Pazopanib for treatment of advanced extraskeletal myxoid chondrosarcoma: a multicentre, single-arm, phase 2 trial

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Summary

Background Extraskeletal myxoid chondrosarcoma is a rare sarcoma with low sensitivity to cytotoxic chemotherapy. Retrospective evidence suggests that antiangiogenic drugs could be a treatment option. We aimed to investigate the activity of pazopanib, an antiangiogenic drug, in patients with advanced extraskeletal myxoid chondrosarcoma.

Methods In this single-arm, open-label phase 2 trial, three parallel independent cohorts of different histotypes of advanced sarcomas were recruited (extraskeletal myxoid chondrosarcoma, typical solitary fibrous tumour, and malignant-dedifferentiated solitary fibrous tumour). In each cohort, patients received pazopanib. In this Article, we report the results of the cohort of patients with advanced extraskeletal myxoid chondrosarcoma. Separate reporting of the three cohorts was prespecified in the study protocol. In this cohort, adult patients (aged ≥18 years) with a diagnosis of *NR4A3*-translocated, metastatic, or unresectable extraskeletal myxoid chondrosarcoma, who had Response Evaluation Criteria in Solid Tumors (RECIST) progression in the previous 6 months, and had an Eastern Cooperative Oncology Group performance status of 0–2, were enrolled at 11 study sites of the Spanish, Italian, and French sarcoma groups. Patients received oral pazopanib (800 mg/day) continuously, until disease progression, unacceptable toxicity, death, non-compliance, patient refusal, or investigator's decision. The primary endpoint was the proportion of patients achieving an objective response according to RECIST 1·1 in the modified intention-to-treat population (patients who provided consent and had a central molecularly confirmed diagnosis of extraskeletal myxoid chondrosarcoma). The safety analysis included all patients who received at least one dose of pazopanib. This study is registered with ClinicalTrials.gov, number NCT02066285.

Findings Between June 24, 2014, and Jan 17, 2017, 26 patients entered the study and started pazopanib. Of these, 23 met the eligibility criteria for the modified intention-to-treat analysis. Median follow-up was 27 months (IQR 18–30). 22 patients (one patient died before the primary analysis) were evaluable for the primary endpoint: four (18% [95% CI 1–36]) had a RECIST objective response. No deaths or grade 4 adverse events occurred. The most frequent grade 3 adverse events were hypertension (nine [35%] of 26 patients), increased concentration of alanine aminotransferase (six [23%]), and increased aspartate aminotransferase (five [19%]).

Interpretation Pazopanib had clinically meaningful antitumour activity in patients with progressive and advanced extraskeletal myxoid chondrosarcoma, and could be considered a suitable option after failure to respond to first-line anthracycline-based chemotherapy in these patients.

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Introduction

Extraskeletal myxoid chondrosarcoma is a very rare sarcoma, mostly arising from soft tissues of the extremities, but potentially originating from any site of the body, including the bone.[1] This tumour carries specific reciprocal translocations involving the *NR4A3* gene (also called *CHN*) on chromosome 9, which can be rearranged with different partners. In most cases, *NR4A3* fuses with *EWSR1*, but other partner genes, namely *TAF15*, *TCF12*, *TFG*, and *HSPA8*, can be detected.[2–8] The presence of the translocation is of major help in differential diagnosis from other similar cancers, such as myoepithelial carcinoma. In addition, data suggest that tumours with *TAF15–NR4A3* fusion might be associated with a more aggressive clinical behaviour than those with *EWSR1–NR4A3* fusion.[10]

Extraskeletal myxoid chondrosarcoma is considered a disease with an indolent behaviour and a slow growth. However, studies with adequately long follow-up showed a high proportion (>40%) of local and distant recurrences, with 65–88% of patients alive at 10 years.[1,10–12] The most common site of distant metastases is the lung, but soft tissues and lymph nodes can also be involved. The standard treatment for primary, localised extraskeletal

Research in context

Evidence before this study

We searched PubMed for all series or trials involving antiangiogenic drugs for the treatment of extraskeletal myxoid chondrosarcoma, published in English between Jan 1, 2000, and Feb 28, 2019. Terms used for the search were "extraskeletal myxoid chondrosarcoma", "*NR4A3*", "advanced", "metastatic", "primary", "systemic treatment", "antiangiogenic", "sunitinib", "pazopanib", "bevacizumab", sorafenib", "regorafenib", "series", and "trial".

Two retrospective series and two case reports were identified, which focused on antiangiogenic treatment for advanced extraskeletal myxoid chondrosarcoma and included, in total, fewer than 15 patients. No prospective clinical trial was found on systemic therapies in advanced extraskeletal myxoid chondrosarcoma, neither with conventional cytotoxic chemotherapy, nor with molecular targeted therapy. Of the two retrospective series on antiangiogenics, one reported on ten patients with extraskeletal myxoid chondrosarcoma treated with sunitinib, whereas in the second retrospective study different chondrosarcoma subtypes were mixed together and no details are available on the two patients with extraskeletal myxoid chondrosarcoma included in that series.

Added value of this study

This study provides the first prospective evidence of antitumour activity of pazopanib (an antiangiogenic drug) in a cohort of patients with advanced extraskeletal myxoid chondrosarcoma. The results support the rationale for the potential use of antiangiogenic drugs in metastatic extraskeletal myxoid chondrosarcoma. This trial provides, in addition, a benchmark for future studies.

Implications of all the available evidence

Pazopanib is active in patients with metastatic and *EWSR–R4A3* translocated extraskeletal myxoid chondrosarcoma, resulting in disease control in more than half of the patients, and represents a treatment option for a disease marked by low sensitivity to conventional chemotherapy. It would be interesting to compare antiangiogenics with anthracycline-based chemotherapy, and antiangiogenics with each other, but these studies could be very challenging in a rare subgroup of a rare family of tumours. The combination of antiangiogenic drugs (such as pazopanib) and immunotherapy drugs would also be worth exploring.

myxoid chondrosarcoma is surgery, but patients with advanced disease need medical treatment with drugs. Anthracycline-based chemotherapy, which is the first-line regimen used in soft-tissue sarcoma, has low activity in this sarcoma subtype.[8,11,13–16] Conversely, retrospective evidence of sunitinib antitumour activity in advanced extraskeletal myxoid chondrosarcoma suggests that antiangiogenic drugs could be an option.[17,18] However, no prospective confirmatory studies on this class of drugs have been done for this disease, and pazopanib is the only antiangiogenic drug approved for second-line and further-line treatment of soft-tissue sarcoma. No prospective data are available on the activity of this drug for extraskeletal myxoid chondrosarcoma.

Therefore, a phase 2 study involving the Spanish, French, and Italian Sarcoma Groups was designed to investigate the activity of pazopanib in adult patients with advanced extraskeletal myxoid chondrosarcoma and solitary fibrous tumour. In this Article, we report the results of the extraskeletal myxoid chondrosarcoma cohort.

Methods

Study design and participants

This investigator-initiated, multicentre, open-label, single-arm, phase 2 clinical study was done in 11 sarcoma reference hospitals in Spain, France, and Italy. The study was designed as a study of three parallel independent cohorts of different histotypes of advanced sarcomas (extraskeletal myxoid chondrosarcoma, typical solitary fibrous tumour, and malignant-dedifferentiated solitary fibrous tumour). In each cohort, patients received pazopanib. In this Article, we report the results of the cohort of patients with advanced extraskeletal myxoid chondrosarcoma, whereas the results of the two cohorts on solitary fibrous tumour are presented separately (results from the malignant-dedifferentiated solitary fibrous tumour cohort have already been reported;[19] results from typical solitary fibrous tumour will be presented in the future). This decision was based on the knowledge that extraskeletal myxoid chondrosarcoma and solitary fibrous tumour are two completely different mesenchymal tumours, from both the molecular and the clinical point of view. Separate reporting of the three cohorts was prespecified in the study protocol.

Eligible patients were adults (aged ≥18 years) with diagnosis of metastatic or locally advanced, unresectable, molecularly confirmed *NR4A3*-translocated extraskeletal myxoid chondrosarcoma, with evidence of objective disease progression by RECIST 1.1 in the 6 months before starting treatment, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients who had received previous antiangiogenic treatment were excluded. Full inclusion and exclusion criteria are listed in the appendix (pp 1–3).

All study procedures were done according to guidelines established by each hospital's ethics committee, in agreement with the Declaration of Helsinki. All patients gave their written, informed consent to participate in the study. Approval from the ethics committee of each

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See **Online** for appendix

participating centre was obtained. One protocol amendment, because of a change in the pazopanib summary of product characteristics document, was introduced and approved by the required ethics committee to increase the number of outpatient scheduled visits and check liver function tests (Nov 24, 2014). The study protocol is available online.

For the **trial protocol** see http://grupogeis.org/GEIS_32act.pdf

For more on **WebGestalt** see http://www.webgestalt.org

For more on **NetworkAnalyst** see https://www.networkanalyst.ca/

Procedures

Patients were administered pazopanib (800 mg orally per day), to be taken without food, at least 1 h before or 2 h after a meal, in a continuous schedule. Every 4 weeks of pazopanib accounted for one cycle of treatment. Dose reductions were planned in accordance with the drug brochure (details in the study protocol). If dose reduction was necessary, pazopanib had to be reduced stepwise, by 200 mg each day at each step. Treatment was administered until one of the following events occurred: confirmed disease progression by RECIST 1.1, unacceptable toxicity (according to investigator evaluation), death, non-compliance, patient's refusal of treatment, or investigator's decision.

Centralised pathological confirmation in accordance with the latest WHO classification[1] at national level was mandatory before enrolment. In addition, a centralised molecular review of all cases was done after the end of the study at the Fondazione Istituto di Ricovero e Cura a Carattere Scientifico Instituto Nazionale Tumori, Milan, Italy, to assess the presence of *NR4A3* rearrangement by fluorescent in-situ hybridisation (FISH) and, on this basis, diagnosis and eligibility.

Radiological assessment was done every 8 weeks by CT or MRI. In addition to RECIST 1.1 assessment, any degree of change in tumour size was also annotated. Centralised radiological review was mandatory.

Adverse events were graded using the National Cancer Institute Common Toxicity Criteria (version 4.0). Adverse events were registered at each study visit and during all the on-treatment period (defined as the period from the first dose of study drugs up to 30 days after the last dose).

For patients who left the study, data on post-protocol therapies were collected and all patients were followed up for at least 1 year after the end of the study.

No major protocol deviations were reported. Minor protocol deviations concerned radiological assessments or laboratory tests done outside of the per-protocol time window.

Central molecular review was mandatory. All tumour samples were first assessed for *NR4A3* gene status. All *NR4A3* rearranged cases were then checked for *EWSR1* and, if negative, for *TAF15*. FISH analysis was done on formalin-fixed paraffin-embedded tumour tissue sections (appendix p 4).

For translational studies, pretreatment formalin-fixed paraffin-embedded samples from patients who had tumour shrinkage following pazopanib treatment and from those who did not respond to pazopanib treatment were selected and compared for transcriptional profile and immune-contexture assessment.

RNA sequencing was done as previously described.[20] All samples had a tumour cellularity of more than 70%. An average of 70 million paired-end reads per sample were generated. Alignment, quantification, principal component analysis (PCA), and differential expression analyses were done by use of the Biomedical Genomics Workbench (version 5.0.1; Qiagen, Aarhus, Denmark). WebGestalt (version 2019), NetworkAnalyst, ConsensusPathDB (Max Planck Institute for Molecular Genetics, Berlin, Germany), and Ingenuity Pathway Analysis (IPA; Qiagen, Aarhus, Denmark) tools were used for functional annotation. Immune contexture was analysed by immunohistochemistry (Dako ASL48 platform; Agilent Dako, Santa Clara, CA, USA), as previously described.[21,22] Deparaffinisation, rehydration, and antigen retrieval were done on PT Link (Dako PT100; gilent Dako, Santa Clara, CA, USA) using the EnVision FLEX Target Retrieval Solution (Agilent, Santa Clara, CA, USA). Presence of intratumoral and peritumoral infiltrate was assessed. In the peritumoral site (around neoplastic mass as a whole or in fibrous septa between smaller nodules inside the neoplastic mass), the infiltrate was scored as absent or present. CD3, CD8, and CD163 were scored in the intratumoral site as number of isolated stained cells per mm^2 counted in the highest density areas. The presence of lymphocytic aggregates was also recorded. The CD8:CD3 ratio was calculated.

Outcomes

The primary endpoint of the study was the proportion of patients achieving an objective response (confirmed complete response or partial response) by RECIST 1.1. Secondary endpoints were progression-free survival (ie, time from onset of treatment to disease progression or death), overall survival (ie, time from onset of treatment to last follow-up or death), clinical benefit (defined as the proportion of patients who reached a complete response, partial response, or stable disease lasting 6 months or more, together with clinical improvement of symptoms; this endpoint will be reported elsewhere) and the toxicity profile. Central pathological and molecular review and the correlation of response with tumour molecular profile and with the biomarkers assessed in the translational part of the study were protocol-prespecified exploratory endpoints.

Statistical analysis

Sample size was estimated with a one-stage phase 2 design (α=0·1 and β=0·2 [ie, 80% power]), having considered the published proportion of patients achieving an objective response based on RECIST 1.1 of 5% and an alternative hypothesis of 20%. Thus, we planned to enrol 21 patients into this study.

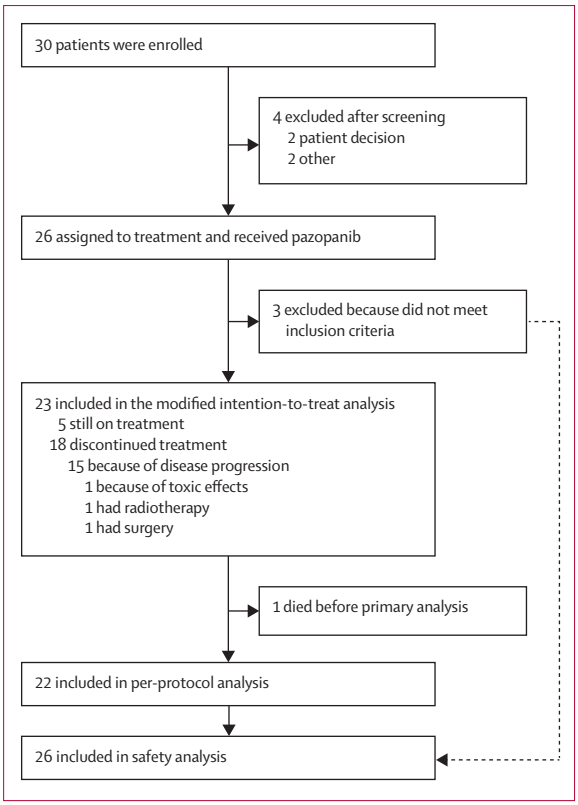

Figure 1: **Trial profile**

	Patients (n=26)
Median age (IQR), years	63 (48–68)
Sex	
Male	21 (81%)
Female	5 (19%)
ECOG PS	
0	15 (58%)
1	10 (38%)
2	1 (4%)
Location (primary tumour)	
Limbs	14 (54%)
Trunk	6 (23%)
Other locations	6 (23%)
Translocation subtype	
EWSR1-positive	20 (77%)
TAF15-positive	3 (11%)
Data not available	3 (11%)
Median primary tumour size at diagnosis (IQR), mm	110 (59–172)
Median tumour burden at baseline (IQR), mm	110 (49–175)
Median time from diagnosis to inclusion (IQR), months	28 (2–70)
Stage at inclusion	
Metastatic	25 (96%)
Locally advanced	1 (4%)
Previous antineoplastic treatments	
Treatment naive	21 (81%)
One line of treatment	2 (8%)
Two or more lines of treatment	3 (11%)
Previous treatment	
Chemotherapy	5 (19%)
Antiangiogenic drugs	0

Data are n (%), unless otherwise specified. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline clinical and pathological patient characteristics in the safety population**

We intended to assess the efficacy endpoints in both the intention-to-treat population (all randomly assigned participants) and the per-protocol population (all patients who received at least 3 weeks of treatment with no major protocol deviations). In October, 2018, the central pathology review identified three patients who did not fulfil inclusion criteria (due to different diagnosis), so we changed the efficacy analysis to a modified intention-to-treat population to include all patients who provided consent and had a central molecularly confirmed diagnosis of extraskeletal myxoid chondrosarcoma. Additionally, from the modified intention-to-treat population, those who received at least 1 month of treatment and had at least one radiological assessment comprised the evaluable (per-protocol) population. The safety analysis included all patients who received at least one dose of pazopanib.

Post-hoc analyses included the correlation between response (tumour shrinkage and best response by RECIST 1.1) and translational variables (gene fusions or immune-contexture by immunohistochemistry) with progression-free survival, evaluated in both the per-protocol and modified intention-to-treat populations.

Variables following binomial distributions (ie, the proportion of patients with objective response and tumour shrinkage) were expressed as frequencies or percentages with 95% CIs. Comparisons between qualitative variables were done using Fisher's exact test or the χ^2 test. Comparisons between quantitative and qualitative variables were done through non-parametric tests (Mann-Whitney *U* test or Kruskal-Wallis test).

Time-to-event variables (overall survival and progression-free survival) were measured from the start of treatment and were estimated according to the Kaplan-Meier method. Survival comparisons between categories of qualitative variables were done by the log-rank test. We did univariate analysis with the following clinicopathological factors as categorical variables: age (categorised according to the median value), sex, tumour size, tumour site and extent at diagnosis, tumour burden (sum of the maximum diameter of all the target lesions at baseline), fusion subtype, response by RECIST 1.1, and evidence of tumour shrinkage. Multivariate analysis with the variables that were significant in the univariate analysis was done according to the Cox proportional hazards regression model. All p values reported were two-sided, and statistical significance was defined as

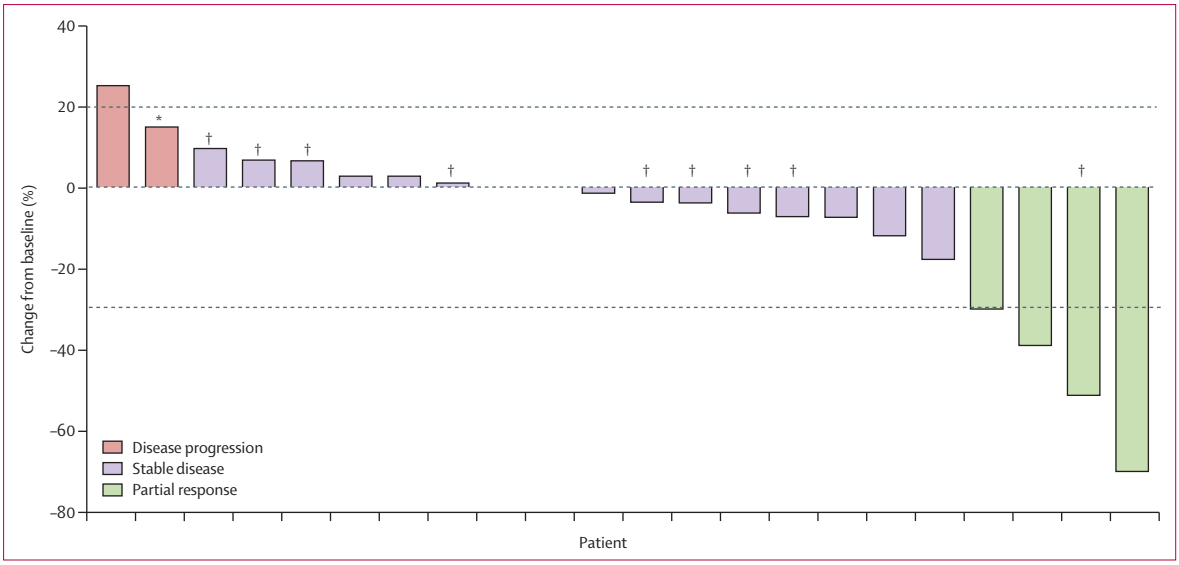

Figure 2: **Dimensional response according to RECIST 1.1**
Percentage change in tumour size from baseline to Oct 9, 2018, in assessable patients (n=22) is presented. The dashed lines represent a 20% increase in tumour diameter and a 30% decrease in tumour diameter (RECIST 1.1 cutoffs for progression and response, respectively). RECIST=Response Evaluation Criteria in Solid Tumours. *Patient had evidence of a new lesion (ie, RECIST progressive disease). †Patients who had reductions in the daily dose of pazopanib.

$p<0·05$. The software package used for statistical analysis was SPSS (version 20).

This study is registered with ClinicalTrials.gov, number NCT02066285.

Role of the funding source

GlaxoSmithKline and Novartis provided the study drug and partially supported expenses for organisational management of the study. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between June 24, 2014, and Jan 17, 2017, 30 patients were enrolled and assessed for eligibility. 26 eligible patients entered the study and started pazopanib treatment (figure 1; appendix p 7). All 26 patients who received at least one dose of pazopanib were included in the safety analysis. Three of 26 patients were excluded from the modified intention-to-treat efficacy analysis because of a negative diagnosis for *NR4A3* rearrangement. This analysis was, therefore, positive in the remaining 23 patients.

At the time of the data cutoff (Oct 9, 2018) the median follow-up was 27 months (IQR 18–30). 18 (78%) of 23 patients had completed their treatment, whereas five (22%) were still receiving pazopanib (figure 1). Reasons for discontinuation were progression of the disease (15 [65%] patients), toxicity (one [4%] patient), and treatment change (two [9%] patients; one to radiotherapy and one to surgery).

Table 1 summarises patient baseline characteristics. *NR4A3* was fused to *EWSR1* in 20 (87%) patients and to *TAF15* in three (13%) patients. All patients had progressive disease in the 6 months before starting pazopanib.

The median number of cycles of pazopanib administered per patient was 15 (IQR 5–19). The median dose intensity for pazopanib was 100% (IQR 51–100). 11 (48%) of 23 patients had to temporarily discontinue pazopanib, whereas one (4%) patient definitively interrupted pazopanib because of toxicity. A permanent dose reduction was necessary in seven (30%) of 23 patients: to 600 mg/day in one (4%) patient, 400 mg/day in five (22%) patients, and 200 mg/day in one (4%) patient.

One patient was not evaluable for the primary endpoint because of death due to cardiorespiratory failure not related to the study drug. Based on central radiological assessment, according to RECIST 1.1, four (18%) of 22 patients assessable for response had a partial response. Based on central radiological assessment, four (18%; 95% CI 1–36) of 22 evaluable patients had an objective response by RECIST 1.1. In addition to these four (18%) patients with an objective response (all of which were partial responses), 16 (73%) patients had stable disease, and two (9%) had progressive disease (figure 2). Radiologically detected tumour shrinkage was observed in 12 (55%) of 22 patients, whereas ten (45%) cases had no change or an increase in tumour size as best response. In prespecified exploratory analyses, all four patients achieving a partial response were found to have the *EWSR1–NR4A3* fusion. Thus, four (21% [95% CI 1–41]) of 19 patients in the *EWSR1–NR4A3*-positive group achieved an objective response.

23 patients (modified intention-to-treat population) were included in the survival analyses. At a 27-month median follow-up, 15 (65%) of 23 patients had events of RECIST progression and two (9%) had died (one had respiratory failure and the other a non-related natural death). Median overall survival was not reached (12-month overall survival 96% [95% CI 87–100]; 24-month overall survival 90% [77–100]; figure 3). Median progression-free survival was 19 months (95% CI 11–27; figure 3): 12-month progression-free survival was 74% (56–92) and 24-month progression-free survival was 40% (18–62).

In a post-hoc univariate landmark analysis, best response according to RECIST 1.1 correlated with progression-free survival: median progression-free survival was not reached for patients with a partial response, because none of them had disease progression at the time of the last data cutoff; median progression-free survival was 5·4 months (95% CI 6·7–24·1) for patients with stable disease and 1·0 month (95% CI not available) for patients with progressive disease (p<0·0001; appendix p 5). 24-month overall survival calculated with the actuarial method for patients with RECIST partial response was 100% versus 94% (95% CI 82–100) for patients without RECIST partial response (p=0·97; table 2). Median progression-free survival was not reached for the 12 (52%) of 22 patients with evidence of tumour shrinkage, whereas it was 7·7 months (95% CI 0–18·9; table 2) in the ten patients without evidence of any decrease in tumour size (p<0·0001; appendix p 5). A post-hoc analysis showed that all patients with tumour shrinkage were progression-free for 15 months or longer, whereas only one (10%) of ten patients without evidence of decrease in tumour size had a disease control lasting more than 15 months (figure 4). In a post-hoc analysis, median progression-free survival for the eight patients who had a permanent pazopanib daily dose reduction was 15 months (95% CI 11–20) versus 19 months (9–29) for patients who did not have a dose reduction.

In a post-hoc analysis, median progression free survival was 19·4 months in the 20 patients with the *EWSR1–NR4A3* fusion versus 4·1 months (0·7–7·5) for the three patients with *TAF15–NR4A3* fusion (p=0·085). 24-month overall survival calculated with the actuarial method was 89% (95% CI 74–100) for patients with *EWSR1–NR4A3* versus 100% in patients with *TAF15–NR4A3* (p=0·59; table 2).

No deaths associated with toxic effects were reported (table 3). One (4%) of 26 patients definitively discontinued pazopanib because of toxicity (grade 3 anal fistula). Eight (31%) of 26 patients in the safety population (seven in the modified intention-to-treat group) had to reduce the daily dose of pazopanib definitively and three (11%) had a temporary dose reduction because of toxicity. The most frequent haematological adverse events was leucopenia and the most frequent non-haematological side-effects were hypertension, increase of alanine aminotransferase or aspartate aminotransferase, and fatigue. One (4%) grade 3 (anaemia) and no grade 4 haematological toxicities were observed. The most frequent grade 3 adverse events were hypertension (nine [35%] of 26 patients), increased concentration of alanine amino-transferase (six [23%]), and increased aspartate aminotransferase (five [19%]). All patients completely recovered from their side-effects.

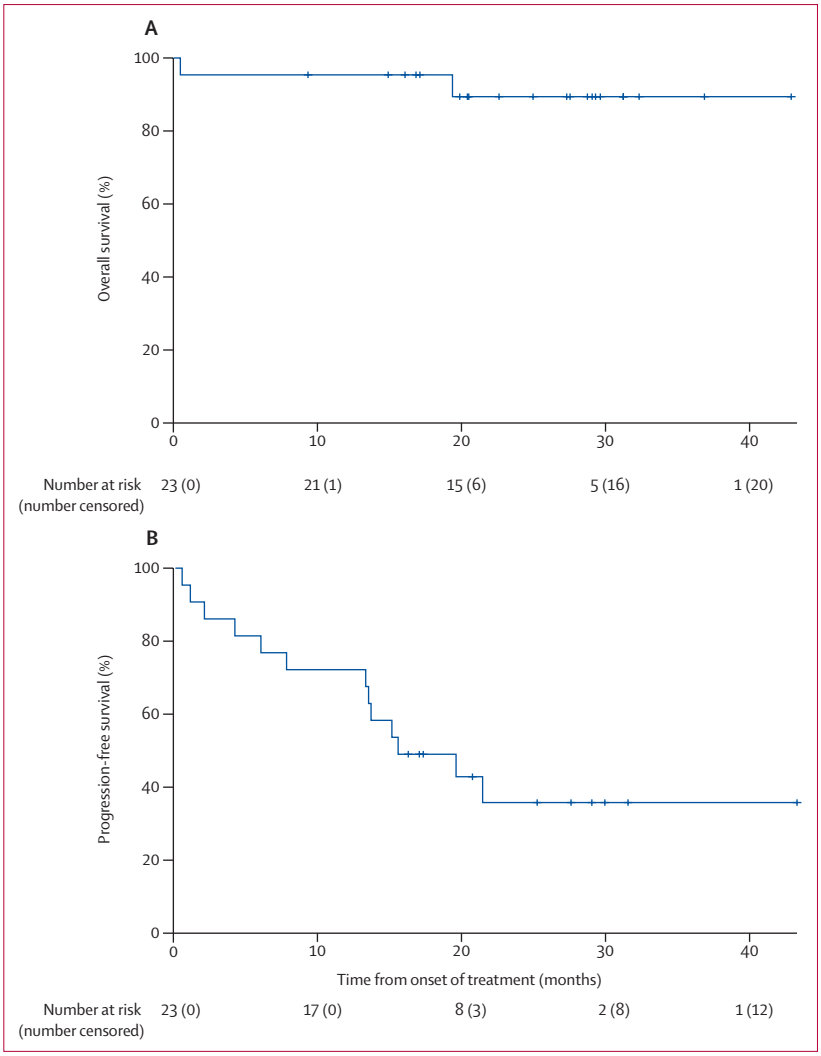

Figure 3: **Survival analyses**
(A) Overall survival. (B) Progression-free survival.

As part of prespecified exploratory analyses, and into gain insights into the molecular basis of the differential response to pazopanib, five tumours undergoing shrinkage after treatment with pazopanib (four partial responses and one stable disease according to RECIST) and five unresponsive tumours (two progressive disease and three stable disease by RECIST without any evidence of tumour shrinkage) were transcriptionally profiled by RNA sequencing. The unresponsive group included also two *TAF15–NR4A3* translocated extraskeletal myxoid chondrosarcomas.

	Modified intention-to-treat population				Per-protocol population			
	Progression-free survival		24-month overall survival		Progression-free survival		24-month overall survival	
	Median (95% CI), months	p value	Proportion of patients (95% CI), %	p value	Median (95% CI), months	p value	Proportion of patients (95% CI), %	p value
Age, years		0·22		0·14		0·11		0·29
18–63 (n=12)	13·3 (10·3–16·4)	..	100%	..	13·3 (10·3–16·4)	..	100% (NA)	
>63 (n=11)	21·2 (NA)	..	79% (54–100)	..	Not reached	..	87% (65–100)	..
Sex		0·57		0·59		0·47		0·71
Male (n=20)	19·4 (10·4–28·3)	..	89% (74–100)	..	21·2 (12–30·4)	..	93% (81–100)	..
Female (n=3)	13·1 (0–30·9)	..	100%	..	13·1 (0–30·9)	..	100% (NA)	..
Stage at diagnosis		0·78		0·074		0·5		0·3
Localised (n=12)	13·3 (9·5–17·1)	..	100%	..	13·3 (9·5–17·1)	..	100% (NA)	..
Locally advanced (n=6)	19·4 (NA)	..	67% (29–100)	..	Not reached	..	80% (45–100)	..
Metastatic (n=5)	21·2 (9·2–33·2)	..	100%	..	21·2 (9·2–33·2)	..	100% (NA)	..
Location at diagnosis		0·80		0·66		0·94		0·3w
Limbs (n=14)	14·9 (11·2–18·7)	..	93% (79–100)	..	15·4	..	100% (NA)	..
Trunk (n=4)	21·2 (0–44·1)	..	100%	..	21·2 (0–44·1)	..	100% (NA)	..
Other (n=5)	19·4 (6·8–32)	..	80% (45–100)	..	19·4 (6·8–32)	..	80% (45–100)	..
Stage at inclusion		0·76		0·0040		0·71		<0·001
Locally advanced (n=1)	19·4 (NA)	..	0%	..	19·4	..	0% (NA)	..
Metastatic (n=22)	15·4 (5·5–25·3)	..	95% (87–100)	..	21·2 (11·6–27·1)	..	100% (NA)	..
Size at diagnosis, mm		0·26		0·15		0·39		0·32
0–90 (n=10)	15·4 (NA)	..	100%	..	15·4	..	100% (NA)	..
>90 (n=9)	13·5 (0–30·5)	..	76% (47–100)	..	13·5 (3·4–23·6)	..	86% (60–100)	..
Tumour burden at baseline, mm		0·61		0·14		0·83		0·29
0–75 (n=12)	15·4 (NA)	..	100%	..	15·4	..	100% (NA)	..
>75 (n=11)	19·4 (0·9–37·8)	..	79% (54–100)	..	19·4 (7·4–31·3)	..	87% (65–100)	..
Time from diagnosis to inclusion, weeks		0·57		0·18		0·37		0·4
0-median (n=11)	19·4 (NA)	..	82% (59–100)	..	19·4	..	90% (71–100)	..
>median (n=12)	13·5 (0–28·8)	..	100%	..	13·5 (0–28·8)	..	100% (NA)	..
Translocation subtype		0·085		0·59		0·051		0·71
EWSR1-positive (n=20)	19·4 (NA)	..	89% (74–100)	..	Not reached	..	93% (81–100)	..
TAF15-positive (n=3)	4·1 (0·7–7·5)	..	100%	..	4·1 (0·7–7·5)	..	100% (NA)	..
Response		0·016		0·97		0·016		0·97
Partial response (n=4)	Not reached	..	100%	..	Not reached	..	100% (NA)	..
Stable disease (n=16)	1·9 (1·8–2·0)	..	94% (82–100)	..	1·9 (1·8–2·0)	..	94% (82–100)	..
Progressive disease (n=2)	1 (NA)	..	100%	..	1 (NA)	..	100% (NA)	..
Tumour shrinkage		<0·0001		0·29		<0·0001		0·29
Yes (n=12)	Not reached	..	100%	..	Not reached	..	100% (NA)	..
No (n=10)	7·7 (0–18·9)	..	87% (NA)	..	7·7 (0–18·9)	..	87% (NA)	..

Size at diagnosis was not available for four patients. NA=not available.

Table 2: **Univariate survival analysis**

Principal component analysis-based unsupervised feature extraction applied to the gene-expression profiles did not identify homogeneous clusters for the two groups of comparison (ie, five sensitive and five unresponsive tumours; appendix p 6). Moreover, no significant separation was observed according to RECIST categories or *NR4A3* fusion partner (appendix p 6).

The comparison of sensitive and unresponsive tumours showed 1715 differentially expressed genes (cutoff absolute fold change of >1·5; p<0·05), 1028 of which were protein-coding genes (appendix pp 8–11). Besides nervous system development and cell adhesion and differentiation, functional over-representation analysis indicated a significant enrichment of Gene Ontology terms related to angiogenesis and vasculature

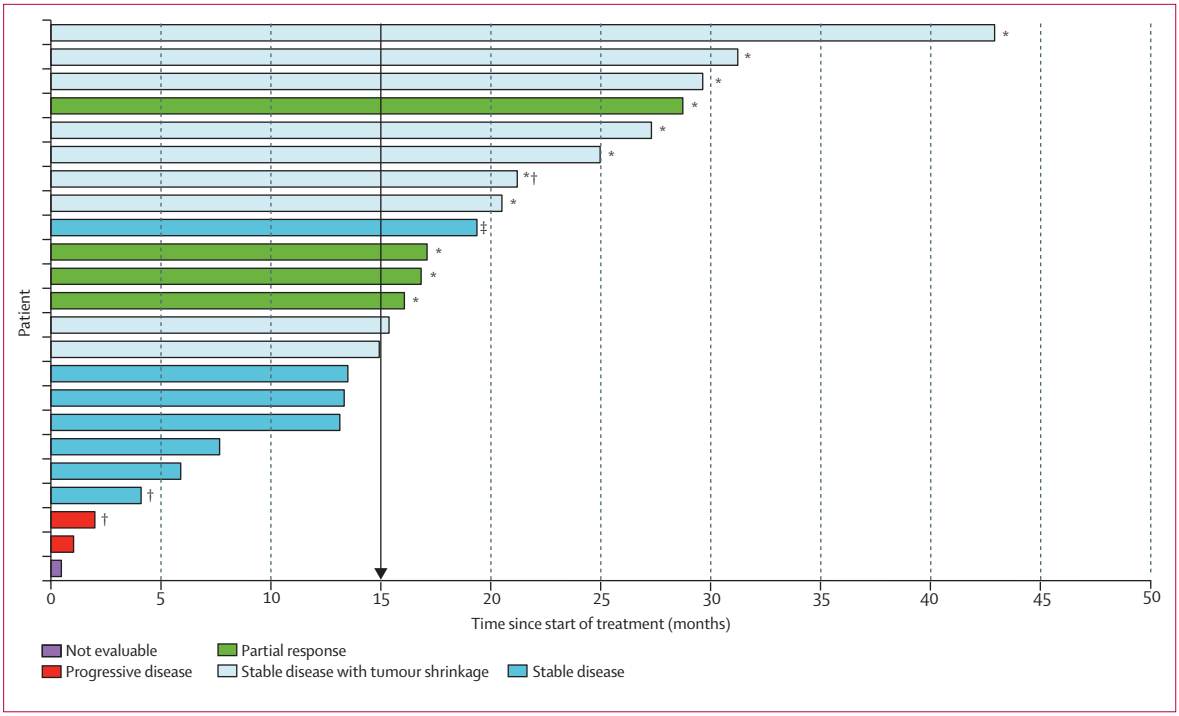

Figure 4: **Duration of treatment response**
Duration of response according to RECIST response and according to the evidence of tumour shrinkage. *Patients with evidence of tumour shrinkage and a progression-free survival longer than 15 months (as indicated by the black arrow). †*NR4A3–TAF15*-positive. ‡Patient died.

development (appendix p 6, pp 8–18). In addition, the canonical pazopanib targets *FLT1 (VEGFR1)*, *KDR (VEGFR2)*, *FLT4 (VEGFR3)*, and cognate ligands (*VEGFA* and *VEGFC*) were overexpressed (>2-fold change) in the sensitive cohort. Up-regulation (>2-fold change) of several components of the Notch pathway was also observed (appendix p 6). Finally, among the differentially expressed genes, *VEGFA* was predicted by the IPA tool as the top upstream regulator (appendix pp 8–18). Focusing on the two extreme RECIST categories, the transcriptional profile of the four partial response cases was compared with that of the two progressive disease cases. Angiogenesis, together with nervous system development and cell adhesion, were the top enriched pathways and *FLT4* (fold change of 9·7; p=0·0032), and *NOTCH1* (fold change of 5·9; p=0·0013), *NOTCH3* (fold change of 4·5; p=0·0035), *NOTCH4* (fold change of 10·9; p=0·0004) were significantly over-expressed in tumours that showed a partial response to treatment (appendix pp 18–22).

In a post-hoc exploratory analysis, the same tumour series was explored for immune contexture by immunohistochemistry. Both lymphoid (CD3-positive, CD8-positive) and myeloid (CD163-positive) infiltration was detected in all cases, irrespective of response to pazopanib. These immune cells were mostly localised in the peritumoral areas. In the intratumoral site, CD163-reactive cells were well represented, whereas few CD3 and CD8 lymphocytes were detected, as reactive isolated cells. Lymphocyte aggregates were absent in all cases (appendix p 23).

Discussion

Extraskeletal myxoid chondrosarcoma is an ultra rare sarcoma marked by low sensitivity to the chemotherapeutic drugs conventionally used in sarcoma. This European, investigator-initiated, single-arm, phase 2 study is, to the best of our knowledge, the first in this sarcoma subtype, and provides prospective evidence supporting the activity of pazopanib in adult patients with advanced disease. An objective response by RECIST 1.1 occurred in four (18%) of 22 patients with previously progressive disease, whereas a detectable degree of tumour shrinkage was observed in 12 (55%) of 22 patients. Responses were durable and disease control was prolonged, with a median progression-free survival of 19 months. In post-hoc analyses, RECIST objective response and decreases in tumour size was associated with with a better progression-free survival. Notably, in post-hoc analyses, all patients achieving a partial response carried the *EWSR1–NR4A3* fusion.

Prospective, investigator-initiated clinical studies in rare tumours pose plenty of challenges, which can be overcome within collaborative networks of institutions with expertise in the disease. Despite the rarity of extraskeletal myxoid chondrosarcoma, the present study enrolled 26 patients in less than 3 years and provided prospective evidence of the activity of an antiangiogenic drug for extraskeletal myxoid

	Grade 1–2	Grade 3	Grade 4	Grade 5
Haematological toxicity				
Leucopenia	13 (50%)	0	0	0
Anaemia	8 (31%)	1 (4%)	0	0
Neutropenia	8 (31%)	0	0	0
Lymphocytopenia	6 (23%)	0	0	0
Thrombocytopenia	4 (15%)	0	0	0
Non-haematological toxicity				
Hypertension	10 (38%)	9 (35%)	0	0
Increased alanine aminotransferase	8 (31%)	6 (23%)	0	0
Increased aspartate aminotransferase	8 (31%)	5 (19%)	0	0
Fatigue	13 (50%)	0	0	0
Diarrhoea	10 (38%)	0	0	0
Hyperglycaemia	9 (35%)	1 (4%)	0	0
Weight loss	6 (23%)	2 (8%)	0	0
Increased bilirubin	8 (31%)	0	0	0
Nausea	7 (27%)	0	0	0
Mucositis, oral	6 (23%)	0	0	0
Hypomagnesaemia	6 (23%)	0	0	0
Sodium decreased (hyponatraemia)	3 (12%)	2 (8%)	0	0
Hypophosphataemia	4 (15%)	1 (4%)	0	0
Anorexia	5 (19%)	0	0	0
Skin or hair hypopigmentation	5 (19%)	0	0	0
Vomiting	4 (15%)	0	0	0
Abdominal pain	3 (12%)	0	0	0
Palmar-plantar erythrodysesthesia syndrome	3 (12%)	0	0	0
Dysgeusia	3 (12%)	0	0	0
Increased creatinine	3 (12%)	0	0	0

Data are n (%). Only the worst toxic effect for each patient is shown.

Table 3: **Adverse events in the safety population (n=26)**

chondrosarcoma, following what was previously observed retrospectively with sunitinib.[17,18] These results are of major importance in a sarcoma with a more than 40% metastatic risk even after optimal local treatment,[10–12] in which no active drugs are approved after failure of anthracycline-based chemotherapy.

Retrospective evidence on the antitumour effect of sunitinib in patients with advanced extraskeletal myxoid chondrosarcoma has been available since 2010.[17] An initial single case report was followed by a retrospective study including ten patients with *NR4A3*-fused advanced extraskeletal myxoid chondrosarcoma treated within a compassionate-use programme, resulting in a RECIST partial response in six (60%) of ten cases, with long-lasting disease control (at a median follow-up of 8·5 months, the median progression-free survival was not reached).[18] The proportion of patients with a RECIST objective response observed with pazopanib in our study was lower than that reported for sunitinib. However, more than half of patients given pazopanib had a decrease in tumour size and, although within the context of a single-arm trial, tumour shrinkage correlated with median progression-free survival. We found that a decrease in tumour size was a better prognosticator of progression-free survival than response as assessed by RECIST, although this was a post-hoc analysis. It would be interesting to compare antiangiogenics with each other, but this study could be very challenging in a rare subgroup of a rare family of tumours. Notably, pazopanib is currently approved for advanced soft-tissue sarcoma, although only for further-line therapy.

Additionally, our results show that pazopanib provided disease control in a population of patients with evidence of disease progression in the 6 months before starting treatment. Evidence of disease progression was selected as an entry criterion to identify a subset of patients with a more aggressive tumour, since the natural history of extraskeletal myxoid chondrosarcoma can be indolent and marked by a slow evolution, even in the advanced phase of disease. In particular, at a median follow-up of 27 months, the median progression-free survival was not reached for patients with tumours that were responsive according to RECIST. The median progression-free survival was not reached even when all patients with evidence of tumour shrinkage were grouped together, with disease control lasting at least 15 months in all patients. By contrast, median progression-free survival was 1 month in patients with progressive disease according to RECIST and 7·7 months in patients with no evidence of any decrease in tumour size.

We acknowledge that the interpretation of our study needs to take into account several limitations. This study is a small, non-comparative, single-arm trial aimed at assessing the activity of pazopanib in an ultrarare sarcoma subtype. Although active, the benefit of the drug on disease control could not be quantified against the natural history of the disease or other available drugs. In addition, no conclusions can be drawn about the effect of this drug on patients' survival because it did not include a control group.

However, with the all the limitations of an external comparison, the results from this study compare favourably with the few data available on the activity of chemotherapy for extraskeletal myxoid chondrosarcoma, which show that the proportion of patients with an objective response to cytotoxic drugs ranges from 0% to 40%, with a short response duration.[8,11–16] It is worth noting that the fact that, in those studies, extraskeletal myxoid chondrosarcoma diagnosis is not always sustained by the presence of *NR4A3* fusion might be a confounding factor.

Remarkably, all three *TAF15–NR4A3*-positive tumours included in this study did not respond, although the small number of patients with tumours harbouring the *TAF15–NR4A3* fusion did not allow us to draw definitive conclusions. In a previous study,[18] we observed that *TAF15–NR4A3* was resistant also to sunitinib. Thus, the absence of responses to pazopanib in *TAF15–NR4A3*-positive cases might also be related to the particularly aggressive clinical behaviour reported for this tumour

variant,[10] which is in line with the apparently more pronounced malignant phenotype of *TAF15–NR4A3* versus *EWSR1–NR4A3* engineered cell models.[23]

The transcriptional profile of a subset of patients achieving tumour shrinkage was compared with that of treatment-insensitive patients. An upregulation of canonical pazopanib targets—namely *FLT1 (VEGFR1)*, *KDR (VEGFR2)*, and *FLT4 (VEGFR3)*—along with several components of the Notch pathway, were observed to be associated with tumour shrinkage. The coordinated activity of VEGF and Notch signals has a key role in regulating endothelial cell differentiation during angiogenesis.[24] Thus, the responsiveness to pazopanib might be due at least in part to an interference with the VEGF–Notch axis, which appears to be over-represented in sensitive extraskeletal myxoid chondrosarcoma.

Although no difference in distribution and frequency of immune cells in pazopanib-sensitive and pazopanib-insensitive cases was observed, extraskeletal myxoid chondrosarcoma displayed an immune infiltration enriched in myeloid CD163-positive cells, a marker for M2 immunosuppressive, protumorigenic macrophages. Since VEGF signalling is known to exert immunosuppressive activity, we could speculate that pazopanib might also exert its therapeutic activity by limiting the VEGF-mediated local immune suppression and possibly restoring a pre-existing immunity.[25,26] This effect suggests that it could be worth exploring the combination of antiangiogenic drugs (such as pazopanib) and immunotherapy drugs for extraskeletal myxoid chondrosarcoma.

In conclusion, this study shows that pazopanib has antitumour activity in advanced extraskeletal myxoid chondrosarcoma. Other antiangiogenic drugs could also show similar activity. The specific mechanism of action remains hypothetical. Half of patients benefited from pazopanib for a prolonged period of time as observed in other rare sarcoma subtypes (eg, alveolar soft part sarcoma and malignant solitary fibrous tumour).[19,27] Clinical studies on the optimal treatment line of pazopanib for extraskeletal myxoid chondrosarcoma and its effect on overall survival would be welcome, although the rarity of this subset is a major obstacle.

Contributors

SS and JM-B conceived and designed the study. SS, SF, AR, NH, EP, MAVS, AMF, AG, AL-P, GG, AI, ALC, SD, JYB, NP, DB, EdA, MK, CM, SB, GPD, MB, RM, PC, JC, and JM-B collected the data. SS, NH, PGC, AG, JYB, ED-A, CM, GPD, VV, CC, MB, DR, RM, PC, and JM-B contributed to the data analysis and interpretation. SS, AR, NH, AMF, PGC, AG, GG, JYB, SB, GPD, CC, MB, RM, PC, and JM-B wrote the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

SS declares personal fees (advisory role) from Bayer, Lilly, and PharmaMar; and grants from Bayer, GlaxoSmithKline, Lilly, Novartis, Pfizer, and PharmaMar, outside the submitted work. AR declares personal fees (advisory role) for Amgen, AstraZeneca, Lilly, Novartis, PharmaMar, Roche, and Tesaro; and grants from Eisai, Pharmamar, and Roche, outside the submitted work. NH reports grants from Novartis, outside the submitted work. EP reports personal fees (advisory role) from Amgen, Daiichi Sankyo, and Lilly; grants from Amgen; non-financial support from Bristol-Myers Squibb, Pfizer, and PharmaMar; and other (travel) support from Lilly, PharmaMar, and Takeda, outside the submitted work. MAVS reports personal fees from Lilly, Celgene, PharmaMar, and Eisai; and grants from Pfizer, outside the submitted work. PGC declares grants from Advenchen Lab, Amgen, Arog Pharmaceuticals, Bayer, Blueprint, Daiichi, Deciphera, Eisai, Lilly, Epizyme, GlaxoSmithKline, Karyopharm, Novartis, Pfizer, and PharmaMar; and personal fees from Bayer, Deciphera, Eisai, Lilly, Nektar Therapeutics, Pfizer, Eisai, and PharmaMar, outside the submitted work. EP reports personal fees from Amgen, Daiichi Sankyo, and Lilly; and non-financial support from Pfizer, PharmaMar, Takeda, Lilly, and Bristol-Myers Squibb, outside the submitted work. GG reports grants from Bayer, and personal fees from Eisai, Lilly, Novartis, and PharmaMar, outside the submitted work. AI declares grants from Merck Sharp & Dohme, Bayer, AstraZeneca, GlaxoSmithKline, PharmaMar, Novartis, and Roche; personal fees from Epizyme and Springworks; and non-financial support from Merck Sharpe & Dohme and Roche, outside the submitted work. ALC reports personal fees from PharmaMar, Lilly, Amgen, and Pfizer, outside the submitted work. JYB declares grants, personal fees, and non-financial support from GlaxoSmithKline and Novartis, outside the submitted work. EdA reports grants from PharmaMar; personal fees from Bayer, Bristol-Myers Squibb, PharmaMar, Pfizer, and Roche; non-financial support from PharmaMar and Roche; and other (travel) support from PharmaMar, outside the submitted work. JC declares personal fees from AstraZeneca, Eisai, Lilly, Roche, Novartis, PharmaMar, and Pfizer; non-financial support from Roche, Novartis, PharmaMar, Eisai, Lilly, and Pfizer; and other support from AstraZeneca, Eisai, Lilly, Roche, Novartis, PharmaMar, and Pfizer, outside the submitted work. JM-B reports grants from Eisai, Lilly, PharmaMar, and Novartis; and other support from PharmaMar, outside the submitted work. SF, AMF, AG, AL-P, SD, NP, DB, MK, CM, SB, GPD, VV, CC, MB, DR, RM, and PC declare no competing interests.

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