Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial

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Summary

Background Patients with Ewing sarcoma or osteosarcoma have a median overall survival of less than 12 months after diagnosis, and a standard treatment strategy has not yet been established. Pharmacological inhibition of MET signalling and aberrant angiogenesis has shown promising results in several preclinical models of Ewing sarcoma and osteosarcoma. We aimed to investigate the activity of cabozantinib, an inhibitor of MET and VEGFR2, in patients with advanced Ewing sarcoma and osteosarcoma.

Methods We did a multicentre, single-arm, two-stage, phase 2 trial in patients with advanced Ewing sarcoma or osteosarcoma recruited from ten centres in the French Sarcoma Group. Key eligibility criteria were aged 12 years or older, Eastern Cooperative Oncology Group performance status of 0–1, and documented disease progression (according to Response Evaluation Criteria in Solid Tumors version 1.1) before study entry. The number of previous lines of treatment was not limited. Patients received cabozantinib (adults 60 mg, children [<16 years] 40 mg/m²) orally once daily in 28-day cycles until disease progression, unacceptable toxicity, the investigator's decision to discontinue, or participant withdrawal. The primary endpoint for Ewing sarcoma was best objective response within 6 months of treatment onset; for osteosarcoma, a dual primary endpoint of 6-month objective response and 6-month non-progression was assessed. All enrolled patients who received at least one dose of cabozantinib were included in the safety analysis, and all participants who received at least one complete or two incomplete treatment cycles were included in the efficacy population. This study was registered with ClinicalTrials.gov, number NCT02243605.

Findings Between April 16, 2015, and July 12, 2018, 90 patients (45 with Ewing sarcoma 45 with osteosarcoma) were recruited to the study. Median follow-up was 31·3 months (95% CI 12·4–35·4) for patients with Ewing sarcoma and 31·1 months (24·4–31·7) for patients with osteosarcoma. 39 (87%) patients with Ewing sarcoma and 42 (93%) patients with osteosarcoma were assessable for efficacy after histological and radiological review. In patients with Ewing sarcoma, ten (26%; 95% CI 13–42) of 39 patients had an objective response (all partial responses) by 6 months; in patients with osteosarcoma, five (12%; 4–26) of 42 patients had an objective response (all partial responses) and 14 (33%; 20–50) had 6-month non-progression. The most common grade 3 or 4 adverse events were hypophosphataemia (five [11%] for Ewing sarcoma, three [7%] for osteosarcoma), aspartate aminotransferase increase (two [4%] for Ewing sarcoma, three [7%] for osteosarcoma), palmar-plantar syndrome (three [7%] for Ewing sarcoma, two [4%] for osteosarcoma), pneumothorax (one [2%] for Ewing sarcoma, four [9%] for osteosarcoma), and neutropenia (two [4%] for Ewing sarcoma, four [9%] for osteosarcoma). At least one serious adverse event was reported in 61 (68%) of 90 patients. No patients died from drug-related toxic effects.

Interpretation Cabozantinib has antitumor activity in patients with advanced Ewing sarcoma and osteosarcoma and was generally well tolerated. Cabozantinib could represent a new therapeutic option in this setting, and deserves further investigation.

Funding Institut Bergonié; French National Cancer Institute; Association pour la Recherche contre le Cancer.

Introduction

Treatment of patients with recurrent Ewing sarcoma or osteosarcoma remains an important clinical challenge. Patients have a median overall survival of less than 12 months and a standard management strategy is yet to be established.[1,2]

MET was originally identified as the protein product of the *TPR-MET* transforming oncogene, which was derived from an osteosarcoma cell line.[3] Several studies have shown that the HGF/SF and MET receptors might function together in activating biological properties that could contribute to osteosarcoma progression.[4]

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Research in context

Evidence before this study

We searched PubMed with the terms "recurrent osteosarcoma" OR "relapsed osteosarcoma" OR "metastatic osteosarcoma" OR "recurrent Ewing sarcoma" OR "relapsed Ewing sarcoma" OR "metastatic Ewing sarcoma" AND "clinical trial" NOT "review" for clinical trials done in humans published in English from database inception to July 31, 2019. Among targeted therapies, the most thoroughly studied drugs are IGF-1R inhibitors for Ewing sarcoma and anti-angiogenic drugs for osteosarcoma. Efficacy results of IGF-1R were disappointing, with objective responses in less than 15% of patients and median progression-free survival of less than 2 months in adults and children with recurrent Ewing sarcoma. Two drugs targeting angiogenic receptors (sorafenib and regorafenib) have shown promising evidence of activity in four phase 2 studies enrolling patients with advanced osteosarcoma. To the best of our knowledge, no previous trials assessing the activity of cabozantinib, an inhibitor of MET and VEGFR2 kinase activity, or other drugs targeting MET in Ewing sarcoma and osteosarcoma have been published.

Added value of this study

Our results show that cabozantinib, which is already approved for the management of medullary thyroid cancer, renal cancer, and hepatocarcinoma, has antitumour activity in patients with Ewing sarcoma and patients with osteosarcoma who have been heavily pre-treated. To our knowledge, CABONE is the first study investigating a therapy targeting both angiogenic and MET receptors in these patients.

Implications of all the available evidence

Our results suggest that cabozantinib could represent a new therapeutic option for patients with advanced Ewing sarcoma and osteosarcoma, and it deserves further investigation in this setting.

Wild-type or constitutively activated *MET* has been shown to drive osteoblast transformation.[4] Moreover, introduction of dominant-negative *MET* inhibits the in-vivo tumorigenicity of osteosarcoma cells.[4] A role for MET has also been shown in Ewing sarcoma tumorigenesis.[5]

Aberrant angiogenesis is crucial for sustained osteosarcoma and Ewing sarcoma growth and metastasis. *VEGFA* is expressed in 74% of patients with osteosarcoma, and progression-free survival in patients with *VEGFA*-positive osteosarcomas is significantly worse than in patients with *VEGFA*-negative osteosarcomas.[6] A similar prognostic effect has been observed in patients with Ewing sarcoma.[7]

Cabozantinib (XL184) is the only VEGFR2 tyrosine kinase inhibitor that also has specific MET receptor inhibitory activity[8] and has shown in-vitro and in-vivo antitumour activity in several osteosarcoma and Ewing sarcoma tumour models.[9] In collaboration with the National Cancer Institute (Cancer Therapy Evaluation Program), the French Sarcoma Group conducted a clinical phase 2 study of cabozantinib in patients with advanced Ewing sarcoma and advanced osteosarcoma.

Methods

Study design and participants

The CABONE study is a multicentre, single-arm, phase 2 trial enrolling patients with Ewing sarcoma and osteosarcoma in ten centres from the French Sarcoma Group (appendix p 1). Patients were eligible if they were at least 12 years of age, had histologically confirmed Ewing sarcoma or osteosarcoma after central review, Eastern Cooperative Oncology Group performance status of 0–1, and adequate renal, hepatic, and cardiac functions (see study protocol for a full list of eligibility criteria, appendix pp 8–108). The number of previous lines of treatment was not limited. For patients with Ewing sarcoma, the histological diagnosis had to be confirmed by fluorescence in-situ hybridisation or RT-PCR for assessment of *EWS* gene rearrangement. Blood tests included an assessment of blood cell count, and measurements of alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, albumin, bilirubin, creatinine, and urea nitrogen. A washout period of 21 days for previous chemotherapy was mandatory. Key exclusion criteria were previous treatment with cabozantinib, radiotherapy for bone metastasis within 2 weeks of study treatment, any other external radiotherapy within 4 weeks of study treatment, and receipt of any small molecule kinase inhibitor within 2 weeks of the first dose of study treatment. All patients with osteosarcoma had centrally documented progressive disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 based on two imaging assessments obtained within less than a 6-month interval.[10] As required by French regulations, the protocol was approved by a central institutional review board (Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France) that reviewed the appropriateness of the clinical trial protocol as well as the risks and benefits to study participants. All patients provided written, informed consent.

See Online for appendix

Procedures

After an assessment of eligibility, patients received cabozantinib 60 mg per day (or 40 mg/m² in patients younger than 16 years old) orally once daily in cycles of 28 days. Treatment was continued until disease progression, unacceptable toxicity, the investigator's decision to discontinue, or withdrawal of patient consent. Participants were monitored for adverse events at every follow-up assessment. Adverse events were graded

according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Laboratory assessments were done at baseline, week 2, week 4, and every 4 weeks afterwards until treatment discontinuation. Dose modifications to manage adverse events were allowed. The dose of cabozantinib could be reduced to 40 mg and then to 20 mg from the starting dose of 60 mg. Dose interruptions were allowed based on the clinical situation. Patients who required a dose interruption (regardless of the reason for the interruption) lasting >28 days (counting from the first day when a dose was missed) had to discontinue cabozantinib. Tumour lesions were assessed according to RECIST version 1.1 at baseline (within 14 days before the first dose of cabozantinib), and every 8 weeks until disease progression or the start of another treatment. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET-CT was performed at baseline and at week 4 after treatment onset.[11] Metabolic response 28 days after the first administration of cabozantinib was assessed according to PERCIST 1.0 criteria.[12]

Outcomes

For Ewing sarcoma, the primary endpoint was objective response within 6 months of treatment onset (6-month objective response). For osteosarcoma, we assessed a dual primary endpoint encompassing 6-month objective response and the proportion of patients who had not progressed at 6 months (6-month non-progression), defined as the percentage of patients with complete response, partial response, or stable disease at 6 months after treatment onset.[13] These endpoints were assessed on the basis of a blinded and central review of the radiological data.

Secondary endpoints were the proportion of patients who had not progressed at 6 months (for patients with Ewing sarcoma only; 6-month non-progression), best overall response, 1-year and 2-year progression-free survival, 1-year and 2-year overall survival, metabolic response as assessed by ^{18}F-FDG PET-CT 28 days after the first dose of cabozantinib, and safety. Best overall response was defined as the best response obtained from the start of treatment to the time of progression and was categorised as complete response, partial response, stable disease, or progressive disease. Progression-free survival was defined as the time from treatment onset to the time of progression or death from any cause, whichever occurred first. Overall survival was defined as the time from treatment onset to the time of death from any cause or last patient contact. Metabolic response was defined according to PET RECIST criteria[11] and classified as complete metabolic response, partial metabolic response, stable metabolic disease, or progressive metabolic disease.

Prespecified, exploratory analyses of potential plasma biomarkers of cabozantinib were done by plasma analysis of VEGF-A, hepatocyte growth factor (HGF), soluble VEGFR2 (sVEGFR2), and soluble MET (sMET).

Statistical analysis

The study on Ewing sarcoma was based on a Simon's optimal two-stage design,[14] with objective response as the primary endpoint (binary variable following a binomial distribution). Assuming a six-month objective response of 5% (null hypothesis, H0) and 20% (alternative hypothesis, H1), a 5% type I error rate, and 90% power, 41 eligible and assessable patients were necessary (21 in the first stage and 20 in the second stage). At the final stage, cabozantinib would be considered promising if at least five patients had an objective response.

The study on osteosarcoma was based on a dual-endpoint design with objective response and non-progression as the primary endpoints (binary variables following a binomial distribution). Assuming an objective response of 5% (H0) and 20% (H1) and non-progression of 25% (H0) and 50% (H1), a 5% type I error rate, and 90% power, 41 assessable patients were necessary (21 in the first stage and 20 in second stage). At the final stage, cabozantinib would be considered promising if at least five patients had an objective response or if at least 16 patients were progression-free at 6 months.

All enrolled patients who received at least one dose of cabozantinib were included in the safety analysis. The efficacy population included all participants who met the eligibility criteria and who received at least one complete or two incomplete treatment cycles. The median follow-up was calculated using the reverse Kaplan-Meier method. Survival endpoints (progression-free survival and overall survival) were described using the Kaplan-Meier method. 4-month and 6-month progression-free survival and 6-month overall survival were also estimated. Data for patients who were alive and progression-free were censored at the date of the last follow-up. Quantitative variables were described using the median and range, and qualitative variables were described using frequency and percentage. All eligible and assessable patients for efficacy were included in the denominator for the calculation of the proportions.

Two post-hoc analyses were done. Firstly, growth modulation index (GMI), defined as the ratio of time to progression with the current therapy to time to progression on the patient's most recent previous line of therapy on which they experienced progression,[15] was estimated in patients who received previous chemotherapy for advanced disease. As suggested by Von Hoff,[16] a GMI of 1·33 or higher was considered to be a marker of meaningful clinical activity. Secondly, median overall survival and progression-free survival were estimated according to metabolic response 28 days after the first dose of cabozantinib.

Estimated parameters were reported with two-sided 95% CIs. p values less than 0·05 (typically ≤0·05) were considered to be statistically significant. Statistical analyses were done using SAS software (version 9.4). This study was registered with ClinicalTrials.gov, number NCT02243605.

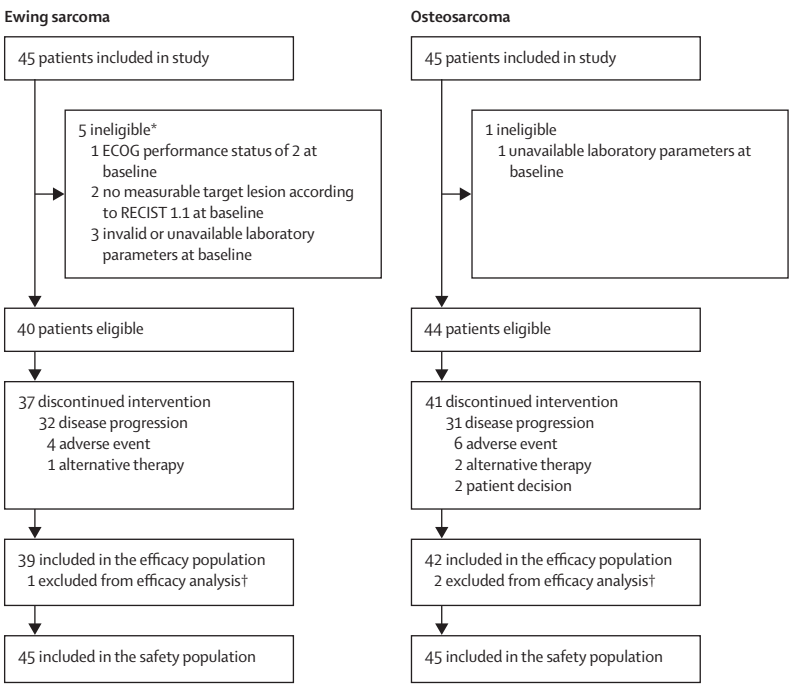

Figure 1: **Study profile**
ECOG=Eastern Cooperative Oncology Group. RECIST=Response Evaluation Criteria in Solid Tumors. *One patient did not meet two eligibility criteria. †Patients excluded because they did not receive at least one complete or two incomplete treatment cycles.

	Ewing sarcoma group (n=45)	Osteosarcoma group (n=45)
Sex		
Men	31 (69%)	27 (60%)
Women	14 (31%)	18 (40%)
Age, years		
Median (IQR)	33 (24–45)	34 (20–53)
<18	2 (4%)	6 (13%)
≥18	43 (96%)	39 (87%)
ECOG performance status		
0	15 (33%)	17 (38%)
1	29 (64%)	26 (58%)
2	1 (2%)	1 (2%)
3	0	1 (2%)
Metastatic sites		
Lung	32 (71%)	39 (87%)
Pleura	5 (11%)	4 (9%)
Bone	17 (38%)	10 (22%)
Liver	2 (4%)	1 (2%)
Other	8 (18%)	5 (11%)
Previous lines of treatment for advanced disease		
0*	3 (7%)	17 (38%)
1	12 (27%)	10 (22%)
2	13 (29%)	10 (22%)
>2	17 (38%)	8 (18%)

Data are n (%) unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. *Patients received standard chemotherapy for locoregional disease.

Table 1: **Baseline characteristics**

Role of the funding source

The study was sponsored by Institut Bergonié, Comprehensive Cancer Center (Bordeaux, France). NCI-CTEP provided cabozantinib under a Cooperative and Development Research Agreement established with Exelixis. The funder of the study (French National Cancer Institute) had no role in study design, data collection, 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 April 16, 2015, and July 12, 2018, 90 patients were recruited to the study (45 with Ewing sarcoma, 45 with osteosarcoma). Six patients with Ewing sarcoma and three patients with osteosarcoma were not eligible for the efficacy assessment due to protocol deviations (figure 1). Therefore, 39 patients with Ewing sarcoma and 42 patients with osteosarcoma were included in the efficacy population. Characteristics of the patients are summarised in table 1. 42 (93%) of 45 patients with Ewing sarcoma and 28 (62%) of 45 patients with osteosarcoma received previous lines of systemic therapy for advanced disease with a median number of previous lines of 2 (IQR 1–3) for both groups. Most patients with osteosarcoma were re-challenged with methotrexate, a platinum-anthracycline-based regimen, or both. Patients with Ewing sarcoma received various regimens, including topotecan combined with cyclophosphamide, irinotecan plus temozolomide, docetaxel combined with gemcitabine, and high-dose ifosfamide.

In the efficacy population and after a median follow-up of 31·3 months (95% CI 12·4–35·4), 13 (33%) of 39 patients with Ewing sarcoma were still alive, with three (8%) patients still undergoing treatment. Ten (26%; 95% CI 13–42) of 39 patients had an objective response (all partial responses; figure 2), and the primary efficacy criterion was reached. Two patients with Ewing sarcoma had no tumour assessment due to early discontinuation of treatment because of disease progression (n=1) or toxic effects (n=1), and were classified as not evaluable according to RECIST 1.1. 19 (49%) of 39 patients had stable disease as the best overall response, including 15 (38%) with tumour shrinkage (range of tumour shrinkage –21·6% to –1·5%). Eight (21%) of 39 patients had progressive disease as the best overall response. 26 eligible and assessable patients with Ewing sarcoma died during the trial and 34 eligible patients had progressive disease (n=32) or died (n=2). Median progression-free survival was 4·4 months (95% CI 3·7–5·6) and median overall survival was 10·2 months (8·5–18·5; figure 3). The proportion of patients with 6-month non-progression was 26% (13–42).

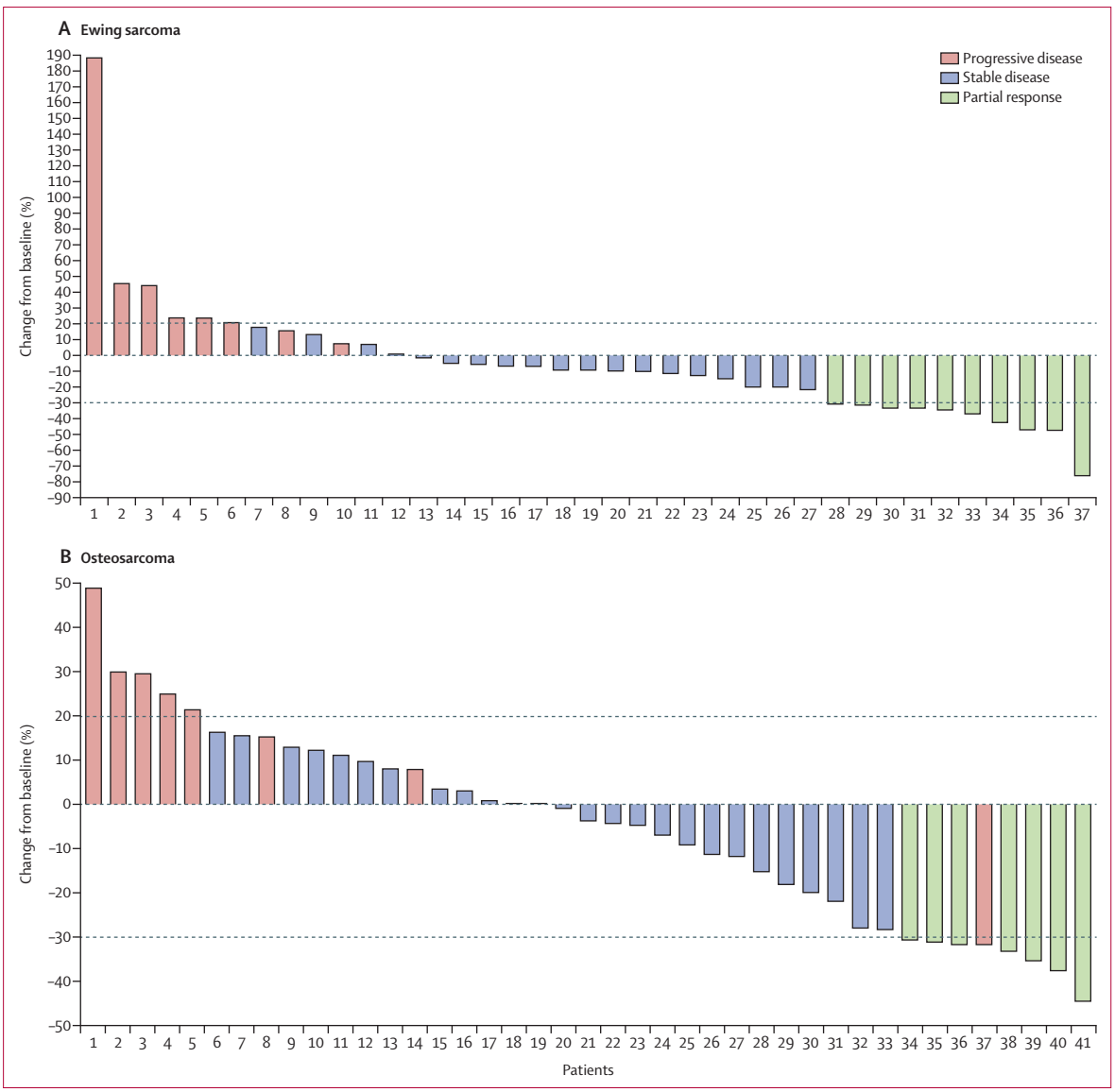

Figure 2: **Best overall response for patients with (A) Ewing sarcoma and (B) osteosarcoma**
Dashed lines represent the cutoffs for partial response (–30%) and progressive disease (+20%), according to RECIST 1.1. Some patients with change of <20% are categorised as progressive disease because of the appearance of new lesions. RECIST=Response Evaluation Criteria in Solid Tumors.

Progression-free survival was 33% (19–48) at 6 months, 18% (8–33) at 12 months, and 5% (<1–19) at 24 months. Overall survival was 84% (68–93) at 6 months, 48% (31–65) at 12 months, and 14% (4–31) at 24 months.

Among the 39 patients with Ewing sarcoma who were eligible and assessable for efficacy, 31 (8%) were evaluable for early metabolic response at the end of one cycle of cabozantinib. Of those, 13 (42%) had partial metabolic response, nine (29%) had stable metabolic disease, and nine (29%) had progressive metabolic disease (appendix p 4). Therefore, the proportion of patients with metabolic tumour response was 42% (95% CI 25–61). Median progression-free survival was 5·4 months (3·7–8·9) for patients with partial metabolic response, 4·2 months (1·7–9·2) for patients with stable metabolic disease, and 2·7 months (0·9–4·4) for patients with progressive metabolic disease (log-rank p=0·002; appendix p 5).

Three patients with Ewing sarcoma did not receive previous chemotherapy for advanced disease; therefore, GMI was assessable as a post-hoc analysis for 36 patients (appendix pp 3, 6). 12 (33%) of 36 patients had a GMI of 1·33 or higher.

In the efficacy population and after a median follow-up of 31·1 months (95% CI 24·4–31·7), ten (24%) of 42 patients with osteosarcoma were still alive, with three (7%) patients still undergoing treatment. Five (12%; 4–26) of 42 patients had an objective response (all partial responses) and 14 (33%; 20–50) were progression-free at

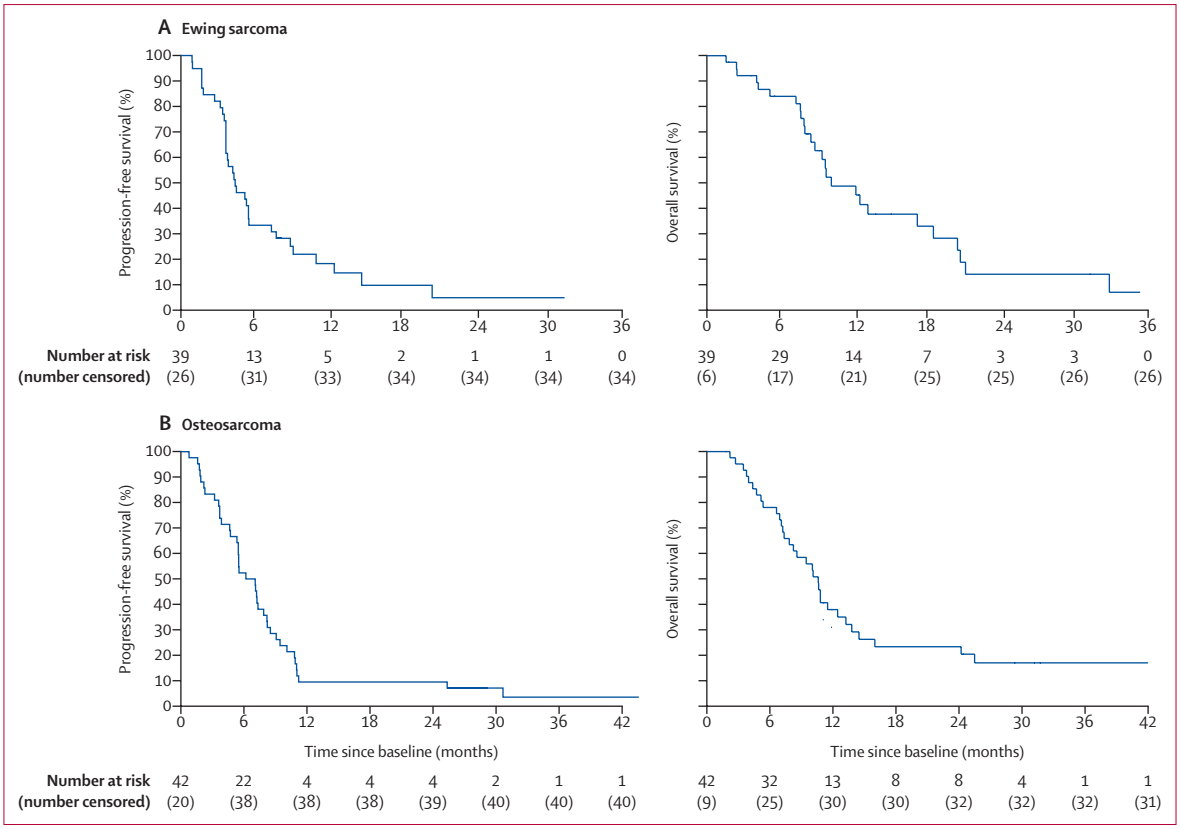

Figure 3: **Kaplan-Meier curves of progression-free survival and overall survival in patients with (A) Ewing sarcoma and (B) osteosarcoma**

6 months (12 patients had stable disease and two had partial responses), and the primary efficacy criterion was reached. The best overall response was partial response in seven (17%) of 42 patients and stable disease in 26 (62%) of 42 patients (figure 2). 14 patients with stable disease (33%) had tumour shrinkage (range –28·4% to –0·9%). Eight (19%) of 42 patients had progressive disease as the best overall response. 32 eligible and assessable patients with osteosarcoma died during the course of the trial and 40 eligible patients had progressive disease (n=31) or died (n=9). Despite tumour shrinkage, one patient with osteosarcoma had progressive disease as the best overall response. This patient had a single tumour assessment during treatment; although shrinkage of the target lesion was observed, a new lesion was identified, which was classified as progressive disease according to RECIST 1.1. One patient with osteosarcoma had no tumour assessment due to early treatment discontinuation because of toxic effects, and was classified as not evaluable according to RECIST 1.1. Median progression-free survival was 6·7 months (5·4–7·9) and median overall survival was 10·6 months (7·4–12·5; figure 3). Progression-free survival was 71% (55–83) at 4 months, 52% (36–66) at 6 months, 9% (3–21) at 12 months, and 9% (3–21) at 24 months. Overall survival was 78% (62–88) at 6 months, 38% (23–53) at 12 months, and 23% (11–38) at 24 months. One patient with partial response to cabozantinib had surgery for lung metastases. A histological assessment 3 weeks after completion of cycle 8 showed no residual tumour cells.

Among the 42 patients with osteosarcoma who were eligible and assessable for efficacy, 31 (74%) were evaluable for early metabolic response at the end of one cycle of cabozantinib. Of those, 20 (65%) had partial metabolic response, eight (26%) had stable metabolic disease, and three (10%) had progressive metabolic disease (appendix p 4). Therefore, the proportion of patients with metabolic tumour response was 65% (95% CI 45–81). Median progression-free survival was 7·2 months (4·7–10·9) for patients with partial metabolic response, 4·5 months (1·8–9·5) for patients with stable metabolic disease, and 1·8 months (0·8–1·9) for patients with progressive metabolic disease (log-rank p<0·0001; appendix p 5).

15 patients did not receive previous chemotherapy for advanced disease; therefore, GMI was assessable as a post-hoc analysis for 27 patients (appendix pp 3, 6). Ten (37%) of 27 patients had a GMI of 1·33 or higher.

All 90 patients received at least one dose of cabozantinib and were evaluated for safety. Treatment with cabozantinib was generally well tolerated, although almost all patients had grade 1 or 2 adverse events related to therapy (table 2). The most common grade 1–2 treatment-related adverse events were fatigue (26 [58%] for Ewing sarcoma, 29 [64%]

for osteosarcoma), diarrhoea (23 [51%] for Ewing sarcoma, 29 [64%] for osteosarcoma), oral mucositis (24 [53%] for Ewing sarcoma, 21 [47%] for osteosarcoma), increased aspartate aminotransferase concentration (20 [44%] for Ewing sarcoma, 16 [36%] for osteosarcoma), and increased ALT concentration (17 [38%] for Ewing sarcoma, 18 [40%] for osteosarcoma). The most common grade 3 or 4 adverse events were hypophosphataemia (five [11%] for Ewing sarcoma, three [7%] for osteosarcoma), AST increase (two [4%] for Ewing sarcoma, three [7%] for osteosarcoma), palmar-plantar syndrome (three [7%] for Ewing sarcoma, two [4%] for osteosarcoma), pneumothorax (one [2%] for Ewing sarcoma, four [9%] for osteosarcoma), and neutropenia (two [4%] for Ewing sarcoma, four [9%] for osteosarcoma). 61 (68%) of 90 patients had at least one serious adverse event. 19 (21%) of 90 patients experienced dose reduction because of a drug-related adverse event. No patients died from drug-related toxic effects.

Twelve (13%) of 90 patients (four with Ewing sarcoma and eight with osteosarcoma) had a pneumothorax related to cabozantinib. A central review of imaging performed at baseline and at the occurrence of pneumothorax showed the presence of pleural or sub-pleural metastases at baseline in all patients and cavitation of lung metastases secondary to cabozantinib-induced tumour necrosis in seven patients. Ten patients underwent pleural drainage with a chest tube, leading to full recovery in nine patients. Treatment discontinuation due to pneumothorax occurred for three patients.

Adverse events led to dose modification or definitive treatment discontinuation in 35 (39%) of 90 patients. Among 84 patients assessable for safety who stopped treatment, overall reasons for treatment discontinuation were disease progression (66 [79%]), adverse events (12 [14%]), death during study period due to disease progression (one [1%]), patient decision (two [2%]), and initiation of a subsequent treatment (three [4%]; appendix p 3).

Among 39 eligible and assessable patients with Ewing sarcoma, results of biomarker analyses were available for 35 (90%) patients. Concentrations of VEGF-A, HGF, MET, and sVEGFR2 were not associated with survival outcomes in patients with Ewing sarcoma (data not shown). Among 42 eligible and assessable patients with osteosarcoma, results of biomarker analyses were available for 36 (86%) patients. We found an association between low VEGF-A concentrations and improved overall survival (13·2 months [10·1 to not reached] for VEGF-A <12·5 pg/mL *vs* 8·2 months [4·0–10·8] for VEGF-A ≥12·5 pg/mL; log-rank p=0·014) and between high sMET concentrations and improved progression-free survival (7·8 months [5·6–10·9] for sMET <300·6 ng/mL *vs* 5·4 months [3·7–6·2] for sMET ≥300·6 ng/mL; log-rank p=0·016; appendix p 7). Concentrations of VEGF-A, HGF, sVEGFR2, and soluble MET were not associated with any other outcomes for osteosarcoma (data not shown).

	Ewing sarcoma (n=45)			Osteosarcoma (n=45)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Fatigue	26 (58%)	3 (7%)	0	29 (64%)	1 (2%)	0
Diarrhoea	23 (51%)	2 (4%)	0	29 (64%)	1 (2%)	0
Oral mucositis	24 (53%)	1 (2%)	0	21 (47%)	3 (7%)	0
Hypothyroidism	22 (49%)	0	0	20 (44%)	0	0
AST increase	20 (44%)	2 (4%)	0	16 (36%)	3 (7%)	0
ALT increase	17 (38%)	2 (4%)	0	18 (40%)	2 (4%)	0
Nausea	19 (42%)	0	0	12 (27%)	0	0
Anorexia	21 (47%)	0	0	9 (20%)	0	0
Hair colour changes	15 (33%)	0	0	15 (33%)	0	0
Palmar-plantar syndrome	11 (24%)	3 (7%)	0	16 (36%)	2 (4%)	0
Thrombocytopenia	13 (29%)	0	0	14 (31%)	2 (4%)	0
Dry skin	11 (24%)	0	0	16 (36%)	0	0
Dysgeusia	9 (20%)	0	0	13 (29%)	0	0
Weight loss	7 (16%)	3 (7%)	0	9 (20%)	0	0
Hypophosphataemia	5 (11%)	5 (11%)	0	10 (22%)	3 (7%)	0
Neutropenia	7 (16%)	2 (4%)	0	5 (11%)	3 (7%)	1 (2%)
Dysphonia	8 (18%)	0	0	4 (9%)	0	0
Alopecia	6 (13%)	0	0	6 (13%)	0	0
Abdominal pain	6 (13%)	0	0	5 (11%)	0	0
Hypomagnesaemia	8 (18%)	1 (2%)	1 (2%)	3 (7%)	2 (4%)	0
Anaemia	4 (9%)	0	0	6 (13%)	1 (2%)	0
Vomiting	4 (9%)	0	0	6 (13%)	0	0
TSH increase	6 (13%)	0	0	4 (9%)	0	0
Hypokalaemia	6 (13%)	0	0	4 (9%)	0	0
Headache	4 (9%)	0	0	6 (13%)	0	0
Proteinuria	6 (13%)	0	0	4 (9%)	0	0
Skin hypopigmentation	5 (11%)	0	0	5 (11%)	0	0
Constipation	5 (11%)	0	0	4 (9%)	0	0
Gastroesophageal reflux disease	3 (7%)	0	0	6 (13%)	0	0
Myalgia	6 (13%)	0	0	3 (7%)	0	0
ALP increase	2 (4%)	1 (2%)	0	6 (13%)	0	0
Erythema multiforme	4 (9%)	0	0	4 (9%)	0	0
Lipase increased	5 (11%)	3 (7%)	1 (2%)	2 (4%)	1 (2%)	1 (2%)
Pneumothorax	3 (7%)	1 (2%)	0	4 (9%)	4 (9%)	0
Dry mouth	1 (2%)	0	0	6 (13%)	0	0
Hypocalcaemia	5 (11%)	0	0	2 (4%)	0	0
Epistaxis	3 (7%)	0	0	4 (9%)	0	0
Leucopenia	3 (7%)	0	0	3 (7%)	2 (4%)	0
Hypertension	3 (7%)	2 (4%)	0	2 (4%)	1 (2%)	0
Dysphagia	2 (4%)	0	0	3 (7%)	0	0
Hyperbilirubinaemia	3 (7%)	0	0	2 (4%)	0	0
CPK increase	1 (2%)	0	0	4 (9%)	0	0
Cough	2 (4%)	0	0	3 (7%)	0	0
Maculopapular rash	4 (9%)	0	0	1 (2%)	0	0

Data are n (%).Grade 1–2 treatment-related adverse events and laboratory abnormalities reported in more than 5% of patientsin one of the two cohorts and all grade 3 or 4 events are shown. No grade 5 adverse events were reported. AST=aspartate aminotransferase. ALT=alanine aminotransferase. ALP=alkaline phosphatase. TSH=thyroid-stimulating hormone. CPK=creatine phosphokinase.

Table 2: **Treatment-related adverse events during the treatment period**

Discussion

The CABONE study reached its primary efficacy endpoint in both the Ewing sarcoma and osteosarcoma cohorts. In patients with Ewing sarcoma, the 6-month objective response was 25·6% (95% CI 13·0–42·1); in patients with osteosarcoma, the 6-month objective response was 11·9% (4·0–25·6) and 6-month non-progression was 33·3% (19·6–49·6).

Topotecan combined with cyclophophamide, irinotecan plus temozolomide, docetaxel combined with gemcitabine, and high-dose ifosfamide are the most commonly used regimens in the setting of refractory or recurrent Ewing sarcoma. Little research has been published on the activity of these regimens, and evidence is mainly based on single-institution retrospective reviews and early phase trials, each including small numbers of evaluable patients.[16] Importantly, most of the patients with Ewing sarcoma in the CABONE study had already received these salvage regimens before inclusion and therefore represented a heavily pre-treated population with highly refractory disease.

Among targeted therapies, IGF-1R inhibitors have been the most thoroughly studied in Ewing sarcoma. Despite promising preliminary results from early-phase studies, phase 2 studies of four different single-agent IGF-1R antibodies have produced disappointing efficacy results, with proportions of objective responses of less than 15% and median progression-free survival of less than 2 months in adults and children with recurrent tumours.[17]

The majority of patients with Ewing sarcoma treated with cabozantinib in this study experienced tumour shrinkage. The objective response was among the highest to have been observed with a tyrosine kinase inhibitor targeting the VEGFR2 pathway in solid tumours, with the exception of renal cell carcinoma, which has a high sensitivity to drugs targeting the VEGR pathway.[18] These data are consistent with preclinical studies that showed inhibition of Ewing sarcoma growth with VEGFR receptor inhibitors.[7] Interestingly, such compounds had little in-vitro activity but significant in-vivo activity, suggesting an anti-angiogenic effect rather than a direct tumour-cell inhibitory effect. MET is ubiquitously expressed in Ewing sarcoma and high expression has been associated with adverse outcomes.[7] Although VEGFR inhibition had no or minimal effect in vitro, cabozantinib induced growth inhibition in several Ewing sarcoma cell lines; this activity was correlated with the amount of MET expression.[7] Therefore, MET inhibition might contribute to the clinical activity of cabozantinib in this setting.

Objective response might not be an appropriate surrogate marker for therapeutic activity in osteosarcoma. Because of the abundant bone matrix, substantial anti-tumour activity might not result in a marked decrease in overall tumour volume. Non-progression is a widely recognised endpoint to assess new investigational agents in patients with advanced sarcoma.[19] For this reason, we chose a dual primary endpoint for the osteosarcoma cohort, combining progression-free survival and objective response. A systematic review of seven negative phase 2 trials, published after the activation of the CABONE study, recommended that an agent should be considered worthy of further investigation in advanced osteosarcoma if it is associated with a 16-week progression-free survival greater than 30%.[20] In the CABONE study, 4-month progression-free survival with cabozantinib was found to be 71% (95% CI 55–83). This level of activity appears to be greater than that reported for other angiogenesis inhibitors, even when used in combination with other anticancer agents.[21–24] Progression-free survival might not be a direct reflection of drug activity and could be influenced by the natural history of the disease. However, and unlike previous advanced osteosarcoma studies that used progression-free survival as their primary endpoint, all patients included in the CABONE study had to have their progressive disease confirmed by a central review of two imaging studies performed in less than 6-month intervals. Moreover, 21 (50%) of 41 patients experienced tumour shrinkage and seven (17%) of 41 had an objective response (the response for two patients occurred more than 6 months after treatment onset). Tumour shrinkage represents a more direct measure of anti-tumour activity attributable to the drug than progression-free survival, and these proportions are the highest ever reported with targeted therapy in osteosarcoma to our knowledge. It is also important to recognise that calcification or necrosis of osteosarcoma lesions can occur even in the absence of tumour shrinkage, as illustrated by the patient who underwent surgery of lung metastases, who showed a complete histological response despite only having a partial response.

The activity of cabozantinib observed in this study might be related at least in part to MET pathway inhibition. Pharmacological MET inhibition with drugs without anti-angiogenic activity significantly inhibited tumour growth and associated osteolysis and osteoid production in several in-vivo osteosarcoma models.[25] The significantly higher progression-free survival observed in this study in patients with high concentrations of sMET at baseline suggest that this biomarker could be predictive of cabozantinib benefit in patients with osteosarcoma. However, in addition to its action on the MET pathway, a study from 2018 suggested that cabozantinib can affect osteosarcoma growth by decreasing the production of RANK ligand by osteoblasts, and therefore reduce the proliferation of RANK-positive overall survival cells.[26]

Two recent meta-analyses have suggested the value of ^{18}F-FDG PET-CT for the diagnosis, staging, and follow-up of patients with Ewing sarcoma or osteosarcoma.[27,28] In this study, the prognostic value of early ^{18}F-FDG PET-CT response in patients with advanced Ewing sarcoma or osteosarcoma treated with a tyrosine kinase inhibitor was reported for the first time to our knowledge. Our results suggested that early metabolic

response assessed by ^{18}F-FDG PET-CT is a potential biomarker for benefit of cabozantinib in this setting. These results could represent a rationale for investigating modifications of therapy based on ^{18}F-FDG PET-CT-guided strategies in further studies assessing cabozantinib and other regimens in Ewing sarcoma and osteosarcoma.

The main limitation of the CABONE study is its non-randomised design. By minimising many sources of potential bias, randomised controlled clinical trials provide the most robust information about the effects of investigational drugs. However, recurrent Ewing sarcoma and osteosarcoma are rare diseases; around 250 new cases of Ewing sarcoma and 300 new cases of osteosarcoma are estimated per year across the EU.[29] Therefore, it can be challenging to recruit sufficient numbers of patients for randomised controlled trials are in these rare cancer types. Therefore, innovative endpoints that incorporate patients as their own control can be useful in this setting. GMI is the ratio of time to progression with nth line of therapy to the most recent previous line of therapy, and a GMI of 1·33 or higher has been proposed as a marker of meaningful clinical activity.[15] In this study, we found that around one-third of patients with Ewing sarcoma or osteosarcoma and treated with cabozantinib had a GMI of 1·33 or higher. Of note, this proportion is similar to that reported in the MOSCATO 01 trial (NCT01566019), which is one of the largest precision medicine studies to have used high-throughput molecular analysis to guide targeted therapy for patients with advanced solid tumours. In the MOSCATO 01 trial, GMI was higher than 1·3 in 33% of the patients treated with an innovative drug matched to the tumour molecular profile.[30] This proportion was also similar to that observed in patients with sarcoma treated with trabectedin, an alkylating agent recently approved by the US Food and Drug Administration for the management of patients with advanced soft-tissue sarcomas.[31] Nevertheless, although the usefulness GMI as an endpoint has been recognised by regulatory authorities such as the European Medicines Agency, the post-hoc analysis we did remains exploratory and further studies are needed to confirm the reliability of GMI for assessing the efficacy of experimental drugs in Ewing sarcoma and osteosarcoma.

The safety profile of cabozantinib was manageable in this study. 12 patients (13%) experienced pneumothorax, which is particularly relevant because sarcomas predominantly metastasise to the lungs. A review investigating the incidence of pneumothorax in patients with sarcoma showed that this complication can occur in every sarcoma histological subtype before or during treatment.[32] Pneumothorax has also been described, with an incidence of up to 14%, in patients receiving pazopanib, a tyrosine kinase inhibitor targeting VEGFR2 and approved for the treatment of advanced soft tissue sarcoma in patients who have received previous chemotherapy.[33,34] The presence of subpleural or pleural metastases and cavitary lung lesions have been identified as the main risk factors. In the CABONE study, all the patients with pneumothorax had subpleural or pleural metastases at baseline. Pneumothorax was observed in both progressive and responding patients, was manageable, and led to treatment discontinuation for only two patients.

In conclusion, cabozantinib shows antitumour activity and has a manageable safety profile in patients with advanced Ewing sarcoma or osteosarcoma and could represent a new therapeutic option for these patients.

Contributors

AI, SM-P, CB, and JW conceived and designed the study. AI, AC, NP, SP-N, EB, CC, FD, NE-W, ES, IR-C, CL, NG, PM-B, HP, MT, and J-YB provided study material or treated patients. All authors collected and assembled data. AI and CB developed the tables and figures, did the literature search, and wrote the report. MK, AC, and AB were involved in data collection. All authors were involved in the critical review of the manuscript and approved the final version.

Declaration of interests

AI reports research grants Merck Sharp & Dohme, Bristol-Myers Squibb, and Roche; personal fees from Epizyme, Bayer, Lilly, Roche, and Springworks; and non-financial support from Merck. OM reports personal fees from Amgen, Bayer Healthcare, Blueprint Medicine, Novartis, Pfizer, Ipsen, Roche, Lilly, Lundbeck, and Janssen. AB is an employee of Immusmol, and reports personal fees from Immusmol and Explicyte. J-YB reports grants from Ipsen and Exelixis, grants and personal fees from Bayer and Novartis, and personal fees from GlaxoSmithKline, during the conduct of the study. All other authors declare no competing interests.

Data sharing

Individual participant data that underlie the results reported in this article will be available after de-identification from 24 months until 48 months after article publication to researchers who provide a methodologically sound proposal. Requests should be sent to the corresponding author.

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