Sunitinib for metastatic progressive phaeochromocytomas and paragangliomas: results from FIRSTMAPPP, an academic, multicentre, international, randomised, placebo-controlled, double-blind, phase 2 trial

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Summary

Background No randomised controlled trial has ever been done in patients with metastatic phaeochromocytomas and paragangliomas. Preclinical and first clinical evidence suggested beneficial effects of sunitinib. We aimed to evaluate the safety and efficacy of sunitinib in patients with metastatic phaeochromocytomas and paragangliomas.

Methods FIRSTMAPPP is a multicentre, international, randomised, placebo-controlled, double-blind, phase 2 trial done at 14 academic centres across four European countries. Eligible participants were adults (aged ≥18 years) with sporadic or inherited progressive metastatic phaeochromocytomas and paragangliomas. Patients were randomly assigned (1:1) to receive either oral sunitinib (37·5 mg per day) or placebo. Randomisation was stratified according to *SDHB* status (mutation present *vs* wild type) and number of previous systemic therapies (0 *vs* ≥1). Primary endpoint was the rate of progression-free survival at 12 months according to real-time central review (Response Evaluation Criteria in Solid Tumours version 1.1). On the basis of a two-step Simon model, we aimed for the accrual of 78 patients, assuming a 20% improvement of the 12-month progression-free survival rate from 20% to 40%, to conclude that sunitinib is effective. Crossover from the placebo group was allowed. This trial is registered with ClinicalTrials.gov, number NCT01371201, and is closed for enrolment.

Findings From Dec 1, 2011, to Jan 31, 2019, a total of 78 patients with progressive metastatic phaeochromocytomas and paragangliomas were enrolled (39 patients per group). 25 (32%) of 78 patients had germline *SDHx* variants and 54 (69%) had used previous therapies. The primary endpoint was met, with a 12-month progression-free survival in 14 of 39 patients (36% [90% CI 23–50]) in the sunitinib group. In the placebo group, the 12-month progression-free survival in seven of 39 patients was 19% (90% CI 11–31), validating the hypotheses of our study design. The most frequent grade 3 or 4 adverse events were asthenia (seven [18%] of 39 and one [3%] of 39), hypertension (five [13%] and four [10%]), and back or bone pain (one [3%] and three [8%]) in the sunitinib and placebo groups, respectively. Three deaths occurred in the sunitinib group: these deaths were due to respiratory insufficiency, amyotrophic lateral sclerosis, and rectal bleeding. Only the latter event was considered drug related. Two deaths occurred in the placebo group due to aspiration pneumonia and septic shock.

Interpretation This first randomised trial supports the use of sunitinib as the medical option with the highest level of evidence for anti-tumour efficacy in progressive metastatic phaeochromocytomas and paragangliomas.

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Introduction

Malignant phaeochromocytomas and paragangliomas are ultra-rare cancers, with an annual incidence of less than one per million, and are defined by the presence of distant metastases.[1,2] Main characteristics of metastatic phaeochromocytomas and paragangliomas include inherited diseases in up to 50% of cases, including germline *SDHB* variants that have prognostic impact,[1,3–5] hormone-related hypertension in up to 80%, and bone metastases in up to 70% of cases.[5,6] As metastatic phaeochromocytomas and paragangliomas are indolent in some cases, the decision to initiate systemic treatment is mainly based on the presence of uncontrolled hormone secretion or documented tumour progression.[1]

So far, no randomised controlled trial in patients with metastatic phaeochromocytomas and paragangliomas has

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Research in context

Evidence before this study

With an annual incidence of less than one per million, metastatic phaeochromocytomas and paragangliomas are ultra-rare cancer entities. Clinical outcome is heterogeneous and some tumours come with an indolent biological behaviour, whereas some patients die rapidly following progressive disease. Because of the rarity of the disease, prospective clinical trials are scarce. At the time of when this trial was designed (2007–08), the optimal management of patients with progressive metastatic phaeochromocytomas and paragangliomas remained undefined, with no approved systemic therapy up to now. A group of experts (FIRSTMAPPP Scientific Board) did a comprehensive literature search using PubMed with search dates between Jan 1, 1990, and Dec 31, 2007. The search terms used were "metastatic pheochromocytoma", "metastatic paraganglioma", "therapy", "chemotherapy", "sunitinib", "MIBG", or "radionuclide therapy" with no language restrictions. This search was updated during preparation of the European Society of Medical Oncology Clinical Guidelines for adrenocortical carcinoma and malignant phaeochromocytoma in May, 2019, and in February, 2023. No randomised controlled trial and only ten prospective studies (with a total number of 311 enrolled patients) and 17 retrospective studies (with 466 patients) have been published. Most studies report on radiolabelled ligand therapy, dacarbazine-based cytotoxic chemotherapy, or multi-targeted receptor tyrosine kinase inhibitors. Complete responses were reported extremely rarely, and partial responses were documented in most studies in less than 25% of patients. At the time of initiating this trial, preclinical data as well as first case series suggested efficacy of sunitinib by targeting the highly vascularised metastatic phaeochromocytomas and paragangliomas. These data formed the basis of the study protocol by the FIRSTMAPPP scientific board together with expert centres of the European Network for the Study of Adrenal Tumors.

Added value of this study

Despite the rarity of metastatic phaeochromocytomas and paragangliomas, we were able to recruit the required number of patients with documented progressive disease for this first ever randomised controlled trial in this tumour entity.
The FIRSTMAPPP trial shows the feasibility but also the prerequisites and conditions required to complete a randomised phase 2 trial, including close collaboration of all expert centres in one continent. Thus, this study provides the best achievable level of evidence in this ultra-rare cancer. Thereby, sunitinib becomes the best validated standard in patients with progressive metastatic phaeochromocytomas and paragangliomas. In addition, higher response rate observed in patients with pathogenic germline *SDHB* variant constitute the first steps towards a personalised approach in this patient cohort than in those without the *SDHB* mutation.

Implications of all the available evidence

Our study has immediate impact for the treatment of patients with progressive metastatic phaeochromocytomas and paragangliomas, as we show for the first time in a randomised controlled trial that sunitinib is effective in this difficult-to-treat disease. In addition, sunitinib might now serve as a standard systemic therapy against which all other treatment options should be tested.

been published. Meta-iodobenzylguanidine therapy and dacarbazine-based cytotoxic chemotherapy constitute the two main historical options in guidelines.[1] In two phase 2 trials investigating low-specific or high-specific meta-iodobenzylguanidine activity therapy in selected patients with metastatic phaeochromocytomas and paragangliomas, partial response rates were 23% and 27% per study.[7,8] Only one old prospective and few retrospective studies are available for cytotoxic chemotherapy, mainly dacarbazine based, reporting partial response rates ranging from 25% to 45%.[1,9–14]

Sunitinib is a multi-targeted receptor tyrosine kinase inhibitor (TKI) directed against VEGFR, PDGFR, and RET. In 2008, a group of experts selected sunitinib as the choice of drug to be investigated in patients with metastatic phaeochromocytomas and paragangliomas based on the following observations: the high frequency of *SDHx* gene alterations in these patients leading to HIF-2α stabilisation and consecutive activation of downstream targets such as VEGF and PDGF and their receptors;[15] the anti-tumour effect of anti-VEGF antibodies in experimental metastatic phaeochromocytoma and paraganglioma models;[16] positive results obtained with sunitinib in a phase 3 trial on pancreatic neuroendocrine tumours;[17] as well as first objective responses seen in patients with advanced metastatic phaeochromocytomas and paragangliomas treated with sunitinib.[18] At the same time, in the absence of robust prospective data, a placebo was chosen as the best control group by the same group of experts.

In this first randomised controlled trial ever done in patients with metastatic phaeochromocytomas and paragangliomas, we aimed to evaluate the safety and efficacy of sunitinib in patients with metastatic phaeochromocytomas and paragangliomas.

Methods

Study design and participants

The FIRSTMAPPP study is an academic, multicentre, international, randomised, placebo-controlled, double-blind, phase 2 trial. A total of 14 academic centres across four European countries were involved (Villejuif, Strasbourg, Angers, Lyon, Paris, Bordeaux, and Marseille [France]; Würzburg, München, and Berlin [Germany]; Brescia, Veneto, and Napoli [Italy]; and Nijmegen [Netherlands]; appendix pp 118).

See **Online** for appendix

Eligible participants met the following inclusion criteria: aged 18 years or older, sporadic or inherited metastatic phaeochromocytomas and paragangliomas, pretreated or not, an Eastern Cooperative Oncology Group status of 0–2, Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) measurable targets, and documented progressive disease within 18 months according to RECIST 1.1. Adequate liver, renal, and cardiac functions (including home blood pressure monitoring) were required. Main exclusion criteria were uncontrolled hypertension, cardiovascular events within the previous 12 months, previous use of VEGF inhibitors, and uncontrolled brain metastasis. Additional eligibility criteria are available in the protocol (appendix pp 8–117).

All patients provided written informed consent. This study was done in accordance with the protocol (appendix pp 8–117), and conformed to the Good Clinical Practice Guidelines, and the Declaration of Helsinki. All ethics committees (Comité de Protection des Personnes Ile de France VIII, Ethik-Kommission des Landes Berlin, Ethik-Kommission des Klinikums der Universität München, Ethik-Kommission der Universität Würzburg, METC Oost-Nederland, Comitato Etico Istituto Oncologico Veneto, Comitato Etico dell'AO Spedali Civili di Brescia, and Comitato Etico per le attività biomediche Università Federico II di Napoli) and national authorities approved this study. The FIRSTMAPPP trial was designed under the auspices of the FIRSTMAPPP Scientific Board and European Network for the Study of Adrenal Tumors. Data were monitored onsite.

Randomisation and masking

Patients were randomly assigned (1:1) to either the sunitinib group or placebo group. Randomisation was done by minimisation with a random component of 20% using the web-based system TENALEA (version 2.2). Randomisation was stratified according to the *SDHB* mutation status (mutation present *vs* wild type) and the number of previous systemic therapies (0 *vs* ≥1), and was done centrally at the Biostatistics Unit of Gustave Roussy (Villejuif, France). Participants and investigators were masked to group assignment.

Procedures

Participants received either 37·5 mg sunitinib or placebo capsules of similar appearance once per day in a continuous oral intake. The dose of sunitinib could be reduced to 25 mg or 12·5 mg per day in case of adverse events. Intra-patient re-escalation was allowed as well as dose escalation to 50 mg per day in participants without tumour response by RECIST and experiencing no or only minor adverse events. Treatment was maintained until RECIST 1.1 documented progression, unacceptable adverse events, or death. Crossover was allowed for patients randomly assigned to the placebo group at the time of confirmed disease progression.

Clinical and biomarker data were collected once a week in the first 4 weeks, then every 4 weeks until week 12, and thereafter every 12 weeks. Patients underwent a neck, chest, abdomen, and pelvic CT or MRI scan, with contrast, at baseline and every 12 weeks during the study. Real-time blinded central review was done according to RECIST 1.1 criteria. In addition, ^{18}[F]fluorodeoxyglucose ([^{18}F]FDG)-PET (or the most informative diagnostic functional imaging according to the protocol) was done every 12 weeks.

Vital signs, blood pressure, heart function, and pain-related symptoms were ascertained according to procedures defined in the study protocol (appendix pp 8–117).

An independent data medical committee was set up to control for safety, including compatibility of hormone and drug-related hypertension, and enrolment rate. Four independent data medical committee meetings over 10 years recommended the continuation of the trial without any change in the protocol.

Outcomes

The primary endpoint was the progression-free survival rate at 12 months associated with sunitinib based on real-time central RECIST 1.1 evaluation.

Secondary endpoints were progression-free survival defined as the time from randomisation to first documentation of objective tumour progression or to death due to any cause, whichever occurs first; overall survival defined as the time from randomisation to death due to any cause; objective response rate defined as complete response plus partial response rates; and duration of response, defined as the time from the first documentation of overall response (complete response or partial response) that is subsequently confirmed, to the first tumour progression or death due to any cause. Safety was evaluated continuously, and the severity of adverse events were assessed by the investigator according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

The assessment of the quality of life was part of an exploratory analysis based on the European Organization for Research and Treatment of Cancer, quality-of-life Questionnaire (EORTC QLQ-C30 [version 3]) that was collected at baseline and then every 3 months. Patients rated pain severity using the Visual Analog Bone Pain Scale at baseline and at 3, 12, and 24 months.

In addition, predefined analyses were done for potential relationships between clinical parameters, previous therapies, adverse events, and cancer-related outcomes.

Prespecified exploratory analyses were planned and will be reported in dedicated studies focusing on blood pressure control, roles of hormone-related biomarkers, and ([^{18}F]FDG)-PET as surrogates of tumour response as well as tissue-related biomarkers depending on tissue availability.

	Sunitinib (n=39)	Placebo (n=39)	Total (n=78)
Median age (years)	58 (50–65)	50 (43–56)	54 (46–63)
Sex			
Male	25 (64%)	21 (54%)	46 (59%)
Female	14 (36%)	18 (46%)	32 (41%)
ECOG performance status			
0	16/38 (42%)	26/38 (68%)	42/76 (55%)
1	18/38 (47%)	10/38 (26%)	28/76 (37%)
2	4/38 (11%)	2/38 (5%)	6/76 (8%)
Location of the primary tumour			
Head and neck	2 (5%)	2 (5%)	4 (5%)
Thorax	2 (5%)	2 (5%)	4 (5%)
Abdomen extra adrenal	10 (26%)	12 (31%)	22 (28%)
Adrenal	17 (44%)	22 (56%)	39 (50%)
Pelvis	2 (5%)	0	2 (3%)
Others	6 (15%)	1 (3%)	7 (9%)
Increased CGA or metanephrines†			
Yes	29 (74%)	26 (67%)	55 (71%)
No	9 (23%)	12 (31%)	21 (27%)
Unknown	1 (3%)	1 (3%)	2 (3%)
SDHB germline mutation*	13 (33%)	12 (31%)	25 (32%)
Hypertension at baseline	16 (41%)	15 (38%)	31 (40%)
Number of metastatic sites			
1	8 (21%)	12/38 (32%)	20/77 (26%)
2	15 (38%)	13/38 (34%)	28/77 (36%)
3	11 (28%)	7/38 (18%)	18/77 (23%)
4	5 (13%)	6/38 (16%)	11/77 (14%)
Bone metastasis	27 (69%)	24 (62%)	51 (65%)
Surgery of the primary tumour‡	35 (90%)	39 (100%)	74 (95%)
Synchronous metastasis			
No	27 (69%)	28 (72%)	55 (71%)
Yes	12 (31%)	11 (28%)	23 (29%)
First-line therapy*	17 (44%)	14 (36%)	31 (40%)
Previous treatment	26 (67%)	28 (72%)	54 (69%)
[^{131}I] MIBG therapy	7 (18%)	14 (36%)	21 (27%)
Cytotoxic chemotherapy	11 (28%)	9 (23%)	20 (26%)
Embolisation	3 (8%)	3 (8%)	6 (8%)
Radiofrequency ablation	4 (10%)	5 (13%)	9 (12%)
Cryoablation	6 (15%)	1 (3%)	7 (9%)
External radiotherapy	14 (36%)	10 (26%)	24 (31%)
Everolimus	1 (3%)	0	1 (1%)
Somatostatin analogues	1 (3%)	6 (15%)	7 (9%)
Interferon	6 (15%)	3 (8%)	9 (12%)
Peptide receptor radionuclide therapy	2 (5%)	5 (13%)	7 (9%)

Data are median (IQR), n (%), or n/N (%). CGA=chromogranin A. ECOG=Eastern Cooperative Oncology Group. MIBG=meta-iodobenzylguanidine. *The study groups did not differ significantly (p>0·05 by Fisher's test). †Increased concentration was defined as twice above the upper limit of the normal range at baseline. ‡Size of the primary tumour was more than 5 cm in 28 (88%) of 32 patients in the sunitinib group and 27 (73%) of 37 in the placebo group.

Table 1: **Demographic and baseline characteristics***

Statistical analysis

This study was designed as a randomised, non-comparative, placebo-controlled trial. The primary endpoint (12-month progression-free survival rate) was assessed on the intention-to-treat population and based upon central imaging review. The basic assumption was a 20% improvement from 20% to 40% of the 12-month progression-free survival rate. The analysis was done according to the Simon two-step design[19] with an alpha of 10% and power of 90%. Consequently, 39 patients were required in each group for a total of 78 patients.

The first analysis (ie, first step) was planned 12 months after the inclusion of 34 patients, 17 in each group. If less than four patients of the sunitinib group showed no progression of disease at 12 months, the trial would have been stopped for futility. The final analysis (ie, second step) was obtained for all the 78 patients. If 11 or more patients showed no disease progression at 12 months, then sunitinib would be considered effective according to the Simon design.

The placebo group served for validation of the hypothesis that without active treatment the 12-month progression-free survival is 20% (within the 90% CI) to confirm the Simon design conclusion. The 20% 12-month progression-free survival rate hypothesis takes into account the request for a documented progression within 18 months before enrolment.

Progression-free survival and overall survival were estimated using the Kaplan–Meier method and presented with Rothman 95% CI. Median follow-up was estimated by reverse Kaplan–Meier method. As an exploratory analysis, we used Cox proportional-hazards models to test the treatment effect within different subgroups. The models used were adjusted by the subgroups analysed.

The QLQ-C30 questionnaire was interpreted as proportions of patients with a deterioration in QLQ-C30 scores (≥10-point decrease or increase for quality of life or symptoms scale) on different subscales.[20] A Visual Analog Bone Pain Scale was applied for evaluation of bone pain severity ratings and deterioration was interpreted as a 2-point increase.[21]

We did all statistical analyses with SAS (version 6.4). This trial is registered with ClinicalTrials.gov, number NCT01371201, and closed for enrolment.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The private donator had no role in data analysis, data interpretation, and writing of the report.

Results

From Dec 1, 2011, to Jan 31, 2019, a total of 78 patients with progressive metastatic phaeochromocytomas and paragangliomas were randomly assigned to a study group (39 patients per group). In total, the median age

was 54 years (IQR 46–63), and 32 (41%) of 78 were women and 46 (59%) were men. Main tumour characteristics were well balanced between both groups (table 1). Previous treatments were given in 54 (69%) of 78 patients, including systemic therapy (ie, meta-iodobenzylguanidine, chemotherapy, everolimus, somatostatin analogues, interferon, or peptide receptor radionuclide therapy) in 22 (56%) of 39 patients in the sunitinib group and 25 (64%) of 39 in the placebo group.

Patients received sunitinib for a median duration of 12 months (IQR 4–18) or placebo for a median duration of 4 months (IQR 3–9). The most common reasons for treatment discontinuation were tumour progression in 24 (62%) of 39 patients in the sunitinib group and 32 (82%) of 39 patients in the placebo group, or adverse events in five (13%) patients in the sunitinib group (figure 1).

Dose interruption was reported in 27 (69%) of 39 in the sunitinib group and six (15%) of 39 in the placebo group. At least one dose reduction to 25 mg per day was reported in 17 (44%) of 39 patients in the sunitinib group and one (3%) of 39 in the placebo group. No dose escalation was reported.

Regarding the primary endpoint in the sunitinib group at the first-step analysis at 12 months, after the inclusion of the first 17 patients, six (35%) of 17 were alive and free of progression; at the second-step analysis on the 39 patients, 14 patients (36% [90% CI 23–50]) showed no progression of disease at 12 months (table 2). At the second-step analysis, in the placebo group, seven patients (19% [90% CI 11–31]) showed no progression of disease at 12 months. As 20% was included in the 90% CI, the hypotheses of our design were validated and sunitinib was considered effective.

In terms of the secondary endpoints, the median follow-up was 29·7 months (IQR 18·4–37·0). Median progression-free survival was 8·9 months (IQR 3·4–19·5) in the sunitinib group and 3·6 months (3·0–8·6) in the placebo group (figure 2A). At 24 months, the progression-free survival rate was 17·6% in the sunitinib group and 8·4% in the placebo group (table 2). Of note, the progression-free survival rate at 24 months confirms previous tumour progression within 18 months in almost all patients. 27 (69%) of 39 patients in the placebo group crossed over and received sunitinib. Median overall survival of the entire population with metastatic phaeochromocytomas and paragangliomas was 29·5 months (IQR 15·4–49·5) and was not significantly different in both groups: 26·1 months (IQR 16·8–36·9) in the sunitinib group and 49·5 months (15·4–52·9) in the placebo group (figure 2B). The cause of death was related to disease progression in 19 (79%) of 24 patients in the sunitinib group and 13 (81%) of 16 in the placebo group. No complete response was documented. Partial response rate was 36·1% (95% CI 20·8–53·8) in the sunitinib group and 8·3% (1·8–22·5) in the placebo group (table 2; figure 3). The median duration of response was 12·2 months (IQR 6·3–27·7) in the sunitinib group.

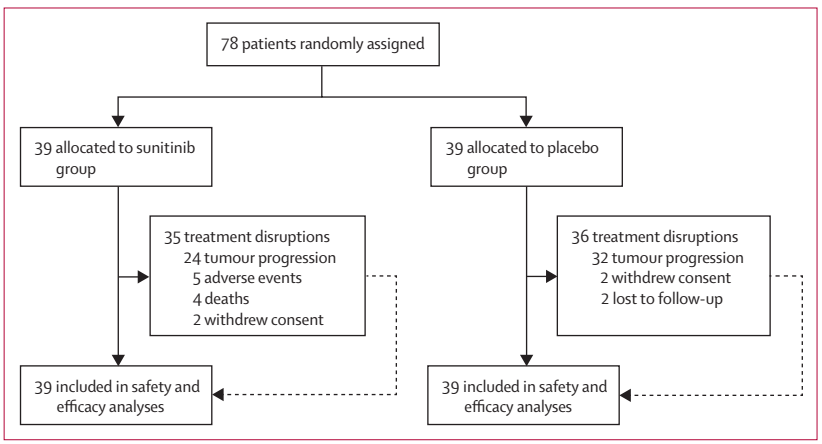

Figure 1: **Trial profile**

	Sunitinib (n=39)	Placebo (n=39)
Progression-free survival		
Number of events	35	34
Number censored	4	5
Median (months)	8·9 (5·5–12·7)	3·6 (3·1–6·1)
6-month rate	66·7% (51·0–79·4)	37·9% (24·3–53·7)
12-month rate	35·9% (22·7–51·6)	18·9% (9·5–34·1)
24-month rate	17·6% (8·7–32·5)	8·4% (2·7–23·7)
Overall survival		
Number of events	24	16
Number of censored	15	23
Median (months)	26·1 (18·7–36·7)	49·5 (15·9–52·9)
6-month rate	92·2% (79·3–97·3)	89·5% (76·0–95·9)
12-month rate	78·3% (62·6–88·6)	75·2% (59·2–86·4)
24-month rate	56·7% (40·1–72·0)	58·1% (39·7–74·5)
Objective tumour response		
Best-observed response*		
Complete response rate	0 (0–9·7)	0 (0–9·7)
Partial response rate	36·1 (20·8–53·8)	8·3 (1·8–22·5)†
Stable disease rate	36·1 (20·8–53·8)	36·1 (20·8–53·8)
Progressive disease rate	27·8 (14·2–45·2)	55·6 (38·1–72·1)
Objective response rate	36·1 (20·8–53·8)	8·3 (1·8–22·5)

Data are n, median (95% CI), or response rate (95% CI). Table 2 shows data of the final second-step analysis. Please note that expression of the primary and secondary endpoint results in table 2 (95% CI time-to-event variable for the primary endpoint and secondary endpoints for consistency) differs from the main text (90% CI binary variable for the primary and IQR expression for some secondary endpoints). Objective tumour response was evaluated according to Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1). Progression-free survival and overall survival rates were estimated using the Kaplan–Meier estimation and their CIs were estimated with Rothman's method. Clopper-Pearson method was used for CIs of objective tumour and best-observed responses.
*Best response according to RECIST 1.1 was not available for six (8%) of 78 patients. These six patients did not have any radiological evaluation available because of death (n=4) or lost to follow-up (n=2) before their first evaluation.
†As an intention-to-treat analysis, one (3%) of 39 patients treated with sunitinib at the time of partial response because of crossover was considered in the placebo group.

Table 2: **Summary of efficacy measures in the intention-to-treat population**

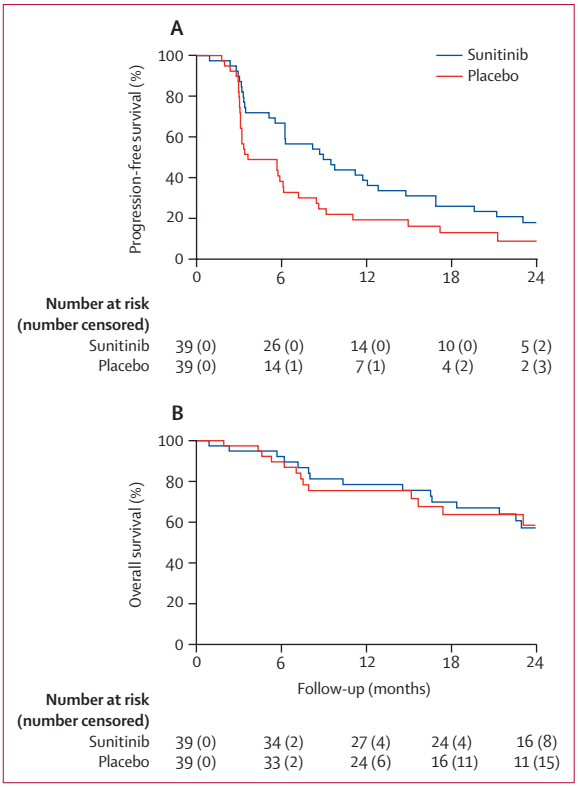

Figure 2: **Kaplan–Meier curves for progression-free survival (A) and overall survival (B)**

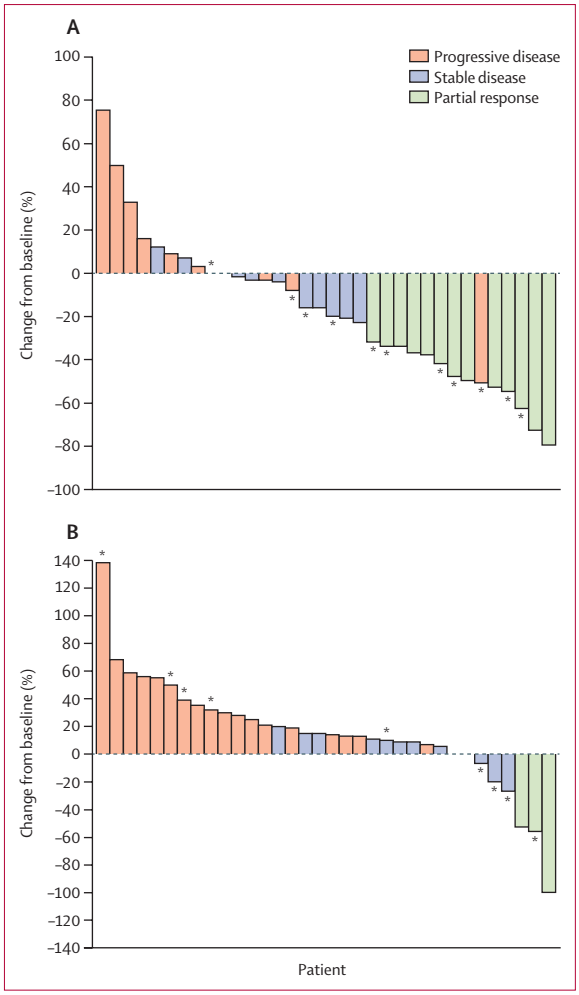

Figure 3: **Percentage change from baseline in the sum of the longest diameters of target lesions at best response according to central Response Evaluation Criteria in Solid Tumours (version 1.1) criteria by patients in the sunitinib group (A) and placebo group (B)**
Ten patients (n=5 in the sunitinib group; n=5 in the placebo group) were not included in these figures: six patients did not have any radiological evaluation (four because of early death and two because of early lost to follow-up) and four patients' sum of target lesions could not be interpreted. Partial responses in the placebo group were related to sunitinib therapy in one patient with *SDHB* mutation classified in the placebo group based on intention-to-treat methodology and abdomen lymph node targets only in two patients. *Patient with *SDHB* mutation.

In some analysed subgroups (*SDHB*-mutated subgroup and patients with arterial hypertension at baseline) of the exploratory analysis, the hazard ratio for progression or death favoured sunitinib compared with placebo (appendix p 2). Partial response rate was higher in patients with germline *SDHB* variants, previous systemic anti-tumour therapies, or with a history of hypertension at baseline in the sunitinib group than in the placebo group (appendix p 3).

EORTC QLQ-C30 data were available for 75 (96%) of 78 patients. The proportion of patients without quality-of-life deterioration was higher in the placebo group than in the sunitinib group at 3 months (89% [95% CI 71–96] *vs* 73% [55–85]), but comparable at 12 months (figure 3; appendix pp 4–5).

Pain severity ratings were available for all patients. Probability of being free of pain was higher in the sunitinib group than in the placebo group, and the largest proportional difference was at 2 years in the sunitinib group compared with the placebo group (79% [95% CI 62–90] *vs* 42% [25–61]; (appendix pp 4–5).

Most adverse events in both groups were grade 1 or 2, and occurred in both groups (table 3). In addition, 28 (72%) of 39 patients in the sunitinib group and 24 (62%) of 39 patients in the placebo group had grades 3–5 adverse events (table 3). Overall, the most common adverse events were asthenia, diarrhoea, hypertension, vomiting, and nausea. The most frequent grade 3 or 4 adverse events were asthenia (seven [18%] of 39 in the sunitinib group and one [3%] of 39 in the placebo group), hypertension (five [13%] in the sunitinib group and four [10%] in the placebo group), and back or bone pain (one [3%] in the sunitinib group and three [8%] in the placebo group). Three deaths occurred in the sunitinib group and were related to respiratory insufficiency, amyotrophic lateral sclerosis (diagnosed 1 year after the end of treatment), and rectal bleeding. This latter death event occurred in a patient with collateral venous circulation of a pelvic bone metastasis

	Sunitinib (n=39)			Placebo (n=39)			Total (n=78)		
	Grades 1–2	Grades 3–4	Grade 5	Grades 1–2	Grades 3–4	Grade 5	Grades 1–2	Grades 3–4	Grade 5
Abdominal pain	6 (15%)	1 (3%)	0	4 (10%)	0	0	10 (13%)	1 (1%)	0
Amyotrophic lateral sclerosis	0	0	1 (3%)	0	0	0	0	0	1 (1%)
Anaemia	11 (28%)	1 (3%)	0	2 (5%)	2 (5%)	0	13 (17%)	3 (4%)	0
Anorexia	13 (33%)	1 (3%)	0	10 (26%)	0	0	23 (29%)	1 (1%)	0
Asthenia	21 (54%)	7 (18%)	0	23 (59%)	1 (3%)	0	44 (56%)	8 (10%)	0
Back or bone pain	8 (21%)	1 (3%)	0	3 (8%)	3 (8%)	0	11 (14%)	4 (5%)	0
Constipation	12 (31%)	2 (5%)	0	6 (15%)	1 (3%)	0	18 (23%)	3 (4%)	0
Diarrhoea	25 (64%)	1 (3%)	0	14 (36%)	0	0	39 (50%)	1 (1%)	0
Dysgeusia	8 (21%)	1 (3%)	0	1 (3%)	0	0	9 (12%)	1 (1%)	0
Gastro-oesophageal reflux	7 (18%)	0	0	1 (3%)	0	0	8 (10%)	0	0
Hair colour changes or skin hypopigmentation	12 (31%)	0	0	4 (10%)	0	0	16 (21%)	0	0
Headache	8 (21%)	0	0	3 (8%)	0	0	11 (14%)	0	0
Hypertension	9 (23%)	5 (13%)	0	9 (23%)	4 (10%)	0	18 (23%)	9 (12%)	0
Insomnia	3 (8%)	0	0	1 (3%)	0	0	4 (5%)	0	0
Leukopenia or neutropenia	11 (28%)	2 (5%)	0	3 (8%)	1 (3%)	0	14 (18%)	3 (4%)	0
Lymphopenia	7 (18%)	0	0	3 (8%)	0	0	10 (13%)	0	0
Nausea	14 (36%)	0	0	10 (26%)	0	0	24 (31%)	0	0
Oedematous legs	7 (18%)	0	0	2 (5%)	0	0	9 (12%)	0	0
Palmar–plantar erythrodysesthesia syndrome	0	0	0	1 (3%)	0	0	1 (1%)	0	0
Pneumonia aspiration	0	0	0	0	0	1 (3%)	0	0	1 (1%)
Proteinuria	5 (13%)	1 (3%)	0	1 (3%)	0	0	6 (8%)	1 (1%)	0
Rectal bleeding*	0	0	1 (3%)	0	0	0	0	0	1 (1%)
Sepsis*	0	0	0	0	0	1 (3%)	0	0	1 (1%)
Shortness of breath*	0	0	1 (3%)	0	0	0	0	0	1 (1%)
Stomatitis, glossitis, or mucositis	8 (21%)	1 (3%)	0	4 (10%)	0	0	12 (15%)	1 (1%)	0
Thrombopenia	12 (31%)	1 (3%)	0	1 (3%)	0	0	13 (17%)	1 (1%)	0
Vomiting	15 (38%)	1 (3%)	0	7 (18%)	1 (3%)	0	22 (28%)	2 (3%)	0
Weight loss	18 (46%)	0	0	8 (21%)	0	0	26 (33%)	0	0

Adverse events were defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). One death was considered as drug related in the sunitinib group due to rectal bleeding in a patient with hypervascularised pelvis bone metastases. No hypertensive crisis was reported as a cause of death. As an intention-to-treat analysis, patients who crossed over were considered in the group of their initial treatment. *Grade 5 events (n=3 in the sunitinib group; n=2 in the placebo group).

Table 3: **Common adverse events among the safety population**

and was considered drug related. Two deaths occurred in the placebo group due to aspiration pneumonia and septic shock. Six adverse events led to discontinuation of sunitinib treatment in five (14%) of 35 patients in the sunitinib group: mouth and nose bleeding (grade 3), proteinuria (grade 3), hyperkalaemia and elevated liver enzymes (grade 3), generalised weakness (grade 3), lower limb ischaemia (grade 3), and cognitive deterioration (grade 2).

Discussion

Ultra-rare cancers have a low access to drug innovation and a low level of evidence for recommendations because of the paucity of randomised controlled trials.[1] The FIRSTMAPPP trial is the first in the field of patients with metastatic phaeochromocytomas and paragangliomas and one of the very few randomised controlled trials in the field of ultra-rare cancers as recently defined by an annual incidence of less than one per million.[2] This study provides the highest level of evidence ever reached to support the anti-tumour role of a systemic treatment option in patients with aggressive metastatic phaeochromocytomas and paragangliomas, and supports sunitinib as a potential candidate for first-line therapy. The best feasible methodology was applied including a placebo-controlled, double-blind randomised trial design, as done in most endocrine and neuroendocrine phase 3 trials, real-time central RECIST evaluation, and independent data medical committee control. Selection of sunitinib and placebo, inclusion criteria, and surveillance of patients with metastatic phaeochromocytomas and paragangliomas were achieved through an expert consensus and were based on data available at the time of trial initiation. Finally, complete accrual was achieved as well as consistent evaluation over a 7-year period despite unique challenges related to comorbid hormone-related symptoms, indolent

courses, or isolated bone metastases of subgroups of patients, which challenged the enrolment rate. As compared with previously mentioned characteristics of the population with metastatic phaeochromocytomas and paragangliomas,[5,6] the 32% *SDHB* germline mutation rate as well as the absence of other germline-mutated patients are remarkable.

The primary endpoint of the FIRSTMAPPP trial was met. Sunitinib is therefore effective and becomes the best validated therapeutic option in progressive metastatic phaeochromocytomas and paragangliomas. This finding is further supported by several secondary endpoints. In addition, the quality of life was maintained and intensity of bone pain decreased. Importantly, sunitinib adverse events were manageable. Overall survival, as shown by the large overlapped CIs, was similar in both groups, which is likely to be affected by the crossover achieved in 69% of patients in the placebo group, the prolonged median overall survival of patients with metastatic phaeochromocytomas and paragangliomas allowing numerous lines of treatments, and the low number of patients studied.

More than 10 years after the inclusion of the first patient in the FIRSTMAPPP trial, the therapeutic options have changed for metastatic phaeochromocytomas and paragangliomas. In addition to the two historical medical options, meta-iodobenzylguanidine and dacarbazine-based chemotherapy, retrospective studies have suggested an anti-tumour activity of peptide receptor radionuclide therapy in somatostatin receptor-positive patients, based on partial response rates of 6–29% and median progression-free survival of 13–39 months.[22–24] Also, progress has been made in the field of meta-iodobenzylguanidine therapy, with a recently published phase 2 trial in patients with metastatic phaeochromocytomas and paragangliomas, using optimised high-specific meta-iodobenzylguanidine activity, which has reported a partial response rate of 23%.[7] In addition, our group reported a partial response of 33% with temozolomide alone, suggesting that the historical cyclophosphamide–vincristine–dacarbazine chemotherapy combination could be challenged.[22–24] Finally, two prospective phase 2 trials with TKI targeting VEGF receptors, showed partial responses in 13–45% of cases and median progression-free survival of 4–11 months,[25,26] thus supporting our results.

Major heterogeneity in the prognosis of metastatic phaeochromocytomas and paragangliomas precludes comparisons between survival endpoints across trials even when prospective. Indeed, we have previously reported progression-free survival of more than 1 year in 46% of patients with metastatic phaeochromocytomas and paragangliomas in whom watch-and-see policy was the first-line strategy.[27] By contrast, the median progression-free survival of 3·6 months and median overall survival of 29·4 months in the placebo group confirms that patients with metastatic phaeochromocytomas and paragangliomas enrolled in FIRSTMAPPP had aggressive tumours. Prognosis heterogeneity of metastatic phaeochromocytomas and paragangliomas makes standardised tumour progression status determination before treatment a key feature of trial development in patients with metastatic phaeochromocytomas and paragangliomas as done in FIRSTMAPPP. As the first randomised controlled trial in the field of patients with metastatic phaeochromocytomas and paragangliomas, FIRSTMAPPP is a major step forward to supporting sunitinib as the best validated treatment option and a potential candidate for first-line therapy in progressive metastatic phaeochromocytomas and paragangliomas. Indeed, 40% of patients were systemic treatment naive when enrolled in FIRSTMAPPP. However, the placebo-control group study design used in FIRSTMAPPP—whether it allows a proper evaluation of benefit-to-safety ratio and best demonstration of the changes in the natural history—does not allow the claim that sunitinib is superior to any other treatment option.

Grades 3–4 or serious adverse events were previously reported with all systemic therapeutic options in patients with metastatic phaeochromocytomas and paragangliomas.[9–11,18,22–24] The indolent course observed in some patients with metastatic phaeochromocytomas and paragangliomas makes the selection of these patients to be treated and the control of comorbid conditions, such as hypertension and bone pain before treatment, both essential as anticipated in FIRSTMAPPP. In the two recent TKI phase 2 trials, using sunitinib 50 mg per day for 4 weeks followed by 2 weeks of observation or another TKI (pazopanib), grades 3–4 adverse events were reported in 23–66%, including hypertension exacerbation and Takotsubo syndrome.[25,26] Of note, both studies were stopped for slow enrolment. In the recent meta-iodobenzylguanidine phase 2 trial, grade 3–4 adverse events—mainly haematological—were reported in 62% of patients and up to 4% of myelodysplastic syndrome has been reported with meta-iodobenzyl-guanidine therapy.[8,9] Although adverse events in the FIRSTMAPPP trial might be in the same range comparable to previous prospective trials, these findings might explain the transient decrease of quality of life at 3 months. In addition, TKI with the highest rate of cardiovascular adverse events[28] should be used with extreme caution in patients with metastatic phaeochromocytomas and paragangliomas. However, no drug withdrawal was related to hypertension and hypertension-related grade 3–4 adverse events were comparable in the sunitinib and placebo groups, which suggest that sunitinib 37·5 mg per day is a good compromise.

Personalised medicine is emerging in metastatic phaeochromocytoma and paraganglioma therapy.[3] Subgroup analysis of the FIRSTMAPPP trial shows a 50% partial response rate in patients with *SDHB* mutations, the highest partial response rate reported in patients with a neuroendocrine tumour treated with

sunitinib, so far. This finding provides the first clinical validation available of the *SDHB*-related pseudo-hypoxic hypothesis.[15] In addition, patients with hypertension (who represent 40% of the entire study cohort) were finally found to be good candidates for sunitinib treatment, but control of hypertension before treatment initiation is mandatory.

The present study has certain limitations. For instance, this study is a non-comparative randomised phase 2 trial and the alpha risk of the primary endpoint was set up at 0·1 to take into account the scarcity of the disease. Nevertheless, a total of 7 years was required to enrol 78 patients in 14 expert centres across four countries in Europe. Thus, although a properly powered randomised phase 3 trial would be desirable, this option seems not to be reachable within the upcoming years. For the same reason, both pretreated or treatment-naive patients with metastatic phaeochromocytomas and paragangliomas were enrolled.

In conclusion, the FIRSTMAPPP trial is the first randomised study achieved in the field of metastatic phaeochromocytomas and paragangliomas. Sunitinib becomes the drug with the highest level of evidence of anti-tumour activity in patients with progressive metastatic phaeochromocytomas and paragangliomas.

Contributors

EB, BG, AB, JH, SL, SN, CdlF, TK, TD, SZ, LA, MH, HT, PN, AF, MoA, LL, FL, DC, SH, FB, and MF did the data collection. EB, BG, SM, MaA, MoA, MT, and MF did the data analysis. EB, BG, AB, JH, SM, SL, SN, CdlF, TK, TD, SZ, LA, MH, HT, PN, AF, LL, FL, DC, SH, FB, MT, and MF did the data interpretation. EB, BG, MT, and MF wrote the manuscript. All authors had full access to all the data in the study and all had final responsibility for the decision to submit for publication. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol.

Declaration of interests

EB has received grants from Novartis and HRA; consulting fees from Novartis; support from HRA, Novartis, and Enterome; has been on the Board or Advisory Board for Ipsen, Novartis AAA, Pfizer, and Hutchinson Ph; has a leadership role for the French ENDOCAN network; and is a recipient of the interventions used in this study (sunitinib and placebo) from Pfizer. AB has received payment or honoraria from Novartis AAA and HRA; and has been on the Board or Advisory Board for Novartis AAA, Amgen, Bayer, and Ferring. JH has received consulting fees from Roche, Lilly, Pharma Mar, and EISAI; payment or honoraria from Novartis AAA; support from Ipsen and Novartis AAA; and has been on the Board or Advisory Board for Lilly. TD has received support from Recordati; has been on the Board or Advisory Board for Recordati; and has a leadership role for the German Pituitary Group. LL has received payment or honoraria from EISAI, Lilly, and ROCHE; and has been on the Board or Advisory Board for Bayer, EISAI, and IPSEN. All other authors declare no competing interests.

Data sharing

We are committed to sharing with all qualified external researchers access to all individual patient data and supporting documents from eligible studies. Any requests should be made to the corresponding author. Requests are reviewed and approved by an independent review panel (three first authors and the last authors) based on scientific merit. All data provided are anonymised to respect the privacy of patients who have participated in the trial, in line with applicable laws and regulations.

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References

1 Fassnacht M, Assie G, Baudin E, et al. Adrenocortical carcinomas and malignant phaeochromocytomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2020; **31:** 1476–90.

2 Stacchiotti S, Frezza AM, Blay JY, et al. Ultra-rare sarcomas: a consensus paper from the Connective Tissue Oncology Society community of experts on the incidence threshold and the list of entities. *Cancer* 2021; **127:** 2934–42.

3 Nolting S, Bechmann N, Taieb D, et al. Personalized management of pheochromocytoma and paraganglioma. *Endocr Rev* 2022; **43:** 199–239.

4 Crona J, Taieb D, Pacak K. New perspectives on pheochromocytoma and paraganglioma: toward a molecular classification. *Endocr Rev* 2017; **38:** 489–515.

5 Turkova H, Prodanov T, Maly M, et al. Characteristics and Outcomes of Metastatic Sdhb and Sporadic Pheochromocytoma/Paraganglioma: a National Institutes of Health Study. *Endocr Pract* 2016; **22:** 302–14.

6 Hescot S, Curras-Freixes M, Deutschbein T, et al. Prognosis of malignant pheochromocytoma and paraganglioma (MAPP-Prono study): an ENS@T retrospective study. *J Clin Endocrinol Metab* 2019; **104:** 2367–74.

7 Pryma DA, Chin BB, Noto RB, et al. Efficacy and safety of high-specific-activity I-131 MIBG therapy in patients with advanced pheochromocytoma or paraganglioma. *J Nucl Med* 2018; **60:** 623–30.

8 Gonias S, Goldsby R, Matthay KK, et al. Phase II study of high-dose [131I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma. *J Clin Oncol* 2009; **27:** 4162–68.

9 Ayala-Ramirez M, Feng L, Habra MA, et al. Clinical benefits of systemic chemotherapy for patients with metastatic pheochromocytomas or sympathetic extra-adrenal paragangliomas: insights from the largest single-institutional experience. *Cancer* 2012; **118:** 2804–12.

10 Huang H, Abraham J, Hung E, et al. Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine: recommendation from a 22-year follow-up of 18 patients. *Cancer* 2008; **113:** 2020–28.

11 Hadoux J, Favier J, Scoazec JY, et al. *SDHB* mutations are associated with response to temozolomide in patients with metastatic pheochromocytoma or paraganglioma. *Int J Cancer* 2014; **135:** 2711–20.

12 Tanabe A, Naruse M, Nomura K, Tsuiki M, Tsumagari A, Ichihara A. Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine in patients with malignant pheochromocytoma and paraganglioma. *Horm Cancer* 2013; **4:** 103–10.

13 Asai S, Katabami T, Tsuiki M, Tanaka Y, Naruse M. Controlling tumor progression with cyclophosphamide, vincristine, and dacarbazine treatment improves survival in patients with metastatic and unresectable malignant pheochromocytomas/paragangliomas. *Horm Cancer* 2017; **8:** 108–18.

14 Patel SR, Winchester DJ, Benjamin RS. A 15-year experience with chemotherapy of patients with paraganglioma. *Cancer* 1995; **76:** 1476–80.

15 Favier J, Igaz P, Burnichon N, et al. Rationale for anti-angiogenic therapy in pheochromocytoma and paraganglioma. *Endocr Pathol* 2012; **23:** 34–42.

16 Denorme M, Yon L, Roux C, et al. Both sunitinib and sorafenib are effective treatments for pheochromocytoma in a xenograft model. *Cancer Lett* 2014; **352:** 236–44.

17 Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med* 2011; **364:** 501–13.

18 Ayala-Ramirez M, Chougnet CN, Habra MA, et al. Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas. *J Clin Endocrinol Metab* 2012; **97:** 4040–50.

19 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10:** 1–10.

20 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16:** 139–44.

21 Olsen MF, Bjerre E, Hansen MD, Tendal B, Hilden J, Hrobjartsson A. Minimum clinically important differences in chronic pain vary considerably by baseline pain and methodological factors: systematic review of empirical studies. *J Clin Epidemiol* 2018; **101:** 87–106.

22 Imhof A, Brunner P, Marincek N, et al. Response, survival, and long-term toxicity after therapy with the radiolabeled somatostatin analogue [90Y-DOTA]-TOC in metastasized neuroendocrine cancers. *J Clin Oncol* 2011; **29:** 2416–23.

23 Zandee WT, Brabander T, Blazevic A, et al. Symptomatic and radiological response to 177Lu-DOTATATE for the treatment of functioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab* 2019; **104:** 1336–44.

24 Severi S, Bongiovanni A, Ferrara M, et al. Peptide receptor radionuclide therapy in patients with metastatic progressive pheochromocytoma and paraganglioma: long-term toxicity, efficacy and prognostic biomarker data of phase II clinical trials. *ESMO Open* 2021; **6:** 100171.

25 Jasim S, Suman VJ, Jimenez C, et al. Phase II trial of pazopanib in advanced/progressive malignant pheochromocytoma and paraganglioma. *Endocrine* 2017; **57:** 220–25.

26 O'Kane GM, Ezzat S, Joshua AM, et al. A phase 2 trial of sunitinib in patients with progressive paraganglioma or pheochromocytoma: the SNIPP trial. *Br J Cancer* 2019; **120:** 1113–19.

27 Hescot S, Leboulleux S, Amar L, et al. One-year progression-free survival of therapy-naive patients with malignant pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab* 2013; **98:** 4006–12.

28 Abdel-Qadir H, Ethier JL, Lee DS, Thavendiranathan P, Amir E. Cardiovascular toxicity of angiogenesis inhibitors in treatment of malignancy: a systematic review and meta-analysis. *Cancer Treat Rev* 2017; **53:** 120–27.