by G D Demetri in collaboration with colleagues at Pfizer, and all logistical aspects of this international study were managed by Pfizer. Data were collected by Pfizer and analysed by G D Demetri as principal investigator of the trial in collaboration with Pfizer and the global team of academic investigators. All authors had full access to all the data and vouch for the accuracy and completeness of the data presentation and analysis. The authors had final responsibility to submit for publication.

Results

Patients

Between December, 2003, and January, 2005, 312 patients were enrolled from 56 centres in 11 countries and were randomised to receive blinded sunitinib (n=207) or placebo (n=105). Figure 1 shows the trial profile. Baseline characteristics and history of disease and treatment are summarised in table 1. All characteristics were well balanced between the groups. The most common metastatic sites were the liver, peritoneum, and mesentery. The sunitinib and placebo groups were also similar in terms of median maximum dose, median daily dose (503 mg *vs* 485 mg), and median cumulative dose (367 400 mg *vs* 376 400 mg) of previous imatinib therapy, as well as in other aspects of treatment history.

The trial was unblinded early (January, 2005) when the planned interim analysis done after the first 149 cases of RECIST-defined disease progression or death showed significantly longer time to tumour progression in patients initially treated with sunitinib than in those on placebo. Treatment was unblinded at the recommendation of the Independent Data and Safety Monitoring Board, and all patients were allowed to cross over to open-label sunitinib. At the time of data cutoff for the interim analysis, dosing information was available for 202 of the 207 patients in the sunitinib group and for 102 of the 105 in the placebo group. Of the patients originally enrolled, 134 (65%) on sunitinib and 34 (32%) on placebo were continuing to receive double-blind treatment at the time of data cut-off; 19 (9%) and 59 (56%), respectively had crossed over to open-label treatment after radiographically documented progression. 72 (35%) patients on sunitinib and 71 patients (68%) on placebo discontinued double-blind treatment; the most frequent reasons for discontinuation were disease progression and adverse events (figure 1).

At the time of unblinding, the median number of treatment cycles was two (range zero to nine) in the sunitinib group and one (zero to six) in the placebo group, and median numbers of days on drug were 56·0 (range 1–236) and 29·5 (2–168), respectively. Dose reductions were needed in 23 (11%) patients receiving

sunitinib, but not in any patients receiving placebo; interruptions of study drug dosing occurred in 57 (28%) sunitinib patients and 20 (20%) placebo patients.

Median trough concentrations of drug in plasma ranged from 45·8 to 57·7 ng/mL for sunitinib, 17·3 to 27·3 ng/mL for the active metabolite SU12662, and 64·8 to 86·3 ng/mL for total drug (sunitinib plus SU12662), on day 14 or 28 of cycles 1–6. The median concentrations met or exceeded the pre-clinically established therapeutic concentration of at least 50 ng total drug per mL. Although trough concentrations were not measured frequently enough to assess steady state in any cycle, median trough concentrations on days 14 and 28 of the first cycle suggested that steady-state conditions were probably achieved by day 14 for sunitinib, SU12662, and total drug. Median concentrations on day 28 in subsequent cycles were similar to those in the first cycle at apparent steady state, indicating that no accumulation occurred over several cycles.

Median time to tumour progression for the ITT population, the primary study endpoint, was more than four times as long with sunitinib (27·3 weeks, 95% CI 16·0–32·1) as with placebo treatment (6·4 weeks 4·4–10·0; HR 0·33, 95% CI 0·23–0·47; p<0·0001) on the basis of central radiology laboratory assessment (figure 2). A clear difference between the treatment groups was noted around week 4. The greater time to tumour progression obtained with sunitinib compared with placebo was confirmed by the stratified analysis when controlling for stratification factors (HR 0·32, 95% CI 0·22–0·46; p<0·0001). The effect of baseline factors on the treatment effect was further analysed using a Cox proportional hazards model (figure 3). For all subgroups, the HR was less than 0·5, indicating that all subgroups analysed benefited from sunitinib therapy compared with placebo. The benefits of sunitinib on disease control as measured by time to tumour progression were observed irrespective of age, weight, race, pain score, performance status, time since initial diagnosis, duration or dose of initial imatinib treatment, or study location. The treatment effect was significant in the entire study population and in the subgroups defined by baseline factors, irrespective of whether the modified ITT or per-protocol populations were analysed, or whether investigator assessments or central radiology assessments were used (data not shown).

The results of the other efficacy analyses were uniformly statistically and clinically significant and lent support to the findings of the primary endpoint analysis. The duration of progression-free survival was similar to that of time-to-tumour progression (median 24·1 weeks [95% CI 11·1–28·3] for sunitinib, 6·0 weeks [4·4–9·9] placebo, respectively; HR 0·33; 95% CI, 0·24–0·47; p<0·0001). In the sunitinib group, 16% (33) of patients were progression-free for at least 26 weeks, compared with 1% (one) in the placebo group (26 weeks [about 6 months] was pre-defined as a point that most clinicians would agree to be clinically meaningful). Despite the availability of the option to cross over, overall survival obtained with initial sunitinib treatment was better that that obtained with placebo (figure 4; HR 0·49, 95% CI 0·29–0·83; p=0·007), although since more than half the

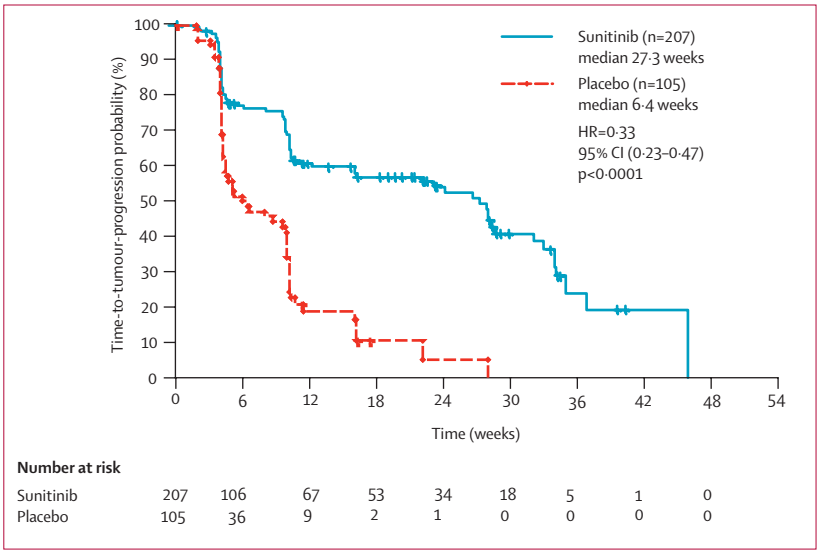


Figure 2: **Kaplan-Meier estimates of time to tumour progression**
Results represent central radiology assessment of ITT population.

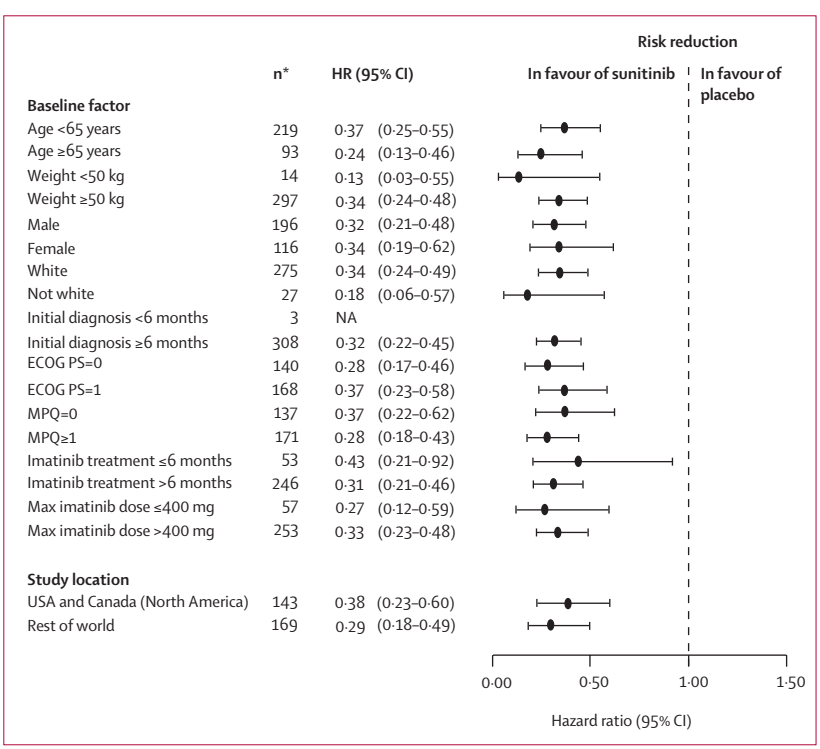
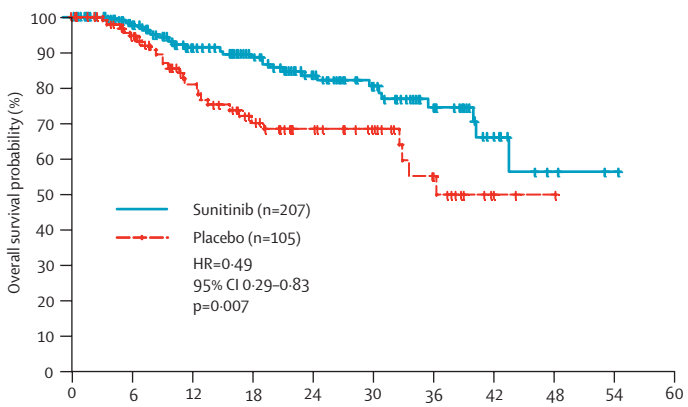


Figure 3: **Cox proportional hazards analysis of time-to-tumour progression treatment comparisons controlling for individual baseline factors**
NA=not applicable. PS=performance status. Max=maximum. MPQ=McGill Pain Questionnaire. *All pairs of baseline factors listed (except ECOG PS; see table 1) encompass entire population (n=312); pairs of n values yielding total <312 are due to unavailability of specific information for all patients.



Number at risk

Sunitinib	207	167	117	97	71	50	31	11	3	1	0
Placebo	105	85	57	43	31	22	13	3	1	0	0

Figure 4: **Kaplan-Meier estimates of overall survival**
Results represent central radiology assessment of ITT population and include open-label treatment subsequent to crossover after progression.

	Sunitinib (n=202)			Placebo (n=102)		
	Grade 1/2	Grade 3	Grade 4	Grade 1/2	Grade 3	Grade 4
Non-haematological*						
Fatigue	58 (29%)	10 (5%)	0 (0%)	20 (20%)	2 (2%)	0 (0%)
Diarrhoea	52 (26%)	7 (3%)	0 (0%)	8 (8%)	0 (0%)	0 (0%)
Skin discolouration	50 (25%)	0 (0%)	0 (0%)	6 (6%)	0 (0%)	0 (0%)
Nausea	47 (23%)	1 (1%)	0 (0%)	10 (10%)	1 (1%)	0 (0%)
Anorexia	38 (19%)	0 (0%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Dysgeusia	36 (18%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Stomatitis	30 (15%)	1 (1%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Vomiting	30 (15%)	1 (1%)	0 (0%)	5 (5%)	1 (1%)	0 (0%)
Hand-foot syndrome	19 (9%)	9 (4%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Rash	24 (12%)	2 (1%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Asthenia	18 (9%)	6 (3%)	0 (0%)	2 (2%)	2 (2%)	0 (0%)
Mucosal inflammation	24 (12%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Dyspepsia	22 (11%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Hypertension	15 (8%)	6 (3%)	0 (0%)	4 (4%)	0 (0%)	0 (0%)
Epistaxis	14 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hair-colour changes	14 (7%)	0 (0%)	0 (0%)	2 (2%)	0 (0%)	0 (0%)
Dry mouth	13 (6%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Glossodynia	11 (6%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Haematological						
Anaemia†	117 (58%)	7 (4%)	0 (0%)	59 (58%)	2 (2%)	0 (0%)
Leucopenia	104 (52%)	7 (4%)	0 (0%)	5 (5%)	0 (0%)	0 (0%)
Neutropenia	86 (43%)	17 (8%)	3 (2%)	4 (4%)	0 (0%)	0 (0%)
Lymphopenia	80 (40%)	18 (9%)	1 (1%)	31 (30%)	2 (2%)	1 (1%)
Thrombocytopenia	72 (36%)	8 (4%)	1 (1%)	4 (4%)	0 (0%)	0 (0%)

Data are number (%). *Treatment-related. †Anaemia was included in the table, despite a difference of less than 5% between the treatment groups, because of its frequency and clinical relevance in GIST.

Table 2: **Adverse events that occurred with a frequency of at least 5% greater on sunitinib than on placebo in per-protocol population**

patients in the sunitinib group were still alive at the time of the interim analysis, a median overall survival value could not be calculated. In terms of best overall objective tumour response for the ITT population, 7% (14) of patients in the sunitinib group showed partial response as the best response, 58% (120) had stable disease, and 19% (39) had progressive disease, compared with rates of 0%, 48% (50), and 37% (39), respectively, in the placebo group. Although relatively low, the confirmed objective response rate was significantly higher in the sunitinib than in the placebo group (7% [14] *vs* 0%; 95% CI 3·7–11·1%; p=0·006). The objective response rate with sunitinib was similar among patients who entered the study after disease progression on imatinib (ten of 198, 5·1%) to that obtained for all patients in the sunitinib group. Six of 59 patients who crossed over to sunitinib from the placebo group also had confirmed partial responses (10·2%, 95% CI 3·8–20·8). Four patients (7% overall) who crossed over to sunitinib from placebo had stable disease for at least 26 weeks after crossover.

The median time to tumour response on sunitinib was 10·4 weeks (95% CI 9·7–16·1 weeks). Of the 14 patients on sunitinib who had a confirmed response, only three had shown subsequent progression at the time of the interim analysis, so duration of response could not be reliably estimated. However, the observed duration of response for these three patients was 15·9–29·9 weeks.

13 patients enrolled in the study were classified as intolerant to imatinib, with nine randomised to receive sunitinib and four to receive placebo. Four of the nine patients in the sunitinib group achieved a partial response, and only one showed progressive disease at the time of analysis. Of the four imatinib-intolerant patients who were randomised to receive placebo, none had a partial response, and three showed progressive disease. Although the numbers were small, the objective response rate seemed to be better in patients who were intolerant of imatinib than in those who were resistant to imatinib.

At the time of data cutoff, treatment-related adverse events of any severity grade were reported in 168 (83%) of sunitinib-treated and 60 (59%) of placebo-treated patients, and serious treatment-related adverse events were reported in 40 (20%) and five (5%) patients in each group, respectively. Adverse events for which a greater incidence was noted in patients on sunitinib than in patients on placebo during double-blinded treatment are summarised in table 2 by maximum grade. Adverse events were generally mild to moderate in intensity and easily managed by dose reduction, dose interruption, or standard supportive medical treatments. 19 (9%) patients in the sunitinib group and eight (8%) in the placebo groups discontinued treatment because of adverse events.

Overall numbers of events of any grade for the most common treatment-related adverse event, fatigue, were 68 (34%) for sunitinib and 22 (22%) for placebo. The incidence of grade 3 fatigue was similar between the

treatment groups; there were no cases of grade 4 fatigue. Other serious treatment-related non-haematological adverse events that seemed to be experienced more frequently on sunitinib treatment included hand-foot syndrome, diarrhoea, and hypertension; serious haematological adverse events also seemed to be more frequent with sunitinib than with placebo (table 2).

We noted no evidence of a systematic mean decrease in left ventricular ejection fraction in either treatment group, and no patients were reported to have had clinical evidence of congestive heart failure or pancreatitis. Eight (4%) sunitinib-treated patients developed hypothyroidism, including one grade 4 case, and one patient on placebo had a grade 1 case. Patients who were intolerant to imatinib on study entry tolerated sunitinib without recurrence of the toxic effects that they had previously experienced on imatinib.

Discussion

Time to tumour progression, progression-free survival, overall survival, and other measures of tumour response were significantly greater in patients treated with sunitinib than in those in the placebo group in a population with advanced gastrointestinal stromal tumour in which treatment with another tyrosine kinase inhibitor had failed. Median time to tumour progression with sunitinib was more than four times greater than with placebo, reducing the relative risk of progression or death by 67% and the relative risk of death by 51%. Since the overall survival analysis included patients who had crossed over from placebo to sunitinib because of disease progression, and these patients were still considered part of the placebo group, the difference observed between the treatment groups might have been reduced for this measure. However, although disease control and survival were better in the sunitinib group than in the placebo group, objective tumour shrinkage measured on the basis of RECIST was not common.

Although a few patients who received sunitinib were characterised as having achieved objective responses, stable disease was the best overall tumour response in 58%, including 17% of patients who had stable disease for at least 22 weeks. Defining clinical benefit as objective tumour response plus stable disease for at least 22 weeks, the rate of clinical benefit of 24·2% in sunitinib-treated patients suggests that this treatment is associated with clinically meaningful tumour control in patients with gastrointestinal stromal tumour after imatinib failure. The clinical benefits of sunitinib were noted in patients in whom treatment with maximum doses of imatinib had failed. A suggested strategy for management of imatinib resistance is to increase the dose to 800 mg daily (which was the median maximum dose received in both groups in this study),[29] but the median time of benefit with such a dose increase is relatively short—estimated at 11·6 weeks.[30] We noted no effect of the maximum previous dose of imatinib on the clinical effectiveness of sunitinib in the sensitivity testing of subsets, although this was a post-hoc subset analysis done for hypothesis generation. The results of the current study suggest an alternative strategy of switching from lower-dose imatinib directly to multitargeted kinase inhibition therapy with sunitinib. Further research is needed to clarify which treatment algorithms will lead to the best clinical outcomes.

The rigorous design of this large randomised, placebo-controlled, multicentre study contributed to the robustness of the results obtained, while the crossover design allowed all patients the opportunity to benefit from access to this active treatment. The choice of placebo control was reasonable when the trial was designed, since imatinib had previously failed to control the disease of all eligible patients. Subsequent preliminary data suggest that discontinuation of imatinib in patients with gastrointestinal stromal tumour increases risk of disease progression and is associated with accelerated disease progression in some patients,[31] although the magnitude of this effect has not been studied in patients after progression on imatinib. With this perspective, continuing imatinib despite progression might have served as an alternative approach for the control group, for reasons of patients' wellbeing and because discontinuation of imatinib therapy might not represent the most current standard of palliative care. In the absence of a trial directly comparing sunitinib with continuing imatinib treatment after imatinib failure, no definitive conclusion about the superiority of switching to sunitinib can be reached. However, progression-free survival obtained with sunitinib in this study (24·6 weeks) compared favourably with the overall benefits reported with dose escalation of imatinib (11·6 weeks).[30] Additionally, the robustness of our findings suggests that sunitinib is highly active in this population.

Overall, sunitinib dosing for the period reported here resulted in acceptable tolerability. Adverse events associated with sunitinib seldom led to treatment discontinuation and were generally easily managed and reversible through dose reduction, dose interruption, or standard supportive medical treatment. Although we noted higher rates of adverse events with sunitinib than with placebo, patients on sunitinib had a longer exposure to study drug and therefore more opportunity to experience adverse events. Fatigue was the most common adverse event reported by patients treated with sunitinib in this trial, but the incidence of grade 3 or 4 fatigue was similar between the sunitinib and placebo groups, supporting the hypothesis that a large proportion of fatigue in this population might be attributed to the burden of advanced gastrointestinal stromal tumour. Although the incidence of hypothyroidism was low, it might be expected to increase with longer follow-up. Previous findings in patients with the disease suggested that long-term sunitinib therapy was associated with a risk of hypothyroidism, and clinicians should be aware of this risk, which can be managed by thyroid hormone

replacement.[32] Serious treatment-related hypertension was reported in 3% of sunitinib-treated patients, and the incidence of any grade of hypertension might increase with longer treatment. This adverse event is probably related to the antiangiogenic properties of sunitinib, since hypertension has been reported as a class effect with other antiangiogenic agents.[33,34] Long-term follow-up of these patients will be important to fully define the tolerability of multitargeted kinase inhibition, while taking into account the fact that these patients have a life-threatening disease.

Future studies of sunitinib in gastrointestinal stromal tumour will investigate further the molecular mechanisms by which sunitinib effects disease control after imatinib failure. Specifically, predictive tumour biomarkers will be studied in an effort to correlate molecular subtypes of the disease with sunitinib activity. Imatinib shows increased efficacy in gastrointestinal stromal tumour associated with *KIT* mutations in exon-11 and reduced efficacy in disease with *KIT* exon-9 mutations.[6,35] Preliminary analysis of patients with imatinib-resistant disease showed that sunitinib treatment yielded relatively higher rates of antitumour response and clinical benefit in tumours with primary *KIT* exon-9 mutations, compared with those with primary *KIT* exon 11 mutations.[22] However, these patients were a non-random population of individuals whose disease had progressed while on imatinib therapy, and who probably had a high incidence of secondary *KIT* mutations. A clear understanding of the effect of primary or secondary *KIT* mutations on sunitinib activity awaits testing of this agent in the first-line setting with imatinib-naive patients.

In addition to inhibiting KIT and PDGFR kinase activities, sunitinib also potently inhibits the activities of all isoforms of the VEGFRs, FLT3, and RET[16–21] (and unpublished data, Pfizer, 2006). This broad-spectrum activity contrasts with the relatively selective spectrum of imatinib action and might contribute to the clinical benefits we noted in patients resistant to and withdrawn from imatinib. Most cases of secondary or acquired resistance to imatinib in patients with gastrointestinal stromal tumour are due to the development of additional mutations in the KIT receptor tyrosine kinase that probably interfere structurally with the interaction of imatinib and the binding pocket of the molecule.[13,14,36–38] The clinical benefits of sunitinib compared with placebo might result from differential KIT binding interactions as well as the ability of sunitinib to block angiogenesis through inhibition of VEGFRs and PDGFRs. Inhibition of several aberrant signalling pathways might also be more beneficial than using a more selective kinase inhibitor. Although the exact molecular mechanisms might be multifactorial and require further study, our findings show that sunitinib is an effective therapeutic option for patients with gastrointestinal stromal tumour after failure of imatinib.

Contributors

The final manuscript was written by G D Demetri with substantive input from all authors, and with logistical and editorial assistance from ACUMED (medical writers Michael Coco and Wendy Sacks). All authors contributed materially to drafts and revisions, the logistics of which were coordinated by ACUMED, and all authors approved the final manuscript.

Clinical centres and investigators

The following people and facilities participated in this multicentre, multinational trial. Australia: Prince of Wales Hospital, Randwick: D Goldstein, M Friedlander, C Lewis; Royal Prince Alfred Hospital; Camperdown: S Clarke, P Beale, M J Boyer, M Tattersall; Flinders Medical Centre, Bedford Park: C Karapetis, J Dickson, B Koczwara, Y-S Yap; The Canberra Hospital, Garran: D Yip, P Craft, A Davis, D Leong, R Stuart-Harris; Peter MacCallum Cancer Institute: G McArthur, M Jefford, R Jennens, L Lim, M Michael, D Rischin, G Toner, J Zalcberg; Ashford Cancer Centre, Ashford: D Kotasek, C Bampton, F Parnis, B Stein, T Wright; Wesley Clinical Research Centre, Auchenflower: D Grimes, J Bashford, G Beadle, I Bunce, P Eliadis, T Olsen; Belgium: Universitaire Ziekenhuizen Leuven Gasthuisberg, Leuven: A T Van Oosterom, P Clement, H Dumez, N Isambert, P Schoffski; Canada: Mount Sinai Hospital, Toronto: M E Blackstein, R L Burkes; Hopital Notre-Dame Du Centre Hospitalier, Montreal: D Soulieres, J-P Ayoub, K Belanger, D Charpentier, B Lemieux, H J Olney, L Yelle; France: Centre Leon Berard, Lyon: J-Y Blay, T Bachelot, P Biron, I Ray-Coquard; Institut Gustave Roussy, Villejuif: A Le Cesne; CHU La Timone, Service d'Oncologie Medicale, Marseille: F Duffaud, L Digue; Italy: Istituto Nazionale per lo Studio e la Cura dei Tumouri, Milano: P G Casali, R M Bertulli, P Coco, E Fumagalli, M Galassi, S Stacchiotti; Istituto per la Ricerca e la Cura del Cancro, Torino: M Aglietta, S Aliberti, G Grignani; Azienda Ospedaliera San Martino, Genova: A Sobrero, F Caprioni, D Comandini, C Curti, G Fornarini, A Guglielmi, S Mammoliti, M S Sciallero; Centro di Riferimento Oncologico, Aviano: S Frustaci, A Buonadonna, A M Colussi, G Tabaro, M Zanetti; U O A Oncologia Ospedale Gradenigo, Torino: A Comandone, M Biscardi, A Boglione, P Pochettino; Istituto Europeo di Oncologia, Milano: F De Braud, G Curigliano, T De Pas, S Manzoni, C Noberasco; Istituto di Ematologia ed Oncologia Medica Lorenzo ed Ariosto Seragnoli, Bologna: G Biasco, M Astorino, G Brandi, M Di Battista, M C Di Marco, R Hakim, M A Pantaleo; Ospedale Niguarda Ca'Granda, Milano: S Siena, I C Andreotti, L Bevilacqua, L Giannetta, M Moroni, P Pedrazzoli, S Secondino; The Netherlands: Erasmus MC, Rotterdam: J Verweij, C M J C Seynaeve; Academisch Ziekenhuis Groningen, Groningen: W T A Van Der Graaf, J A Gietema; Singapore: John Hopkins-NUH International Medical Centre, Singapore: A Y C Chang, A R Alam, W Hsieh; National University Hospital, Singapore: R Soo, R S Lim, C I Wong; National Cancer Centre, Singapore: K F Foo, SY-K Ong, L T Soh, M H Tay; Spain: Hospital 12 de Octubre, Madrid: LGP-A Rodriguez, C Ballestin, D Castellano, A Lopez, V Martinez; Hospital de la Santa Creu i Sant Pau —Oncology, Barcelona: A Lopez-Pousa, O Gallego, J Llauger; Institut Català d'Oncologia, Barcelona: X G Del Muro; Switzerland: Centre Hospitalier Universitaire Vaudois, Lausanne: S Leyvraz, J Bauer, V Elsig, F Luethi, R Stupp, C M Thuerig; UK: Newcastle General Hospital, Newcastle: M W Verrill, A R A Razak, F Azribi, C J Bale, E R Plummer, A Srivastava; ICRF Cancer Med Research, Leeds: M Leahy; The Meyerstein Institute, UCL Hospital, London: B Seddon, J Whelan, O A Khan; CRUK Centre for Cancer Therapeutics, The Royal Marsden NHS Trust, Sutton: I R Judson, I Chau, R Jones, I D Padilla, M Parton, M Scurr, B Seddon; USA: UCLA Medical Center, Los Angeles: P J Rosen, C D Britten, R J Hecht; New York Presbyterian Hospital, New York: R N Taub, M L Keohan, C S Hesdorffer; Memorial Sloan-Kettering Cancer Research Center, New York: R G Maki, C R Antonescu, A M Covey, D D'Adamo, G K Schwartz, L Schwartz; Washington University School of Medicine, St Louis: J Picus, M J Naughton, B R Tan; SC Lutheran General Cancer Care Center, Park Ridge: P E Kaiser, B L Samuels, J D Bitran, W Fried, A G Galvez, A L Hooberman, T M Lestingi, C Nabhan, J M Richards; Duke University Medical Center, Durham: H I Hurwitz, G Blobe, N Fernando, J O Moore, M A Morse; Harper Hospital, Detroit: A F Shields, B F El-Rayes, S M Gadgeel, P A Philip, U N Vaishampayan; Premiere Oncology, Santa Monica:

L S Rosen, S P Chawla, M Mulay, A M Siney-Yeh; Cleveland Clinic Foundation, Cleveland: G T Budd, E C Borden, V J M Cline-Burkhardt, R J Pelley; Vanderbilt University Medical Center, Nashville: A C Lockhart, C Lockhart, J D Berlin, D Carbone, K R Hande, J A Means-Powell, D Morgan, B Roth, M L Rothenberg, A B Sandler, J Sosman, K W Wyman; Washington Hospital Center, Washington: D A Priebat, A Aggarwal, D J Perry; Jackson Memorial Hospital, Miami: C R Lima; H Lee Moffit Cancer Center & Research Institute, Tampa: C R Garrett; The Ohio State University Medical Center, Columbus: M Shah, T Bekaii-Saab, W J Hicks, E Martin, M Walker, Y Xu; Fox Chase Cancer Center, Philadelphia: M Von Mehren; University of Wisconsin Hospital and Clinics, Madison: KD Holen, D L Mulkerin, J P Thomas; Stanford University Medical Center, Stanford: G A Fisher Jr, T Kuo; Oregon Health and Science University, Portland: C D Blanke, C Corless, M Heinrich, M Lewis, C Lopez, D Ryan, R Townsend, E Yung; Dana-Farber Cancer Institute, Brigham and Women's Hospital, and Harvard Medical School, Boston: G D Demetri, K H Albritton, L J Appleman, M H Chen, J P Eder Jr, C D Fletcher, J A Fletcher, S George, J Morgan, S Silverman; City of Hope Medical Group, Pasadena and City of Hope National Medical Center, Duarte: W A Chow, M Koczywas, S Koehler, L A Leong, D W Lim, T Luu, K A Margolin, M McNamara, R J Morgan Jr, M Polonsky, J Portnow, S I Shibata, G Somlo, P W Twardowski, Y Yen; Fairview-University Medical Center and Masonic Cancer Center, Minneapolis: K M Skubitz, A Dudek; Seattle Cancer Care Alliance and University of Washington Medical Center, Seattle: J E Butrynski, S M Schuetze, J A Thompson; Pfizer Inc: Z Aguilar, R Allred, M Collier, S DePrimo, A Gentile, S Lanzalone, L Porem, W Sargent, V Tassell.

Conflict of interest statement

G Demetri has served as a consultant for Pfizer, Novartis, and Bristol-Myers Squibb, and has received honoraria from and provided expert testimony for Pfizer and Novartis. G McArthur has received financial compensation for a consultant role with Pfizer, research funding from Pfizer and Novartis, and speaker honoraria from Novartis. I Judson has received reimbursement from Pfizer for expenses associated with an oral presentation and an advisory board meeting. M Heinrich has received financial compensation for a consultant role with both Pfizer and Novartis and a speaker's bureau from Novartis, and research support for his institution from Pfizer and Novartis. C Bello, X Huang, and C Baum are employees of Pfizer with stock ownership. J Desai has received speaker's honoraria from Pfizer. J Morgan received travel support from Pfizer to attend a conference. P G Casali has received honoraria for lectures from Pfizer, Novartis, and Sigma-Tau, and compensation for a consultant role from Novartis. None of the other authors have potential conflicts of interest to disclose, other than the fact that the study sponsor, Pfizer, provided funds to offset the costs of participation in this study.

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