Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial

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Summary

Background Pazopanib, a multitargeted tyrosine kinase inhibitor, has single-agent activity in patients with advanced non-adipocytic soft-tissue sarcoma. We investigated the effect of pazopanib on progression-free survival in patients with metastatic non-adipocytic soft-tissue sarcoma after failure of standard chemotherapy.

Methods This phase 3 study was done in 72 institutions, across 13 countries. Patients with angiogenesis inhibitor-naive, metastatic soft-tissue sarcoma, progressing despite previous standard chemotherapy, were randomly assigned by an interactive voice randomisation system in a 2:1 ratio in permuted blocks (with block sizes of six) to receive either pazopanib 800 mg once daily or placebo, with no subsequent cross-over. Patients, investigators who gave the treatment, those assessing outcomes, and those who did the analysis were masked to the allocation. The primary endpoint was progression-free survival. Efficacy analysis was by intention to treat. The trial is registered with ClinicalTrials.gov, number NCT00753688.

Findings 372 patients, who were registered and 369 were randomly assigned to receive pazopanib (n=246) or placebo (n=123). Median progression-free survival was 4·6 months (95% CI 3·7–4·8) for pazopanib compared with 1·6 months (0·9–1·8) for placebo (hazard ratio [HR] 0·31, 95% CI 0·24–0·40; p<0·0001). Overall survival was 12·5 months (10·6–14·8) with pazopanib versus 10·7 months (8·7–12·8) with placebo (HR 0·86, 0·67–1·11; p=0·25). The most common adverse events were fatigue (60 in the placebo group [49%] vs 155 in the pazopanib group [65%]), diarrhoea (20 [16%] vs 138 [58%]), nausea (34 [28%] vs 129 [54%]), weight loss (25 [20%] vs 115 [48%]), and hypertension (8 [7%] vs 99 [41%]). The median relative dose intensity was 100% for placebo and 96% for pazopanib.

Interpretation Pazopanib is a new treatment option for patients with metastatic non-adipocytic soft-tissue sarcoma after previous chemotherapy.

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Introduction

Soft-tissue sarcomas are a group of rare mesenchymal cancers that include about 50 histological types, and account for 1% of all adult cancers.1,2 The yearly incidence of soft-tissue sarcomas in the USA is roughly 11 280 cases, with an overall mortality of 3900 deaths per year.3 In Europe the estimated yearly incidence is five cases per 100 000 people.1

The development of new systemic treatments for soft-tissue sarcomas has progressed little in the past few decades, with the exception of treatments for gastrointestinal stromal tumours. Patients with metastatic soft-tissue sarcomas have a median overall survival of about 12 months. The conventional first-line treatment for advanced soft-tissue sarcomas other than gastrointestinal stromal tumours is an anthracycline (usually doxorubicin), either as monotherapy or in combination with ifosfamide.4 The only truly new treatment approved for sarcoma failing standard therapy is trabectedin (approved by the European Medicines Agency in 2007).5 Gemcitabine with dacarbazine or docetaxel6–10 and paclitaxel for angiosarcoma11 seem to improve progression-free and overall survival in non-randomised and adaptively randomised trials.

Targeted therapies such as imatinib and sunitinib have activity for gastrointestinal stromal tumours and dermofibrosarcoma protuberans.12–14 Despite the large number of genomic mutations in soft-tissue sarcomas no other targeted treatment is effective and the role of anti-angiogenic treatment is unclear.15–17"""" Three phase 2 studies have been done to test anti-angiogenic treatment.18–20 However, until now, no phase 3 trial has been done. The small-molecule vascular endothelial growth factor inhibitor pazopanib—a synthetic indazolpyrimidine—is a multitargeted tyrosine kinase inhibitor, with activity against vascular endothelial growth factors 1, 2, and 3, and platelet-derived growth factors.21 Pazopanib is registered for the treatment of advanced renal cell cancer.22 In a stratified phase 2 clinical trial in relapsed or metastatic soft-tissue sarcoma, the proportion of patients who were free of progression at 3 months was 44% for patients with leiomyosarcoma, 49% for patients with synovial sarcoma, 39% for patients with other types of soft-tissue sarcoma, and 26% for...
patients with adipocytic sarcoma. These data justified further investigation for soft-tissue sarcoma, along with a previous analysis that linked progression-free survival at 3 months of more than 40% with clinic effectiveness.21

On the basis of these data, this trial (PAzopanib expLorEd in SoFT-Tisue Sarcoma—a phasE 3 study; PALETTE) was designed to compare the efficacy and safety of pazopanib with placebo for soft-tissue sarcoma (excluding gastrointestinal stromal tumours and adipocytic sarcomas).

Methods

Study design and participants

This multicentre phase 3 study was designed and jointly done by the Soft Tissue and Bone Sarcoma Group of the European Organisation for Research and Treatment of Cancer (EORTC) and GlaxoSmithKline between Oct 9, 2008, and Feb 26, 2010. The study included patients from 72 institutions worldwide. Eligible patients were 18 years or older, with metastatic soft-tissue sarcoma and progressive disease according to Response Evaluation Criteria In Solid Tumors (version 1.0)22 during the 6 months before start of study drug or 12 months for previous adjuvant treatment. Patients had at least one regimen containing anthracycline and a maximum of four previous lines of systemic therapy for metastatic disease (no more than two lines of combination regimens).

The most common histological types of soft-tissue sarcoma were allowed; excluded were all types of adipocytic sarcoma, embryonal rhabdomyosarcoma, chondrosarcoma, osteosarcoma, Ewing tumours, primitive neuroectodermal tumour, gastrointestinal stromal tumour, dermatofibrosarcoma protubersans, inflammatory myofibroblastic sarcoma, malignant mesothelioma, and mixed mesodermal tumours of the uterus. Pathology materials (tumour blocks and representative slides) were centrally reviewed.

Entry criteria included a WHO performance status of 0 or 1; absence of CNS metastases and leptomeningeal metastases; and adequate bone marrow function (absolute neutrophil count ≥1·5×10⁹ cells/L, platelets ≥100×10⁹ per L, haemoglobin ≥9 g/dL), renal function (serum creatinine ≤1·5 mg/dL, or, if >1·5 mg/dL, calculated creatinine clearance >50 mL/min), hepatic function (bilirubin ≤1·5×upper limit of normal), aspartate aminotransferase and alanine aminotransferase ≤2·5×upper limit of normal), and cardiac function (left ventricular ejection fraction assessed by multigated acquisition scan or echocardiogram, normal lead electrocardiogram [no prolongation of corrected QT interval >480 ms] and no history of any of the following in the past 6 months: cardiac angioplasty or stenting, myocardial infarction, unstable angina, coronary artery bypass graft surgery, symptomatic peripheral vascular disease class III or IV congestive heart failure, as defined by the New York Heart Association). Blood pressure had to be below 150/90 mm Hg, spontaneously or controlled with antihypertensive medication. Anticoagulant therapy was permitted with stable coagulation tests. Patients with recent (within 6 months) thromboembolic events who were stable, taking anticoagulating drugs for at least 6 weeks were eligible.

Patients who had had a cerebrovascular accident, pulmonary embolism, or untreated deep venous thrombosis in the past 6 months were ineligible. Patients were also excluded if they had had clinically significant gastrointestinal disorders in the past 6 months, active bleeding from any site, major surgery, wound healing difficulties, or trauma within 28 days before start of study drug. Previous treatment with inhibitors of angiogenesis or vascular endothelial growth factor or drugs that target vascular endothelial growth factor receptor were not permitted, but previous exposure to mammalian target of rapamycin inhibitors was allowed.

The trial was approved by the institutional review board of each participating institution and complied with good clinical practice guidelines and the Declaration of Helsinki. All patients gave written informed consent.

![Table 1: Baseline characteristics of patients](data:image/png;base64,iVBORw0KGgoAAAANSUhEUgAAAIgAAAAHcAl xmlns:sketch="sketch" xmlns:svg="svg">
Randomisation and masking
Eligible patients were registered with EORTC in an online randomised trial access system, and treatments were allocated with the GlaxoSmithKline online registration and medication ordering system. Patients were stratified according to number of previous lines of systemic therapy for advanced disease (none or one vs two or more), and WHO performance status (0 vs 1). They were then randomly assigned with an interactive voice randomisation service to receive either pazopanib 800 mg once daily or placebo (2:1), by permuted block randomisation (block sizes of six). Patients, investigators who gave the treatment, those assessing outcomes, and those who did the analysis were masked to the allocation. Treatment allocation remained masked until the database was locked, and the list of treatment codes was transferred to EORTC on March 1, 2011. Progression-free survival and objective responses were assessed by masked independent radiology review.

Procedures
Study drug was taken orally once daily. Dose modifications for adverse events were done according to the protocol. Clinical assessments of safety, including medical history and physical examination, and laboratory assessment, were done at baseline, and week 4, 8, and 12, and at 8-week intervals thereafter.

Treatment was continued until disease progression (according to Response Evaluation Criteria In Solid Tumors, version 1.0), unacceptable toxic effects, withdrawal of consent, or death. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria for adverse events (version 3.0). Quality of life was assessed with the EORTC QLQ-C30 (version 3) questionnaire, global health status/quality-of-life score, and EQ5D, at baseline, and weeks 4, 8, and 12. Quality of life will be assessed in full in a separate report.

Post-protocol treatment was given at the discretion of patients and their physicians. Unmasking of the study treatment occurred at study analysis or at the physician’s request, without notification of the study team at EORTC or the study sponsor. An independent data monitoring committee monitored safety and reviewed the interim overall survival data. At disease progression, no crossover was permitted. All patients were followed up for survival (until death from any cause or withdrawal of consent). Serious adverse events were directly reported to the GlaxoSmithKline pharmacovigilance database. Cardiac dysfunction was defined as an absolute decrease of left ventricular ejection fraction of 15% or more compared with baseline, or a drop of left ventricular ejection fraction below 5% below the lower normal limit of the institution, or as symptomatic heart failure with any otherwise unexplained decrease in left ventricular ejection fraction below the lower limit of normal. The primary endpoint was progression-free survival; secondary endpoints were overall survival, response rate, safety, and quality of life.

Statistical analysis
Progression-free survival was defined as time from randomisation to either first disease progression (per independent radiology review of images) or death from any cause. Patients alive at the time of analysis were censored at the date of last disease assessment. Overall survival was measured from the date of randomisation to the date of death (from any cause). The trial was powered to detect a 15% difference in progression-free survival at 6 months, from 15% in the control group (based on retrospective analysis of data from the Soft Tissue and Bone Sarcoma Group) to 30% in the pazopanib group (based on the EORTC 62043 phase 2 trial done in the same patient population), corresponding to a hazard ratio (HR) of 0·63. 274 events were needed to detect the targeted difference with 95% power at a 5% significance level. The final analysis of the primary endpoint was done with a clinical cutoff date at which at least 274 patients had disease progression or at least 195 had died.

The trial provided 90% power at the 5% significance level with 279 events to detect a 33% decrease in the death HR, corresponding to an increase of median overall survival from 8 months to 12 months. An interim analysis of overall survival was done at the time
of the analysis of the primary endpoint. The significance for overall survival was calculated with the Lan and DeMets α spending function with O’Brien-Fleming stopping rule.

Survival was estimated by the Kaplan-Meier method. The treatment groups were compared with a two-sided stratified Wald test. All analyses were done in the intention-to-treat population.

We did a prognostic factor analysis for progression-free survival with a univariate Cox model; significant factors were subsequently included in a multivariable Cox regression model (p<0·05). For a predictive analysis of progression-free survival Cox models were generated with the investigated factor, treatment, and their interaction, with a significance value of p<0·05.

The main quality-of-life objective was to test that patients who received pazopanib had an improved quality of life compared with the placebo group. This analysis was done by fitting a linear mixed model with treatment, a (linear) time effect, and a time-treatment interaction as fixed effects, and a patient-specific random effect, for all randomly assigned patients. Score estimates, standard errors, the associated CIs, and resulting tests (χ²) were obtained from the model, including a general overall post-baseline test for no difference between the two treatment groups at all post-baseline timepoints, by an overall F-test statistic. Differences of at least 10 points (on a 0–100 scale) were classified as the minimum clinically meaningful change in a health-related quality-of-life (HRQOL) parameter. Because missing data are problematic in most HRQOL studies, sensitivity analyses were done, investigating the informative drop-out by graphical assessment and which variables affect compliance by linear regression. For the primary HRQOL scale, explicit regression imputation was used in which imputed values were predicted from a regression model that included factors (time, treatment group, sex, age, WHO performance score, and number of previous lines of systemic treatment for advanced disease) related to a missingness mechanism applied to data.

East (version 5) was used to calculate sample size and stopping boundaries; all other statistical analyses were done with SAS (version 9.2).

Table 1 shows demographics and patients’ baseline characteristics. The median age was 55 years (IQR 44–64), 94 (25%) patients had received previous adjuvant or neoadjuvant therapy, 342 (93%) had received previous systemic therapy for advanced disease, 207 (56%) had had two or more lines of treatment, and 78 (21%) had had three or more. 364 (99%) had received anthracyclines (301 [82%] for advanced disease), 263 (71%) ifosfamide or analogues, 127 (34%) gemcitabine, 104 (28%) docetaxel, 127 (34%) gemcitabine, 104 (28%) docetaxel,
60 (16%) trabectedin, and 57 (15%) dacarbazine. Histological review was done for all but seven patients.

Three patients were not assigned to a group (figure 1), therefore the intention-to-treat population consisted of 369 patients. Six of the 369 patients never started treatment (one withdrew consent, two had rapid progression of disease, three had newly diagnosed thromboembolic events) and information was unavail-
able for one patient, who had drug prescribed but died at home shortly after randomisation, and no information could be obtained. Consequently, the safety population consisted of 362 patients.

The median treatment duration was 8·1 weeks (range 1–52, IQR 4·0–13·6) for placebo and 16·4 weeks (range 0–79, IQR 6·3–30·0) for pazopanib. The relative dose intensity was 100% for placebo and 96% for pazopanib. Treatment was interrupted in 11 (9%) patients receiving placebo and 118 (49%) receiving pazopanib, dose reductions occurred in five (4%) versus 92 (39%). Reasons for treatment discontinuation were disease progression in 118 (96%) patients in the placebo group and 167 (70%) in the pazopanib group, and toxic effects related to study drug in one (1%) patient in the placebo group and 34 (14%) in the pazopanib group.

At the time of the primary analysis, with the data cutoff date of Nov 22, 2010, median follow-up was 14·6 months in the pazopanib group.

The main reasons for dose reductions were hypertension, fatigue, diarrhoea, nausea, weight loss, and hypertension. Venous thromboembolic events occurred in three (2%) patients in the placebo group and 13 (5%) patients in the pazopanib group. Pneumothorax occurred in eight (3%) patients taking pazopanib and in one (1%) taking placebo.

A drop in left ventricular ejection fraction occurred in three patients in the placebo group and in 16 patients in the pazopanib group (of which three were symptomatic) during or after treatment. At the primary clinical cutoff, left ventricular ejection fraction had improved in eight patients, of whom, five continued pazopanib and three discontinued for other reasons. No follow-up data are available for the other patients.

The main reasons for dose reductions were hypertension, fatigue, diarrhoea, anorexia, nausea and vomiting, hand-foot syndrome, and increased concentrations of liver enzyme. Of eight fatal serious adverse events in the pazopanib group, one was multiorgan

Table 3 shows the main adverse events. The most common adverse events with pazopanib were fatigue, diarrhoea, nausea, weight loss, and hypertension. Venous thromboembolic events occurred in three (2%) patients in the placebo group, and 13 (5%) patients in the pazopanib group. Pneumothorax occurred in eight (3%) patients taking pazopanib and in one (1%) taking placebo.

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Table 2: Prognostic factors for progression-free survival

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status (0 vs 1)</td>
<td>0·72 (0·53–0·97)</td>
</tr>
<tr>
<td>Number of lines of previous systemic therapy (0–1 vs 2–4)</td>
<td>0·72 (0·53–0·99)</td>
</tr>
<tr>
<td>Sex (female vs male)</td>
<td>0·80 (0·59–1·09)</td>
</tr>
<tr>
<td>Age (&lt;50 years vs ≥50 years)</td>
<td>0·99 (0·72–1·36)</td>
</tr>
<tr>
<td>Grade (I–II vs III)</td>
<td>0·61 (0·44–0·86)</td>
</tr>
<tr>
<td>Histology subtype</td>
<td></td>
</tr>
<tr>
<td>Other sarcoma</td>
<td>1·00</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>0·88 (0·63–1·21)</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>0·82 (0·51–1·32)</td>
</tr>
<tr>
<td>Locoregional disease (yes vs no)</td>
<td>0·86 (0·62–1·22)</td>
</tr>
<tr>
<td>Liver metastases (yes vs no)</td>
<td>0·98 (0·68–1·41)</td>
</tr>
</tbody>
</table>

*p for leiomyosarcoma versus other versus synovial sarcoma.

Figure 3: Predictive analysis of histological type
Common adverse events

<table>
<thead>
<tr>
<th>Event</th>
<th>Placebo group (n=123)</th>
<th>Pazopanib group (n=239)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>60 (49%)</td>
<td>6 (5%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>20 (16%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (28%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Weight loss</td>
<td>25 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (7%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>24 (20%)</td>
<td>0</td>
</tr>
<tr>
<td>Hair hypopigmentation</td>
<td>3 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14 (11%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>5 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Rash or desquamation</td>
<td>13 (11%)</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>4 (3%)</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are n (%).

Table 3: Common adverse events

Failure that might have been related to the study drug or to antibiotics. In the placebo group six fatal serious adverse events occurred, unrelated to study drug.

The most relevant laboratory abnormalities for anti-angiogenic tyrosine kinase inhibitors were increased concentrations of liver enzymes (table 4).

Global health and quality-of-life scores did not differ significantly between groups (appendix) although the QLQ-C30 showed significant differences for diarrhoea, loss of appetite, nausea or vomiting, and fatigue, with 10 point or more worse symptom scores for pazopanib. Because data for quality of life were not collected after 12 weeks, few conclusions can be made about the effect of pazopanib on quality of life for the entire progression-free period.

At the data cutoff of Nov 22, 2010, 350 patients (94%) were off-protocol, of whom 221 received post-protocol treatment (appendix). 24 patients (7%) had surgery and 64 (18%) had radiotherapy. 75 (62%) patients in the placebo received chemotherapy versus 103 (45%) in the pazopanib group. 17 (14%) versus 22 (10%) received targeted therapies.

Discussion

The findings from this phase 3, placebo-controlled trial show that pazopanib significantly increased progression-free survival compared with placebo. Patients included in this study had a very poor prognosis, as shown by the low median progression-free survival and the high number of adverse events in the placebo group. The eligible histological types of soft-tissue sarcoma in the study were selected on the basis of the results of the previous EORTC phase 2 study, which did not show sufficient benefit for adipocytic soft-tissue sarcoma, although the different subtypes of adipocytic sarcomas were not taken into account.28 With the inclusion of leiomyosarcomas, synovial sarcomas, and many other histological types, most soft-tissue sarcoma subtypes were included, which makes the results relevant for almost all patients with soft-tissue sarcoma. This study is unique because it is the first placebo-controlled phase 3 trial of a tyrosine kinase inhibitor for soft-tissue sarcoma (panel).

The final overall survival analysis did not show a significant benefit for pazopanib, which matches data from the interim analysis. In view of the median overall survival of 10.7 months in the placebo group, which was 2.7 months longer than that estimated for the design of the trial, the actual power of this study to detect a 3 month benefit for overall survival with pazopanib was less than 50%. A trial powered (80% power) to detect a 3 month benefit, would need a sample size of more than 750 patients, which was not deemed feasible. Dilution might be explained by the long survival compared with the time to progression of disease or the post-progression therapy that was administered. In this study, post-progression therapy was given frequently and varied substantially (possibly because of the different reimbursable treatment options in the different participating countries). Whether this variability affected the final overall survival results is unknown, because it applied to both groups.

The range of adverse events was consistent with the safety data for pazopanib in patients with renal cell cancer, but a higher proportion of all grade adverse events occurred in those with soft-tissue sarcoma, particularly for fatigue, nausea, anorexia, weight loss, and dysgeusia.22 High rates of fatigue and weight loss also occurred in the placebo group, and the overall quality of life of patients treated with pazopanib was not significantly worse than that of the patients given placebo.

Newly reported adverse events were venous thromboembolic events, pneumothorax, and cardiotoxicity. The incidence of venous thromboembolism was in the same range as has been reported in patients with primary and relapsed (extremity) sarcomas, therefore the high frequency in the pazopanib group might not be related to the drug.27 Case series show that the prevalence of pneumothorax is roughly 2% in sarcoma patients.24 This proportion is much the same as in our study population. Whether the treatment effect of pazopanib contributed to increased pneumothorax because necrosis of peripheral pulmonary or pleural metastases in this study population, is unknown.24 Because of anthracycline pretreatment, special attention was paid to cardiac adverse events. Furthermore, cardiotoxicity is a risk with sunitinib,27 which belongs to
Panel: Research in context

**Systematic review**

We searched PubMed with the terms “vascular endothelial growth factor receptor”, “angiogenesis inhibitor”, and “soft tissue sarcoma”, for clinical trials of advanced non-gastrointestinal stromal tumour soft-tissue sarcomas and for specific targeted agents (pazopanib, sunitinib, and sorafenib). We included reports in English, published up to March 5, 2012. No randomised phase 3 trials comparing a multitargeted kinase inhibitor with placebo in non-gastrointestinal stromal tumour soft-tissue sarcoma have been reported.

**Interpretation**

To date, this trial is the only placebo-controlled phase 3 study done in non-gastrointestinal stromal tumour soft-tissue sarcoma, and is the only randomised phase 3 study of treatment after second-line therapy. Our results show that pazopanib significantly increases progression-free survival by a median of 3 months compared with placebo, showing the activity of pazopanib after second-line treatment. This study is the only randomised phase 3 study of soft-tissue sarcoma that shows improvement in progression-free survival. On the basis of these results, pazopanib is a new oral treatment option, after previous chemotherapy, for metastatic non-gastrointestinal stromal tumour, non-adipocytic soft-tissue sarcoma.

Although the exact mechanism by which pazopanib affects soft-tissue sarcoma is unknown, progression-free survival improved in patients of all ages, for most histological subgroups (leiomyosarcoma, synovial sarcoma, and others), and after one or more lines of previous systemic treatment.

Pazopanib is an active drug for patients in the heterogeneous group of non-adipocytic soft-tissue sarcomas. After the breakthroughs of imatinib and sunitinib for gastrointestinal stromal tumour, pazopanib is the first active oral agent for patients with non-gastrointestinal stromal tumour soft-tissue sarcomas and is a meaningful addition to the treatment armamentarium for patients with this rare group of tumours.

**Contributors**

WTAvdG, J-YB, and GDD designed the trial, searched the published work, accrued patients, collected and interpreted data, and prepared the report, with assistance from the study statistician MO. SPC, D-WK, BB-N, PGC, PS, MA, APS, YB, ALC, HG, IRJ, NA, and PH contributed to data collection, data interpretation, preparation of the report, and patient accrual. RH and MO were responsible for data interpretation and statistical assistance. SM was responsible for trial design, search of the published work, data interpretation, and preparation of the report. CC was responsible for data interpretation, preparation of the report, and statistical analysis. MRD was involved in trial design and data interpretation and preparation of the report. CDF and APDT were involved in the data collection and interpretation.

**Other local investigators**


**Conflicts of interest**

J-YB has received research support and honoraria from GlaxoSmithKline, Novartis, Roche, PharmaMar, and Merck, Sharp, and Dohme. IRJ has received research support and honoraria from GlaxoSmithKline and has been on an advisory board for GlaxoSmithKline. GDD has received consultant and research support from GlaxoSmithKline, Pfizer, Novartis, Sanofi, Ariad, Merck, Johnson and Johnson, PharmaMar, Daichi-Sankyo, and Amgen; and has been a consultant for ZioPharm. D-WK has been a consultant for GlaxoSmithKline. PS has received research funding from GlaxoSmithKline, and has been a consultant for and received honoraria from GlaxoSmithKline. PGC has received honoraria from Novartis, Pfizer, and PharmaMar. RH and MRD are employees of GlaxoSmithKline and hold shares in GlaxoSmithKline. HG has received research grants from GlaxoSmithKline, Novartis, and Pfizer. APS has received research support from GlaxoSmithKline. SPC has been a consultant for GlaxoSmithKline. PGC has received honoraria and travel grants from and is on advisory boards for Bayer, GlaxoSmithKline, Merck, Novartis, Pfizer, and PharmaMar, MA, WTAH, SM, NA, APDT, CDF, FH, BB-N, MO, CC, and YB declare that they have no conflicts of interest.

**Acknowledgments**

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References


