Ombrabulin plus cisplatin versus placebo plus cisplatin in patients with advanced soft-tissue sarcomas after failure of anthracycline and ifosfamide chemotherapy: a randomised, double-blind, placebo-controlled, phase 3 trial

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Summary

Background Ombrabulin (AVE8062) disrupts the vasculature of established tumours and has shown preclinical synergistic anti-tumour activity when combined with cisplatin. In this phase 3 trial, we aimed to assess the efficacy and safety of ombrabulin plus cisplatin compared with placebo plus cisplatin in patients with advanced soft-tissue sarcomas.

Methods We did this multinational, randomised, double-blind, placebo-controlled phase 3 study at 44 centres in ten countries. Patients aged 18 years and older with metastatic soft-tissue sarcomas, an Eastern Cooperative Oncology Group performance status of 0–2, and who had previously received treatment with anthracycline and ifosfamide were randomly assigned (1:1) to intravenous infusion of ombrabulin 25 mg/m² plus cisplatin 75 mg/m² or intravenous infusion of placebo plus cisplatin 75 mg/m² every 3 weeks. Patients were allocated to treatment using a permuted blocks randomisation scheme (block size of four) via an interactive voice-response system, and stratified by histological subtype. Patients, medical staff, study investigators, and individuals who handled and analysed the data were masked to treatment assignment. Our primary endpoint was median progression-free survival in the intention-to-treat population. Safety analyses were done on all randomised patients who received at least one dose of study drug. This trial is now closed, and is registered with ClinicalTrials.gov, number NCT00699517.

Findings Between June 13, 2008, and April 26, 2012, we randomly assigned 355 patients to ombrabulin plus cisplatin (n=176) or placebo plus cisplatin (n=179). Median duration of follow-up was 27·9 (IQR 20·9–33·2) in the placebo group and 30·5 months (20·7–37·6) in the ombrabulin group. Progression-free survival was slightly, but significantly, improved in the ombrabulin group compared with the placebo group (median 1·54 months [95% CI 1·45–2·69] *vs* 1·41 [1·38–1·58] months; hazard ratio 0·76 [95% CI 0·59–0·98]; p=0·0302). Grade 3 or 4 adverse events occurred more frequently in individuals in the ombrabulin group than in those in the placebo group and included neutropenia (34 [19%] in the ombrabulin group *vs* 14 [8%] in the placebo group) and thrombocytopenia (15 [8%] *vs* six [3%] for placebo). Adverse events leading to death occurred in 18 patients in the ombrabulin group and 10 patients in the placebo group.

Interpretation The combination of ombrabulin and cisplatin significantly improved progression-free survival; however, it did not show a sufficient clinical benefit in patients with advanced soft-tissue sarcomas to support its use as a therapeutic option. Predictive biomarkers are needed for the rational clinical development of tumour vascular-disrupting drugs for soft-tissue sarcomas.

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Introduction

Sarcomas are a heterogeneous set of uncommon malignancies that share a mesenchymal tissue origin and can arise nearly anywhere in the body. The complexity of sarcomas is evident (they comprise more than 50 histopathological subtypes in the most recent WHO classification),[1] but they account for fewer than 1% of adult cancers, with a worldwide incidence of 1·8–5·0 cases per 100 000 people per year.[2] Soft-tissue sarcomas make up most (more than 75%) cases worldwide in adults.[1] Cytotoxic chemotherapy, either as a single drug or as part of combination regimens, with anthracyclines (doxorubicin, liposomal doxorubicin, and epirubicin), alkylating agents (such as ifosfamide), and trabectedin (outside the USA) are standard treatments for metastatic or unresectable soft-tissue sarcomas.[3–5] However, chemotherapy does not seem to improve overall survival in this setting.[6] In 2012, regulatory authorities in the USA and European Union approved pazopanib, which inhibits several kinases including VEGF receptor, for patients with soft-tissue sarcomas for which treatment with conventional chemotherapy has

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failed. Pazopanib was approved based on a clinically significant improvement of progression-free survival in patients with soft-tissue sarcoma excluding liposarcoma.[7] Taxanes (docetaxel or paclitaxel) and gemcitabine also have activity in soft-tissue sarcomas, particularly in combination regimens and in selected subtypes of disease.[5,6] Despite these standard options for palliation, treatment for these tumours continues to be a pressing clinical challenge and development of new drugs is needed.

As with all cancers, neovasculature and the existing blood vessel networks are important for primary tumour growth and metastatic potential and may represent an important therapeutic target across histopathological subsets of soft-tissue sarcomas.[8,9] Many soft-tissue sarcomas are highly vascularised[1,10,11] and have some of the highest documented concentrations of systemic pro-angiogenic proteins such as VEGF and basic fibroblast growth factor.[1,10,11] Tumour vascular-disrupting drugs are a promising new strategy for treatment of soft-tissue sarcomas and have shown efficacy in a range of preclinical models of sarcomas.[12–14] In preclinical studies, tumour vascular-disrupting drugs show particular activity in the poorly perfused, central regions of bulky solid tumours.[15] Therefore, there is a strong rationale for combining tumour vascular-disrupting drugs with standard chemotherapy to target highly oxygenated and proliferating peripheral regions of tumours.[15]

Ombrabulin (AVE8062, AC-7700) is a tubulin-depolymerising tumour vascular-disrupting drug of the combretastatin A-4 class; previous studies have shown rapid and irreversible devascularisation and necrosis of tumours in a range of preclinical models.[16–18] In a phase 1 study of single-agent ombrabulin in advanced solid tumours, a patient with rectal cancer had a partial response, and eight patients had stable disease for 4 months or longer before relapse.[19] Ombrabulin has also shown synergistic preclinical anti-tumour activity with cisplatin in vivo[20] and a phase 1 study in which the ombrabulin and cisplatin combination was used to treat patients with solid tumours showed a dramatic decrease in tumour blood perfusion by dynamic contrast-enhanced ultrasonography.[21] The proportion of patients with metastatic sarcomas that respond to standard doses of single-agent cisplatin is low (4–7%);[22,23] however, trials of combination cytotoxic regimens have reported responses in the range of 32–54%.[24–26] Phase 1 studies have shown that ombrabulin 25 mg/m² plus cisplatin 75 mg/m² are the recommended doses for this combination in patients with solid tumours.[27,28] Phase 2 studies in patients with ovarian cancer and non-small-cell lung cancer have combined 35 mg/m² ombrabulin with paclitaxel and carboplatin, and with docetaxel plus cisplatin or carboplatin, respectively.[29,30] In this phase 2 study, we assessed the efficacy and safety of ombrabulin plus cisplatin versus placebo plus cisplatin in patients with anthracycline and ifosfamide refractory advanced soft-tissue sarcomas.

Methods

Study design and participants

In this multicentre, randomised, double-blind, placebo-controlled phase 3 trial, we recruited patients from 44 centres in ten countries. Patients were eligible if they were aged 18 years or older and had an Eastern Cooperative Oncology Group [ECOG] performance status of 2 or lower, measurable disease (by Response Evaluation Criteria in Solid Tumors [RECIST] version 1.1), histologically confirmed metastatic soft-tissue sarcomas, and had previously received two or more chemotherapies (including anthracyclines and ifosfamide) for advanced disease. Patients were required to have documented disease progression on imaging within 1 month before randomisation. Exclusion criteria were life expectancy of shorter than 12 weeks, previous treatment with tyrosine-kinase inhibitors, and previous intensive chemotherapy with autologous stem-cell rescue. Patients who had been treated for less than 3 weeks prior to randomisation with any anti-tumour therapy (eg, chemotherapy, targeted agents, and radiotherapy) or any investigational treatments were also ineligible. The washout period for patients treated with nitrosoureas or mitomycin C was 6 weeks or longer. We also excluded patients with brain metastases or sarcomatous leptomeningeal disease or both, inadequate organ function, and those with a history of cardiovascular disease, including a left ventricular ejection fraction below the institutional lower limits of normal. Laboratory safety assessments on haematology, blood chemistry, coagulation, urinalysis, and pregnancy were done within 8 days before randomisation to confirm adequate organ function for eligibility.

All patients provided written informed consent. Study approval was obtained from ethics committees of all centres according to national laws. The study was undertaken in accordance with the Declaration of Helsinki revised edition, the International Conference on Harmonisation (ICH) of technical requirements for registration of pharmaceuticals for human use, good clinical practice, and local ethical and legal requirements. An independent data monitoring committee (Erasmus University Medical Center, Rotterdam, Netherlands; IRCCS Ospedale San Raffaele, Milan, Italy; Centre Oscar Lambret, Lille, France; Atlanstat, Rezé, France) reviewed safety and interim efficacy data.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to receive either ombrabulin plus cisplatin (ombrabulin group) or placebo plus cisplatin (placebo group) with a randomisation sequence generated in permuted blocks of four within each stratum by an interactive voice response system provider (Clinphone, Burlington, MA, USA). Randomisation was stratified by four histological