**Cediranib in alveolar soft part sarcoma (CASPS), a double blind, placebo-controlled randomised phase II trial**

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## Abstract

**Background**: Alveolar Soft Part Sarcoma (ASPS) is a rare soft tissue sarcoma which is unresponsive to chemotherapy. Cediranib, a tyrosine kinase inhibitor, has shown significant activity in ASPS in non-randomised studies. CASPS was designed to discriminate the impact of cediranib from the intrinsically indolent nature of ASPS.

**Methods:** CASPS (NCT01337401, EudraCT2010-021163-33) was a double-blind trial in which patients aged ≥16 years, performance status 0-1, with metastatic ASPS, progressive in the previous 6 months were randomised (2:1 ratio) between cediranib (30mg od) and matching placebo. No anti-cancer treatment within 4 weeks prior to trial entry was allowed with exception of palliative radiotherapy. Allocation utilised computer generated random permuted blocks. Patients were unblinded at week 24 or at RECISTv1.1 progression if sooner; those on placebo crossed over to cediranib. The primary endpoint was percentage change in sum of target marker lesions (TMLsum) between baseline and week 24 or progression if sooner in the evaluable population (44/48 patients). Recruitment is complete and the trial is in follow-up. Here, the principal analysis is presented.

**Findings:** Forty-eight patients (32 cediranib, 16 placebo) were recruited between Jul 15, 2011 and Jul 29, 2016 from 12 sites (7 UK/3 Spain/2 Australia); 48% were female, median age 31 years (IQR: 27-45). Median follow-up was 34.3 months (IQR: 23.7-55.6) at the time of analysis. Median change in TMLsum on cediranib was −8.3% (IQR: −26.5-+5.9) vs placebo: +13.4% (IQR: 1.1-21.3), one-sided p=0.001. Most common grade ≥3 adverse events on (blinded) cediranib were hypertension (6 patients, 19%) and diarrhoea (2 patients, 6%). 15 serious adverse reactions were reported. One probable treatment-related death (intracranial haemorrhage) occurred on whilst on open-label cediranib.

**Interpretation:** Given the high incidence of metastatic disease and poor long-term prognosis of ASPS, together with the lack of efficacy of conventional chemotherapy, the confirmation of significant clinical benefit with cediranib in this disease represents an important step towards the goal of long-term disease control for these young patients.

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## Introduction

Alveolar soft part sarcoma (ASPS) is rare representing <0.5% of all soft tissue sarcomas (STS). It predominantly affects young people, with a median age at presentation of 25 years, with most patients aged <30 years at diagnosis (1). ASPS commonly involves the lower limb, with a slight female preponderance and a high incidence of metastatic disease at diagnosis (1). Although metastases may behave in an indolent fashion the long-term outlook is poor (2). Lieberman et al (2) report that only 15% of patients with no metastases at diagnosis remained metastasis-free at 20 years, with a median metastasis-free period of 6 years, and median survival following the development of metastases of 2 years. Median survival if presenting with metastases was 3 years, compared with 11 years for patients metastasis-free at diagnosis and there was a tendency to worsening survival with increasing age. Unusually in STS, in addition to lung metastases, the disease also metastasises to brain and bone (3). Histologically the disease is characterised by uniform polygonal cells arranged in a pseudoalveolar pattern separated by vascular septae and molecular studies have demonstrated a characteristic non-reciprocal translocation involving chromosomes X and 17, t(X;17)(p11.2:q25) resulting in the *ASPSCR1-TFE3* fusion gene which replaces the N-terminal portion of *TFE3* in a fashion consistent with transcriptional deregulation (4).

ASPS cells possess PAS positive precrystalline granules which contain monocarboxylate transporter 1 (MCT1) and its chaperone CD147 (5). In a genetically engineered mouse study which used the *ASPSCR1-TFE3* gene to drive oncogenesis, the mice developed tumours in the brain and orbit, i.e. the cranial vault, a region known to have the highest lactate concentrations in the mouse (6). Metabolic studies demonstrated that ASPS cells in this model used lactate as an energy source. Lactate is imported via MCT1 and is converted directly to pyruvate for entry into the citric acid cycle. In addition to supplying energy, lactate acts to stimulate cell proliferation and angiogenesis since excess lactate generates pyruvate, which upregulates hypoxia inducible factor 1 alpha (HIF1α) via inhibition of the prolyl hydroxylase responsible its degradation (7) raising the possibility that the lactate transporter MCT1 could be a therapeutic target for inhibition of tumour angiogenesis (8).

Cediranib is a receptor tyrosine kinase inhibitor (TKI) whose targets include vascular endothelial growth factor receptors (VEGFR) 1, 2 and 3, KIT and platelet derived growth factor receptors. Following the observation of a prolonged partial remission in a patient with locally advanced, metastatic ASPS treated in a phase II hypertension management study (NCT00264004) (9), another 6 patients with ASPS were treated in a cediranib pharmacodynamic study in STS patients (10). There was strong evidence of clinical activity against ASPS leading to further studies including a single-arm phase II trial conducted by the US National Cancer Institute (11).

Other TKIs have also been shown to have activity in ASPS. A direct anti-tumour effect has been shown with sunitinib mediated by PDGFRB, VEGFR2 and RET, with 5 PRs in 9 patients and median PFS of 17 months (12). In adults a retrospective study reported 1 CR and 7 PRs in 30 patients treated with pazopanib, with a median PFS of 13.6 months and only limited activity with trabectedin (13). In 40 patients with ASPS and a *TFE3* gene rearrangement treated with the ALK and MET inhibitor crizotinib there was 1 PR and 35 had stable disease (SD) as best response with a 1 year PFS of 37.5% (14). Anlotinib has also been reported to have activity in a prospective basket study in which 6/13 patients with ASPS had PR and median PFS was 21 months (15). Pazopanib is the only multi-targeted TKI approved for second or further line treatment of all STS. Preliminary reports of activity with immunomodulatory agents have been presented recently.

CASPS (NCT01337401) aimed to evaluate the efficacy of cediranib in the treatment of ASPS. The double-blind placebo-controlled design was chosen because of the unusual biology of this cancer, which although having strong metastatic potential is characterised by indolent metastatic tumour growth and periods of spontaneous stabilisation, making single group uncontrolled studies difficult to interpret (3,12). There were ethical challenges in having a placebo group, mitigated by having a 2:1 randomisation favouring active treatment, limiting the no-treatment period to 24 weeks and allowing crossover to active treatment on disease progression or, if no progression, after week 24. At entry patients were required to have progressed in the previous 6 months hence this duration was chosen as the period for comparison between cediranib and placebo. A preliminary report of CASPS was presented at the 2017 Annual General Meeting of the American Society of Clinical Oncology (16).

## Methods

### Trial design and patients

CASPS was a randomised phase II, multi-centre, double-blind, placebo-controlled clinical trial allocating patients between cediranib and placebo. Eligible patients were women or men ≥16 years old, with a histologically confirmed diagnosis of ASPS. A tumour block was required for central review and confirmation of the presence of the t(X;17)(p11.2:q25) translocation. Patients were required to have measurable metastatic disease which had progressed according to RECIST v1.1 in the previous 6 months, an ECOG performance status 0-1, life expectancy >12 weeks and adequate bone marrow, hepatic and renal function (absolute neutrophil count $>1.5x10^9$/L, platelet count $>100x10^9$/L, bilirubin <1.5x upper limit of normal (ULN), unless proven Gilbert's syndrome, alanine transaminase (ALT) or aspartate transaminase (ASP) <2.5xULN or <5xULN if liver metastases present, creatinine <1.5xULN or creatinine clearance >50mL/min). The restrictive criterion of progression in the previous 6 months was based on the known indolent nature of the disease. CASPS thus differs from other ASPS studies which have not similarly

restricted eligibility. Patients with brain metastases were eligible provided their disease was controlled with a stable dose of corticosteroid.

Exclusion criteria included history of gastrointestinal disorder likely to impair absorption of cediranib; poorly controlled hypertension; any severe or uncontrolled co-morbidity, e.g. active infection; prolonged QT interval - QTc ≥480 msec (using Bazetts correction) or familial long QT syndrome; significant recent haemorrhage; major thoracic or abdominal surgery in previous 14 days; recent history of thrombosis; pregnant or breast-feeding women; anticancer treatment in previous 4 weeks with exception of palliative radiotherapy; prior treatment with cediranib (added by approved protocol amendment on the advice of the joint Independent Data Monitoring and Steering Committee (IDMSC)); history of other malignancy except cancer in situ unless disease-free for >2 years and with tissue diagnosis of ASPS from target lesion; other concomitant anticancer therapy except steroids.

The study was approved by the South West London Research Ethics Committee 4 (REC reference 10/H0806/118) in the UK; the Clinical Research Ethics Committee of Hospital de la Santa Creu i Sant Pau, Barcelona (12/070 (R)) in Spain; and by the Metro South Health Service District Human Research Ethics Committee, Queensland (HREC/12/QPAH/10) and the Sydney Local Health District Human Research Ethics Committee (HREC/12/RPAH/26) in Australia. Patients provided written informed consent before enrolment. The Clinical Trials and Statistics Unit at The Institute of Cancer Research, London, UK (ICR-CTSU), had overall responsibility for trial coordination with two international trials groups (Grupo Español de Investigación en Sarcomas (GEIS), Madrid, Spain and Australasian Sarcoma Study Group (ASSG), Melbourne, Australia) having responsibility for regulatory and ethics submissions, monitoring and safety reporting within their respective countries. Safety and efficacy data were reviewed regularly by the IDMSC. A Trial Management Group was responsible for the day-to-day running of the trial. ICR-CTSU undertook all central statistical monitoring, interim and final analyses.

Randomisation and masking

Patients were randomly allocated, in a 2:1 ratio, to cediranib or matching-placebo by computer generated random permuted blocks derived by ICR-CTSU who conducted the randomisation centrally. Due to the small trial size no stratification factors were used. Both the patients and their clinicians were blinded to treatment allocation until week 24 or until disease progression, if sooner.

Procedures

Depending on treatment allocation, patients received cediranib or matching placebo 30 mg orally once daily, for the first 24 weeks of the study. At 24 weeks, or sooner if the patient had confirmed disease progression according to RECIST v1.1, patients

were unblinded. Patients allocated placebo crossed over to open-label cediranib and continued on treatment until disease progression or death. Patients allocated cediranib who had not progressed by 24 weeks continued on cediranib until progression or death. Patients could withdraw from the trial at any point.

Clinical assessments, including physical examination, symptom review and routine blood and urine investigations, took place at 2 and 4 weeks then 4 weekly until week 24, every 8 weeks up to 48 weeks then every 12 weeks until progression or treatment discontinuation. Assessments for patients crossing over from placebo to cediranib were recommenced as for the first 24 weeks. Tumour assessments (CT, MRI if indicated) were made at baseline, every 8 weeks to week 48, then every 12 weeks until disease progression. Blood pressure monitoring was performed at least weekly for the first 4 weeks, then monthly up to 24 weeks. Blinded radiology review was not planned as part of this study, although translational imaging studies are due to be conducted.

Treatment-related toxicity grade 3 or more, or repeated episodes of grade 2 toxicity not responding to adequate supportive measures was managed initially with dose interruptions of 2-5 days, with re-introduction on resolution at the same dose. Longer interruptions up to 14 days were permitted for chronic problems such as nausea, diarrhoea, hand and foot syndrome if refractory to supportive treatment, e.g. antiemetics, loperamide. If toxicity continued, a dose reduction to 20 mg daily was permitted. Treatment with cediranib was to be discontinued permanently for gastrointestinal perforation, wound dehiscence, severe haemorrhage or severe uncontrolled hypertension. Abnormal thyroid function was treated with L-thyronine as appropriate.

Toxicity was assessed using National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4. Coding was by the Medical Dictionary for Regulatory Activities (version 14).

Outcomes

The primary endpoint was percentage change in the sum of the longest diameters (or shortest if nodal disease) of target marker lesions (TMLsum), measured at 24 weeks (or progression if sooner) from the date of randomisation. Protocol-defined secondary endpoints included the proportion of patients with objective response (OR) at week 24, defined as the proportion of patients having either partial (PR) or complete response (CR) at the end of blinded treatment; best response up to week 24, defined as best response experienced at any point during blinded treatment; duration of response calculated as time from first response (CR or PR) to date of progression; best percentage reduction of target marker lesions during blinded treatment; PFS defined as time from randomisation to disease progression (defined by RECIST v1.1) or death from any cause. Patients who were alive and progression-free were censored at the date of last known follow-up. Patients with non-RECIST

confirmed progression (e.g. radiologically confirmed but lesions not measured according to RECIST, or patients with clinical evidence of progression only were censored at the date of their progression); PFS estimate at 12 months; overall survival, defined as time from randomisation to death (any cause); and safety and tolerability of cediranib.

Statistical analysis

In the AstraZeneca phase II study (D8480C00046) the 6 patients with metastatic ASPS had a mean tumour size reduction at 8 weeks of 25% with a coefficient of variation (CV) of 19% (10). The second scan at 16 weeks showed 4/6 patients had a reduction in size of >30%, i.e. a PR. It was assumed that a smaller effect and greater CV might be observed in a larger trial, therefore CASPS required 36 patients to detect a 20% reduction in the TMLsum at 24 weeks between placebo and cediranib with a CV of 25%, 80% power and a one-sided significance level of 5%. This was calculated for a two-sample t-test of the log transformation of the sum of TMLs diameters using the Stata sampsi command. A formal interim analysis was conducted after 18 patients (12 cediranib and 6 placebo) had 24 weeks follow up (or had disease progression if sooner). Recruitment to the study was not halted while the interim analysis was conducted.

The primary endpoint was compared between cediranib and placebo groups using the Wilcoxon Mann Whitney test. Medians and interquartile range limits (IQR; denoted as $25^{th}$-$75^{th}$ centiles) and non-parametric tests were chosen *a priori* due to the uncertainty around whether the data would be normally distributed. Graphical representation utilised waterfall plots. The principal analysis population for the primary endpoint was the evaluable population, defined as all patients randomised, as per an Intention to Treat (ITT) population, who had a scan at week 24 (or a scan at progression if earlier) with TMLs measured. A sensitivity analysis, based on this population, but excluding two patients who had received cediranib before entering the study (an exclusion criterion added after these two patients were enrolled) was conducted.

Binary endpoints were reported as proportions with 2-sided 90% confidence intervals (CIs) and compared between treatment groups using Fisher's exact test (one-sided). The population analysed for best response also included patients who had a scan prior to 24 weeks but were not evaluable for the primary endpoint. For survival-related endpoints, the ITT population was used; thus patients allocated to placebo who subsequently crossed-over were still analysed as belonging to the placebo group. Kaplan-Meier curves were plotted and treatment groups compared by the log-rank test. Hazard ratios (HRs) and 95% CIs were calculated from Cox proportional hazards regression models, with HRs<1 favouring cediranib. Analyses were unadjusted. Two additional sensitivity analyses were planned for PFS; one to include patients who had non-RECIST confirmed progression and a second, landmark

analysis, also including patients who had non-RECIST confirmed progression, but censoring patients 26 weeks after randomisation to provide insight into PFS in the absence of crossover.

The safety analysis population included all treated patients with the worst grades of adverse events (AEs) during the blinded treatment phase summarised. No formal comparisons between treatment groups were made in relation to safety due to small patient numbers. Any AE reported in ≥10% patients in either treatment group, or ≥1 patient for grade 3+ events are presented here.

Analyses are based on a database snapshot taken on Apr 11, 2018. All analyses were done with STATA version 13.1. CASPS is registered (ISRCTN63733470, NCT01337401, EudraCT2010-021163-33).

Role of the funding sources

The funders of the study had no material role in study design, data collection, analysis or interpretation, or writing of the report. The corresponding author had full access to all data and final responsibility for the decision to submit for publication.

## Results

Between Jul 15, 2011 and Jul 29, 2016 a total of 48 patients entered the trial from 12 centres in 3 countries: UK (31 patients; 7 centres), Spain (9 patients; 3 centres) and Australia (8 patients; 2 centres). The inflation in the recruitment total was recommended by the IDMSC to account for 4 patients not being evaluable for the primary endpoint and 2 patients who had received prior cediranib (Figure 1).

The baseline characteristics were well balanced between the treatment groups (Table 1). The median age at randomisation was 31 years (IQR: 27-45), with the most prevalent decade being the 20-29 years age group. More than half the patients were diagnosed ≤2.5 years before trial entry, the commonest site of disease was the upper leg and 11/48 (23%) patients had known brain metastases at trial entry. Twenty of the 48 (42%) patients had received prior TKI treatment, including 2/48 (4%) with prior cediranib.

One of the 32 (3%) patient randomised to cediranib did not start treatment. Median time on blinded treatment was 23.9 weeks (IQR: 20.1-24.6) for patients allocated cediranib and 22.2 weeks (IQR: 9.6-23.8) for patients allocated placebo. Fourteen of the 31 (45%) patients allocated cediranib and 4/16 (25%) patients allocated placebo had at least one dose modification, dose delay or missed dose during blinded treatment due to AEs. Eleven of the 31 (35%) patients who received blinded cediranib did not continue to open-label treatment; 8/31 (26%) due to disease progression, 1/31 (3%) due to haematemesis, 1/31 (3%) due to palmar-plantar

erythrodysesthesia and fatigue and 1/31 (3%) due to general poor tolerance and planned surgery. All patients allocated placebo (100%) went on to have at least one dose of open-label cediranib. Of the 37/48 (77%) patients who started open-label cediranib, 9 (6 cediranib, 3 placebo) were still on treatment at the time of analysis. Reasons for discontinuation in the remaining 28 were as follows: 21 disease progression, 2 adverse events, 4 patient choice, 1 death. Median time on open-label cediranib was 41.6 weeks (IQR: 21.0-67.0) for the remaining 20 patients randomised to cediranib and 40.3 weeks (IQR: 12.2-108.6) for those randomised to placebo.

Using the evaluable population (44/48 (92%)), there was a statistically significant difference in the median percentage change in the TMLsum at 24 weeks of −8.3% (IQR: -26.5-+5.9) on cediranib compared with 13.4% for placebo (IQR: −0.6-+23.5), one-sided p=0.001 (Figure 2). Best percentage change in TMLsum by 24 weeks was -15.7% (IQR: -26.3--2.4) for cediranib and 1.2% (IQR: -2.4-+10.9) for placebo, one-sided p=0.0001 (Appendix p2). Similar results were obtained in the cediranib naïve population (42/48 (88%) patients) (% change at 24 weeks: cediranib -4.4%; IQR: -26.3-+6.0, vs placebo 14.4%; IQR: 1.1-22.6, one-sided p=0.002 and best % change: cediranib -15.0%; IQR: -26.3--2.4, vs placebo 1.3%; IQR: -2.5-+11.8, one-sided p=0.0001). The proportion of patients with an objective response, based on best response during the blinded treatment phase was 19.4% with 6/31 patients on cediranib having a PR. However at week 24, 3 of these patients no longer met RECIST criteria for PR with the proportion of patients with objective response at week 24 being 10.7% (3/28). No placebo patients had a PR during the blinded treatment phase (one-sided p=0.07 cediranib vs placebo). Fourteen of the 28 (50.0%) cediranib patients and 7/16 (43.8%) patients in the placebo group had stable disease at 24 weeks; thus the proportion of patients with clinical benefit at 24 weeks was 60.7% (17/28 patients) for cediranib and 43.8% (7/16 patients) for placebo. Of the 7/16 (44%) patients who were stable on placebo at 24 weeks, 3/16 (19%) had received no treatment in the 6 months prior to randomisation, 1/16 (6%) had surgery to the primary disease site and the other 3/16 (19%) were on another TKI until a month prior to randomisation. All 6/32 (19%) patients with PR during the blinded treatment phase have subsequently progressed. Median duration of response was 16.0 months (IQR: 15.7-26.0). Of the patients randomised to cediranib, 2/32 (6%) patients who had stable disease up to week 24 subsequently acheived a PR. It is noteworthy that at the time of the primary analysis with a minimum of 6 months follow-up post-randomisation, 4/16 patients (25%) in the placebo arm had still not progressed, with a progression-free survival at 12 months of 22.5%. Spaghetti plots illustrate the percentage change in the TMLsum from randomisation to beyond week 24 (Appendix p3 and p4).

At the time of this analysis (median follow-up 34.3 months (IQR: 23.7-55.6)) the follow-up period was dominated by time on open-label cediranib and 43/48 (90%) patients (29 cediranib, 14 placebo) had had RECIST confirmed progression or death prior to confirmed progression. There was no evidence of a statistically significant

difference in PFS between the treatment groups although as described above, this analysis was confounded by crossover to open-label cediranib (Figure 3). With prolonged follow-up the PFS curves will increasingly converge owing to the proportional impact of crossover to active therapy in those originally allocated placebo. The first planned sensitivity analysis included 3/48 (6%) patients (1 cediranib, 2 placebo) who had non-RECIST confirmed progression (Appendix p5). The landmark sensitivity analysis showed a significant improvement in PFS for patients allocated cediranib (Appendix p6). An unplanned exploratory analysis to determine the impact of prior TKI on PFS was difficult to assess as small numbers preclude formal comparisons (Appendix p7). At the time of analysis 24/48 patients (50%) had died (16 cediranib, 8 placebo). As expected, there was no evidence of a difference in overall survival. Twelve month survival estimates were 90.3% (95%CI: 72.9, 96.8) for cediranib and 68.8% (95%CI: 40.5, 85.6) for placebo (Figure 4).

The safety population included 47/48 (98%) patients who had at least one dose of trial treatment. The side-effect profile was as expected for a VEGFR inhibitor. The most common AEs on blinded treatment were diarrhoea, hypertension, fatigue and nausea. AEs on cediranib of grade ≥3 were mainly hypertension and diarrhoea and were managed by dose reduction (Table 2). Fifteen serious adverse reactions (SARs) were reported in 12 patients (Appendix p8). Twelve of the 15 SARs occurred on open-label cediranib. The most common symptoms were dehydration (2 patients), vomiting (2 patients) and proteinuria (2 patients). One of the 48 (2%) patients died due to an intracranial haemorrhage whilst on open-label cediranib with no evidence of cerebral metastases. This event was considered as probably treatment-related. All other deaths were ASPS-related.

## Discussion

CASPS has confirmed the activity of cediranib in patients with advanced, metastatic ASPS with a significant difference in the TMLsum at 24 weeks compared with placebo. The primary endpoint was chosen to demonstrate the degree of tumour shrinkage occurring in response to cediranib without being confounded by treatment crossover. This was considered a more reliable index of treatment effect than PFS, in light of known indolent progression, spontaneous stabilisation and spontaneous regression in this disease (12). In addition this unconventional endpoint was considered more sensitive than PFS and thus required fewer patients to demonstrate a significant difference between the two groups, an important consideration in such a rare disease. The difference in median PFS at the time of the analysis was not statistically significant, with absolute values of 10.1 months (IQR: 5.3-19.0) observed for cediranib and 4.9 months (IQR: 1.9-20.0) for placebo. Cediranib has again been shown to stabilise metastatic disease and produce objective remissions, with 19.4% having PR in the first 24 weeks. Some patients with SD and PR had long-lasting disease control and the median duration of response was 16 months.

Analyses of secondary endpoints such as PFS and OS are recognised to be underpowered. However, the rarity and indolence of ASPS and the incorporation of crossover within the randomised trial dictated the use of an unconventional primary endpoint and acceptance that demonstration of superiority using more conventional criteria would not be possible. PFS and OS are reported to enable comparison with other agents, none of which have been studied in a prospective randomised trial. The majority of the data on other TKIs are derived from reports on small single centre studies, or larger studies in STS of which ASPS comprised a small component. The toxicity was as expected for a drug of this class and was generally manageable with dose interruptions or reductions with few patients allocated cediranib withdrawing due to treatment side-effects. Only 4 patients withdrew for reasons other than disease progression. One death due to a vascular event was deemed probably treatment-related, thrombo-embolic events being a known side effect of VEGFR inhibitors. It was undoubtedly challenging to conduct a randomised trial in such a rare disease, which has an incidence estimated at 0.25/million/year.

The belief that inhibitors of angiogenesis, such as VEGFR inhibitors like cediranib, might be active against ASPS was prompted by the observations of dormancy and spontaneous stabilisation, in the belief that some form of angiogenic switch might be responsible (17). An additional explanation, which is not mutually exclusive, is that this behaviour could be due to immune surveillance, for which there is now supportive clinical data from the use of immunomodulatory agents.

The demonstration of lactate as an energy source in ASPS (6) with consequent upregulation of HIF1α and VEGF may partially explain the activity of agents that inhibit VEGFR, although other targets may be involved. Spontaneous regression could be mediated via the immune system. A study of the VEGFR inhibitor axitinib in combination with pembrolizumab investigating immunomodulation in STS (NCT02301039) is ongoing (18). In patients with ASPS the proportion responding was 45.5% and with a 3 month progression-free estimate of 90.9%.

None of the molecularly targeted agents discussed above have been studied as extensively as cediranib in ASPS or have demonstrated superior activity. A randomised phase II study comparing cediranib with sunitinib monotherapy (NCT01391962) is yet to report. This study lacks a no treatment group, precluding control for spontaneous stabilisation or regression or variations in the rate of disease progression between the groups.

In CASPS the proportion of patients responding (19%) was lower than that reported in the Kummar NCI phase II trial (35%) (11) in which patients had a slightly lower median age: 27 years compared with 31 years, but a similar proportion had received prior anti-angiogenic therapy: 26% compared with 33% in CASPS. A potential key difference between the studies is that patients were not required to have demonstrated disease progression in the previous 6 months in the Kummar study. Although CASPS was open to patients aged ≥16 (in the Kummar study the threshold

was 18 years) only 1 patient aged <20 years was recruited into CASPS, reflecting the predominantly adult referral practice of participating centres,

The decision to conduct CASPS as a randomised trial was vindicated by the fact that 7/16 (44%) patients in the placebo group had stable disease at 24 weeks in spite of all patients having documented progressive disease prior to study entry. At the time of the primary analysis with a minimum of 6 months follow-up post-randomisation, 4 patients (25%) in the placebo group have still not progressed. In light of these data it would seem reasonable to follow patients with ASPS for at least 3 months to confirm progressive disease before considering systemic therapy. The decision to allow crossover was made on ethical grounds to enable all patients in the study access to cediranib at some stage. This has inevitably led to confounding in the interpretation of OS and long-term PFS as illustrated by the apparent convergence of the PFS curves at 12 months.

The study shows once again that anti-angiogenic therapy is active against advanced ASPS. It is unclear whether the spectrum of receptor tyrosine kinases inhibited by cediranib is substantially different from that of other drugs, such as sunitinib, which are active in this disease. Based solely on hypertension incidence as a surrogate marker, cediranib appears to be a potent VEGFR inhibitor. Comparative data on relative potency in vitro against different receptor tyrosine kinases do not seem helpful in predicting toxicity profiles and hypertension is not a reliable efficacy biomarker (19).

Given the high incidence of metastatic disease and poor long-term prognosis of ASPS, together with the lack of efficacy of conventional chemotherapy, the confirmation of significant clinical benefit with cediranib in this disease represents an important step towards the goal of long-term disease control for these young patients. Further studies using cediranib in ASPS and other sarcomas, in conjunction with other agents with potential activity in the disease are warranted.

## Contributors

IJ - Chief Investigator, trial design, protocol development, participant recruitment, data collection, data interpretation, writing, Trial Management Group member; JM - trial design, protocol development, statistical analysis, data interpretation, Trial Management Group member; LK - statistical analysis, data interpretation, writing, Trial Management Group member; ML - participant recruitment, data collection, Trial Management Group member; CB - participant recruitment, data collection; VB - participant recruitment, data collection, Trial Management Group member; QCH - participant recruitment, data collection, Trial Management Group member; RC - participant recruitment, data collection, Trial Management Group member; AD - participant recruitment, data collection, Trial Management Group member; LF - protocol development, trial management, data collection, data management, Trial

Management Group member; IH - participant recruitment, data collection, Trial Management Group member; KJ - data collection, data management; WJ - participant recruitment, data collection, Trial Management Group member; SK - trial management, data collection, data management, Trial Management Group member; ALP - participant recruitment, data collection, Trial Management Group member; CM - participant recruitment, data collection; BS - participant recruitment, data collection, Trial Management Group member; CS - protocol development, trial management, Trial Management Group member; MT - participant recruitment, data collection, Trial Management Group member; CT - trial management, data collection, data management, Trial Management Group member; JMT - participant recruitment, data collection, Trial Management Group member; JB - trial design, protocol development, statistical analysis, data interpretation, writing, Trial Management Group member. All authors reviewed the manuscript prior to submission.

## Declaration of interests

IJ, JM, LK, LF, KJ, SK, CS, CT and JB report grants and non-financial support in the form of study drug provision and distribution from AstraZeneca during the conduct of the study.

IJ also reports personal fees from Eli Lilly, Bayer, Nektar, PharmaMar, GSK, Ariad and The Institute of Cancer Research outside the submitted work.

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ML, CB, AD, VB, QCH, RC, IH, WJ, ALP, CM, BS, MT and JMT have nothing to disclose.

## Data sharing statement

The ICR-CTSU supports the wider dissemination of information from the research it conducts, and increased cooperation between investigators. Trial data is collected, managed, stored, shared and archived according to ICR-CTSU Standard Operating Procedures in order to ensure the enduring quality, integrity and utility of the data. Formal requests for data sharing are considered in line with ICR-CTSU procedures with due regard given to funder and sponsor guidelines. Requests are via a standard proforma describing the nature of the proposed research and extent of data requirements. Data recipients are required to enter a formal data sharing agreement which describes the conditions for release and requirements for data transfer, storage, archiving, publication and Intellectual Property. Requests are reviewed by

the Trial Management Group (TMG) in terms of scientific merit and ethical considerations including patient consent. Data sharing is undertaken if proposed projects have a sound scientific or patient benefit rationale as agreed by the TMG and approved by the Independent Data Monitoring and Steering Committee as required.

Restrictions relating to patient confidentiality and consent will be limited by aggregating and anonymising identifiable patient data. Additionally all indirect identifiers that may lead to deductive disclosures will be removed in line with Cancer Research UK Data Sharing Guidelines.

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**Figure legends**

Figure 1: Trial profile

Figure 2: Percentage change in sum of target marker lesions from baseline to week 24 (or progression if sooner) for all evaluable patients

Figure 3: Kaplan Meier curve for progression free survival by randomised treatment group
*Footnote: Excluding patients with prior cediranib treatment, unadjusted HR=0.76 (0.43, 1.35); one sided p-value = 0.21*

Figure 4: Kaplan Meier curve for overall survival by treatment group.
*Log rank p-value (one-sided) = 0.48*
*Excluding patients with prior cediranib treatment, log rank p-value (one sided) = 0.42*

## Tables

Table 1: Baseline demographic and clinical characteristics and previous treatments received for ASPS prior to trial entry by randomised treatment group

| | **Cediranib (N = 32)** | | **Placebo (N = 16)** | |
|---|---|---|---|---|
| | **n** | ***%*** | **n** | ***%*** |
| Sex | | | | |
| Male | 17 | *53* | 8 | *50* |
| Female | 15 | *47* | 8 | *50* |
| | | | | |
| Age at randomisation (years) | | | | |
| <20 | 0 | *0* | 1 | *6* |
| 20 – 29 | 15 | *47* | 5 | *31* |
| 30 – 39 | 8 | *25* | 4 | *25* |
| 40 – 49 | 4 | *13* | 5 | *31* |
| 50 – 59 | 4 | *13* | 0 | *0* |
| 60 – 69 | 0 | *0* | 1 | *6* |
| ≤70 | 1 | *3* | 0 | *0* |
| Median (IQR) | 30.3 (26.8, 44.7) | | 33.1 (29.3, 43.5) | |
| | | | | |
| ECOG performance status | | | | |
| 0 | 16 | *50* | 9 | *56* |
| 1 | 16 | *50* | 7 | *44* |
| | | | | |
| Time since original ASPS diagnosis (years) | | | | |
| ≤2.5 | 18 | *56* | 8 | *50* |
| 2.5 – 5 | 4 | *13* | 6 | *38* |
| 5 - 7.5 | 2 | *6* | 0 | *0* |
| 7.5 – 10 | 2 | *6* | 0 | *0* |
| >10 | 6 | *19* | 2 | *13* |
| | | | | |
| Site of primary disease | | | | |
| Upper leg/groin | 14 | *44* | 7 | *44* |
| Upper limb | 6 | *19* | 2 | *13* |
| Lower leg/foot | 3 | *9* | 3 | *19* |
| Trunk | 4 | *13* | 2 | *13* |
| Buttock | 3 | *9* | 0 | *0* |
| Pelvis | 1 | *3* | 2 | *13* |
| Cranial-facial | 1 | *3* | 0 | *0* |
| | | | | |
| Synchronous metastases at trial entry | | | | |

| | Cediranib (N = 32) | | Placebo (N = 16) | |
|---|---|---|---|---|
| | n | % | n | % |
| Yes | 5 | *16* | 0 | *0* |
| No | 27 | *84* | 16 | *100* |
| | | | | |
| Previous treatment for ASPS: | | | | |
| Any localised treatment | | | | |
| No | 7 | *22* | 5 | *31* |
| Yes | 25 | *78* | 11 | *69* |
| Surgery | 21 | *66* | 11 | *69* |
| *To the primary disease site* | *19* | *59* | *10* | *63* |
| *For metastatic disease* | *10* | *31* | *4* | *25* |
| | | | | |
| Radiotherapy | 21 | *66* | 7 | *44* |
| *To the primary disease site* | *12* | *38* | *7* | *44* |
| | | | | |
| Any systemic treatment | | | | |
| No | 19 | *59* | 7 | *44* |
| Yes | 13 | *41* | 9 | *56* |
| *Chemotherapy* | *5* | *16* | *4* | *25* |
| *TKI* | *12* | *38* | *8* | *50* |
| *Crizotinib* | *5* | *16* | *5* | *31* |
| *Sunitinib* | *1* | *3* | *2* | *13* |
| *Axitinib* | *2* | *6* | *0* | *0* |
| *Pazopanib* | *2* | *6* | *0* | *0* |
| *Cediranib* | *1* | *3* | *0* | *0* |
| *Cediranib + Dovitinib* | *0* | *0* | *1* | *6* |
| *Sunitinib + Pazopanib* | *1* | *3* | *0* | *0* |
| *MET-inhibitor (ARQ197)* | *1* | *3* | *0* | *0* |
| *HDAC inhibitor (PXD101)* | *0* | *0* | *1* | *6* |

Table 2: Adverse events reported during the blinded treatment phase by randomised treatment group

| | **Cediranib (N=31)** | | | | | | | | | **Placebo (N=16)** | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **G1+2** | | **G3** | | **G4** | | **G5** | | | **G1+2** | | **G3** | | **G4** | | **G5** | |
| | **n** | ***%*** | **n** | ***%*** | **n** | ***%*** | **n** | ***%*** | | **n** | ***%*** | **n** | ***%*** | **n** | ***%*** | **n** | ***%*** |
| Diarrhoea | 26 | *84* | 2 | *6* | 0 | *0* | 0 | *0* | | 6 | *38* | 0 | *0* | 0 | *0* | 0 | *0* |
| Hypertension | 20 | *65* | 6 | *19* | 0 | *0* | 0 | *0* | | 9 | *56* | 0 | *0* | 0 | *0* | 0 | *0* |
| Fatigue | 16 | *52* | 1 | *3* | 0 | *0* | 0 | *0* | | 6 | *38* | 0 | *0* | 0 | *0* | 0 | *0* |
| Nausea | 12 | *39* | 0 | *0* | 0 | *0* | 0 | *0* | | 3 | *19* | 0 | *0* | 0 | *0* | 0 | *0* |
| Dyspnoea | 11 | *35* | 0 | *0* | 0 | *0* | 0 | *0* | | 2 | *13* | 1 | *6* | 0 | *0* | 0 | *0* |
| Decreased appetite | 9 | *29* | 0 | *0* | 0 | *0* | 0 | *0* | | 6 | *38* | 0 | *0* | 0 | *0* | 0 | *0* |
| Arthralgia | 9 | *29* | 0 | *0* | 0 | *0* | 0 | *0* | | 2 | *13* | 0 | *0* | 0 | *0* | 0 | *0* |
| Weight decreased | 9 | *29* | 0 | *0* | 0 | *0* | 0 | *0* | | 2 | *13* | 0 | *0* | 0 | *0* | 0 | *0* |
| Headache | 9 | *29* | 0 | *0* | 0 | *0* | 0 | *0* | | 4 | *25* | 0 | *0* | 0 | *0* | 0 | *0* |
| Hypothyroidism | 9 | *29* | 0 | *0* | 0 | *0* | 0 | *0* | | 1 | *6* | 0 | *0* | 0 | *0* | 0 | *0* |
| Cough | 8 | *26* | 1 | *3* | 0 | *0* | 0 | *0* | | 6 | *38* | 0 | *0* | 0 | *0* | 0 | *0* |
| Abdominal pain | 9 | *29* | 0 | *0* | 0 | *0* | 0 | *0* | | 4 | *25* | 0 | *0* | 0 | *0* | 0 | *0* |
| Pain in extremity | 7 | *23* | 1 | *3* | 0 | *0* | 0 | *0* | | 6 | *38* | 0 | *0* | 0 | *0* | 0 | *0* |
| Constipation | 8 | *26* | 0 | *0* | 0 | *0* | 0 | *0* | | 3 | *19* | 0 | *0* | 0 | *0* | 0 | *0* |
| Mucosal inflammation | 6 | *19* | 1 | *3* | 0 | *0* | 0 | *0* | | 1 | *6* | 0 | *0* | 0 | *0* | 0 | *0* |
| Palmar-plantar erythrodysaesthesia syndrome | 7 | *23* | 0 | *0* | 0 | *0* | 0 | *0* | | 0 | *0* | 0 | *0* | 0 | *0* | 0 | *0* |
| Stomatitis | 5 | *16* | 0 | *0* | 0 | *0* | 0 | *0* | | 1 | *6* | 0 | *0* | 0 | *0* | 0 | *0* |
| Back pain | 5 | *16* | 0 | *0* | 0 | *0* | 0 | *0* | | 1 | *6* | 0 | *0* | 0 | *0* | 0 | *0* |
| Blood bilirubin increased | 4 | *13* | 0 | *0* | 0 | *0* | 0 | *0* | | 1 | *6* | 0 | *0* | 0 | *0* | 0 | *0* |
| Dry skin | 4 | *13* | 0 | *0* | 0 | *0* | 0 | *0* | | 0 | *0* | 0 | *0* | 0 | *0* | 0 | *0* |

| | Cediranib (N=31) | | | | | | | | | Placebo (N=16) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | G1+2 | | G3 | | G4 | | G5 | | | G1+2 | | G3 | | G4 | | G5 | |
| | n | % | n | % | n | % | n | % | | n | % | n | % | n | % | n | % |
| Insomnia | 4 | 13 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lymphocyte count decreased | 3 | 10 | 1 | 3 | 0 | 0 | 0 | 0 | | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| Upper respiratory tract infection | 4 | 13 | 0 | 0 | 0 | 0 | 0 | 0 | | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| Asthenia | 3 | 10 | 1 | 3 | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Neutrophil count decreased | 4 | 13 | 0 | 0 | 0 | 0 | 0 | 0 | | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| Vomiting | 4 | 13 | 0 | 0 | 0 | 0 | 0 | 0 | | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rash | 4 | 13 | 0 | 0 | 0 | 0 | 0 | 0 | | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nasopharyngitis | 3 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | | 4 | 25 | 0 | 0 | 0 | 0 | 0 | 0 |
| Chest pain | 4 | 13 | 1 | 3 | 0 | 0 | 0 | 0 | | 4 | 25 | 0 | 0 | 0 | 0 | 0 | 0 |
| Proteinuria | 3 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dysphonia | 3 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Gamma-glutamyltransferase increased | 3 | 10 | 0 | 0 | 0 | 0 | 0 | 0 | | 0 | 0 | 1 | 6 | 0 | 0 | 0 | 0 |
| Oedema peripheral | 2 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Epistaxis | 2 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dry mouth | 2 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Haemoptysis | 2 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Oropharyngeal pain | 2 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Blood amylase increased | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pain | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |

| | Cediranib (N=31) | | | | | | | | | Placebo (N=16) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | G1+2 | | G3 | | G4 | | G5 | | | G1+2 | | G3 | | G4 | | G5 | |
| | n | % | n | % | n | % | n | % | | n | % | n | % | n | % | n | % |
| Anaemia | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | | 3 | 19 | 0 | 0 | 0 | 0 | 0 | 0 |
| Injection site haematoma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pruritus | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Monoparesis | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Lower respiratory tract infection | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | | 2 | 13 | 0 | 0 | 0 | 0 | 0 | 0 |
| Blood alkaline phosphatase increased | 1 | 3 | 1 | 3 | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Alanine aminotransferase increased | 1 | 3 | 1 | 3 | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Pyrexia | 2 | 6 | 1 | 3 | 0 | 0 | 0 | 0 | | 1 | 6 | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypophosphataemia | 2 | 6 | 1 | 3 | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Amenorrhoea | 1 | 3 | 1 | 3 | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Partial seizures | 0 | 0 | 1 | 3 | 0 | 0 | 0 | 0 | | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

G=CTCAE Grade

## Research in Context

### Evidence before this study

Prior to undertaking this study the available data concerning the activity of the experimental drug cediranib (previously AZD2171) in the treatment of ASPS consisted of the index case of a prolonged response in ASPS in a phase II trial, a phase II study of cediranib in the treatment of GIST and STS including ASPS, (of the 6 ASPS patients 4 had a durable PR and 1 had prolonged SD) and a phase II single arm study, which was ongoing at the time the CASPS trial was being developed which has since demonstrated activity in ASPS: the proportion responding was 35%, with 15 of 43 patients achieving a PR, 26 patients (60%) had SD as best response, with 84% patients with disease control (PR + SD) at 24 weeks. Other studies involving ASPS, ongoing and completed were identified using the Clinicaltrials.gov website, PubMed (searching for tyrosine kinase inhibitor, anti-angiogenic agent, alveolar soft part sarcoma – 2000 to current), via presentations at international meetings and personal communications. Other agents with reported activity in ASPS included sunitinib: 5 PRs in 9 patients, median PFS 17 months; pazopanib: 1 CR, 7 PRs in 30 patients, median PFS 13.6 months; anlotinib: 6 PRs in 13 patients, median PFS 21 months.

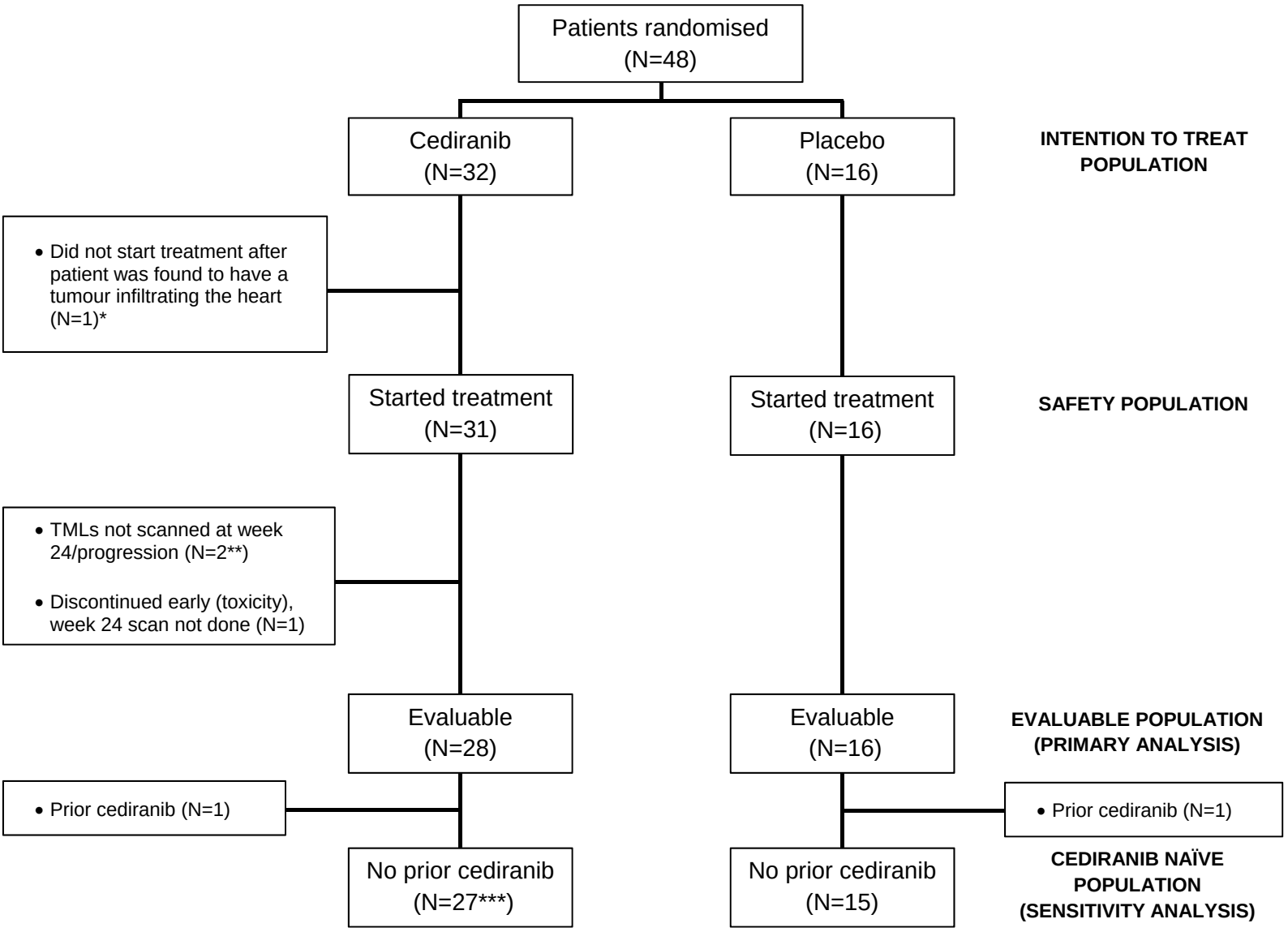
### Added value of this study

ASPS has a high metastatic potential but usually slow disease progression and sometimes spontaneous disease arrest and even, rarely, regression may occur. This makes PFS an unreliable endpoint. By conducting a placebo-controlled randomised trial with tumour size as the primary endpoint we ensured that the activity of cediranib could be measured reliably. This is the only randomised study to be reported in ASPS to date. A randomised study comparing cediranib with sunitinib has no placebo group, hence no control for spontaneous disease stabilisation or regression.

### Implications of all the available evidence

Although the precise molecular targets of cediranib in ASPS are not known, this study has definitively confirmed the value of this drug in the treatment of advanced ASPS. The relative importance of angiogenesis inhibition and immunomodulation are the subject of active investigation and translational research from this study will be published in due course.

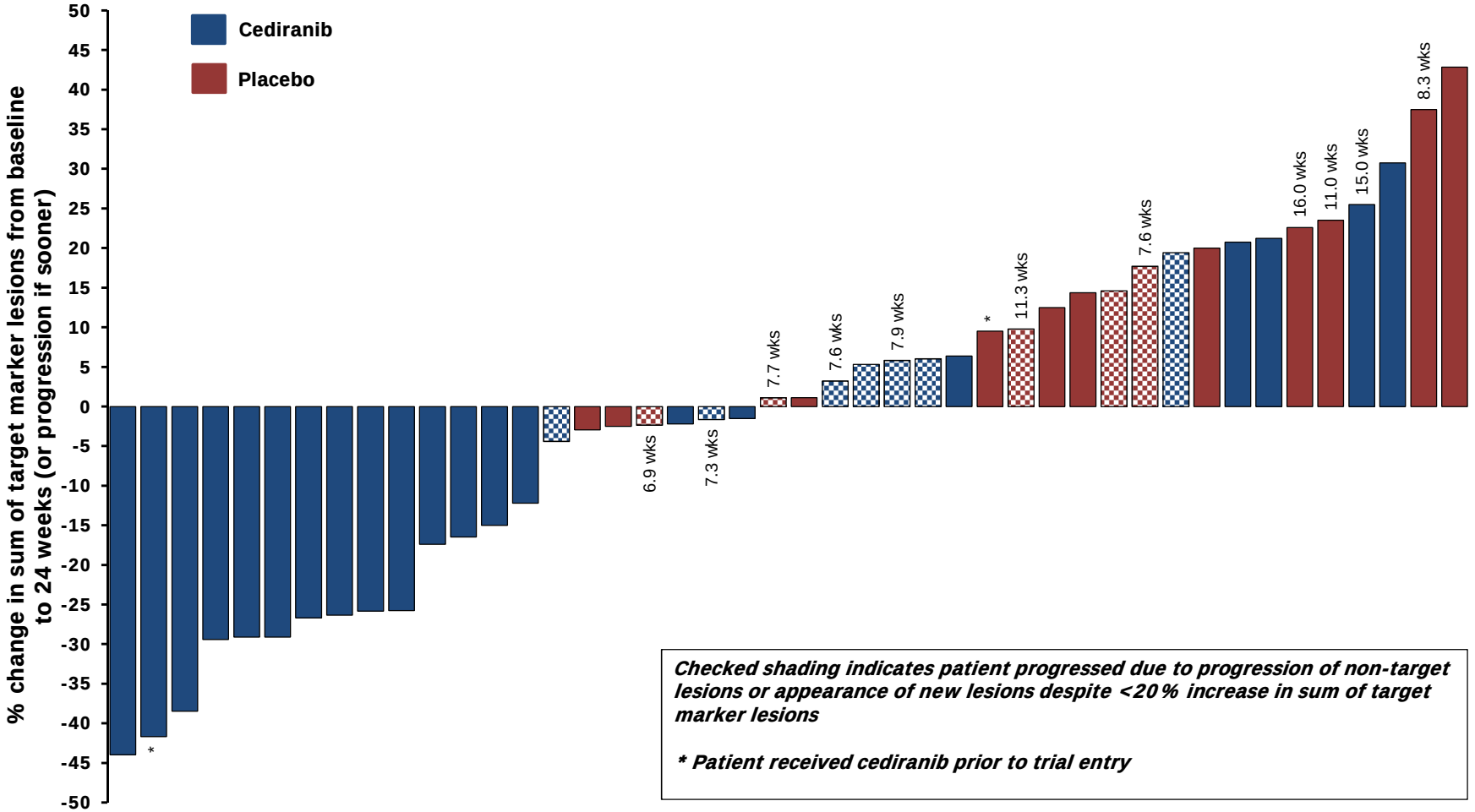
Figure 1: Trial profile




* patient was also subsequently found to be ineligible due to unconfirmed progression within 6 months prior to trial entry

** one patient was also subsequently found to be ineligible due to unconfirmed progression within 6 months prior to trial entry

***one patient was subsequently found to be ineligible due to unconfirmed progression within 6 months prior to trial entry but is included in the analysis




***Checked shading indicates patient progressed due to progression of non-target lesions or appearance of new lesions despite <20 % increase in sum of target marker lesions***

**** Patient received cediranib prior to trial entry***

**Figure 3**

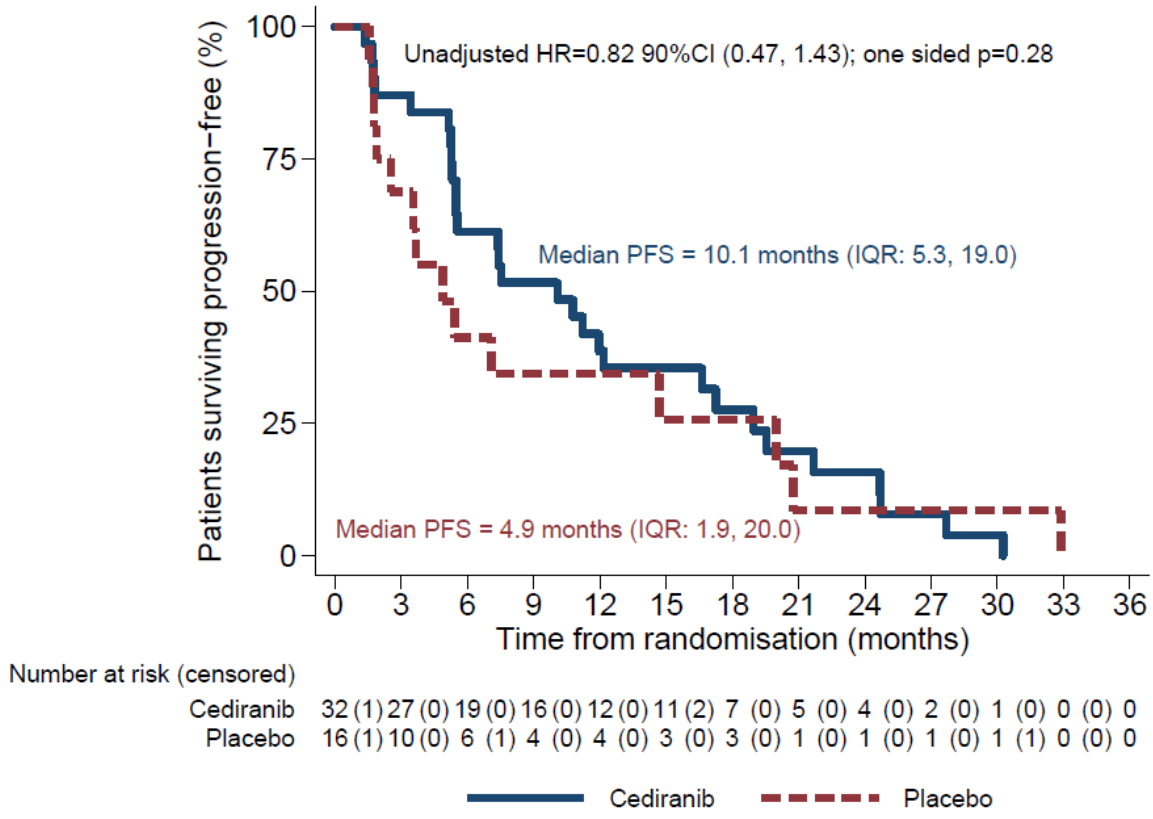
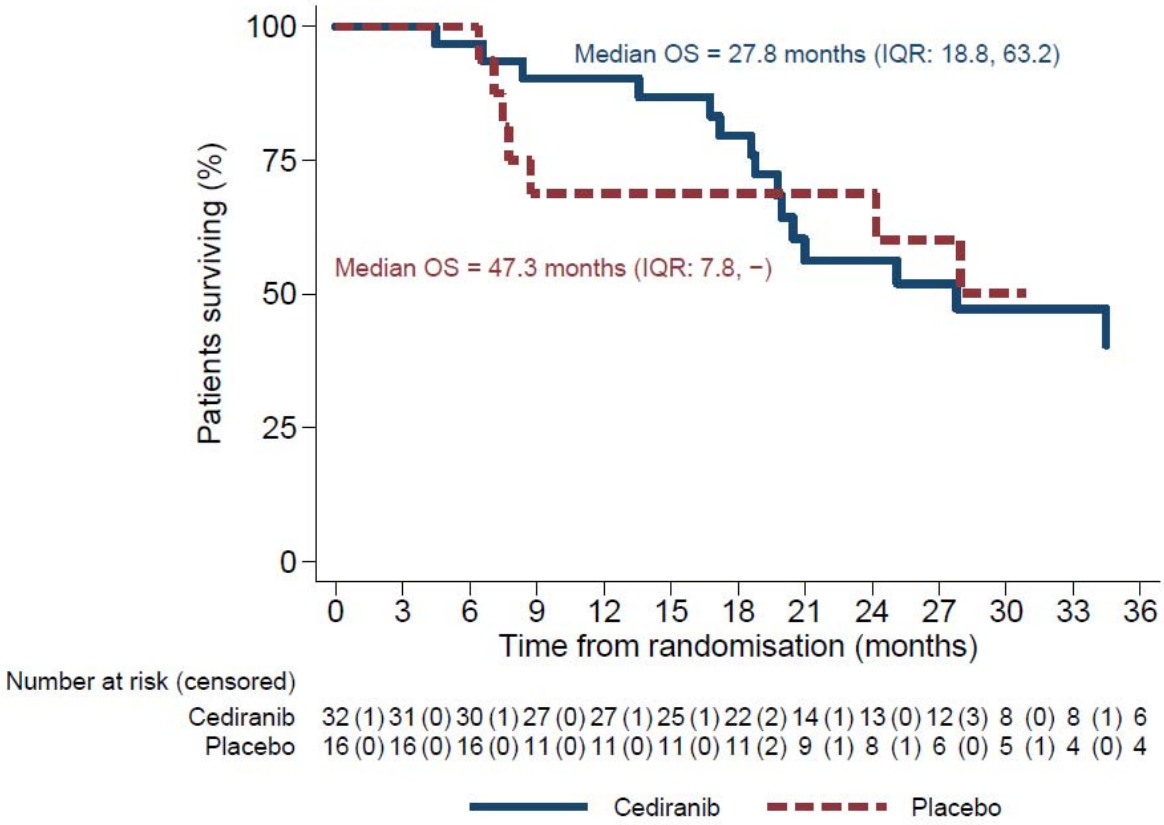

Patients surviving progression−free (%)
100
75
50
25
0
Unadjusted HR=0.82 90%CI (0.47, 1.43); one sided p=0.28
Median PFS = 10.1 months (IQR: 5.3, 19.0)
Median PFS = 4.9 months (IQR: 1.9, 20.0)
0 3 6 9 12 15 18 21 24 27 30 33 36
Time from randomisation (months)
Number at risk (censored)
Cediranib 32 (1) 27 (0) 19 (0) 16 (0) 12 (0) 11 (2) 7 (0) 5 (0) 4 (0) 2 (0) 1 (0) 0 (0) 0
Placebo 16 (1) 10 (0) 6 (1) 4 (0) 4 (0) 3 (0) 3 (0) 1 (0) 1 (0) 1 (0) 1 (1) 0 (0) 0
Cediranib
Placebo

**Figure 4**


Median OS = 27.8 months (IQR: 18.8, 63.2)
Median OS = 47.3 months (IQR: 7.8, −)
Patients surviving (%)
100
75
50
25
0
0 3 6 9 12 15 18 21 24 27 30 33 36
Time from randomisation (months)
Number at risk (censored)
Cediranib 32 (1) 31 (0) 30 (1) 27 (0) 27 (1) 25 (1) 22 (2) 14 (1) 13 (0) 12 (3) 8 (0) 8 (1) 6
Placebo 16 (0) 16 (0) 16 (0) 11 (0) 11 (0) 11 (0) 11 (2) 9 (1) 8 (1) 6 (0) 5 (1) 4 (0) 4
Cediranib
Placebo