Cancer Association of South Africa (CANSA)

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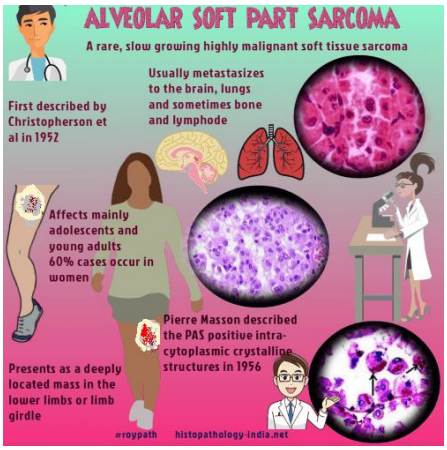
Fact Sheet
on
Alveolar Soft-Part Sarcoma

Introduction

Carcinomas and sarcomas are two of the main types of cancer.

Carcinomas are cancers that develop in epithelial cells, which cover the internal organs and outer surfaces of your body. Sarcomas are cancers that develop in mesenchymal cells, which make up both your bones and soft tissues, such as muscles, tendons, and blood vessels.

[Picture Credit: Alveolar Soft-Part Sarcoma Picture]



Cancer happens when cells start to divide uncontrollably and spread to other tissues. This creates masses called tumours. Most cases of cancer involve either a carcinoma or a sarcoma.

Alveolar Soft-Part Sarcoma (ASPS)

Alveolar soft part sarcoma (ASPS) is a rare, poor prognosis, slow growing soft tissue tumour of an unclear cause. It is among the least common sarcomas, representing 0.2-1 percent of large studies of soft tissue sarcomas. It represents tumours that start in the soft connective tissues of the body such as fat, muscles or nerves.

ASPS is characterized by a painless mass that most commonly arises in the leg or buttock, with a particular affinity to travel to the lungs as multiple nodules, presumably while the sarcoma itself is still small.

This disorder is very rare because it involves a specific breaking and joining event between two chromosomes, called an “unbalanced translocation”. This finding is observed in essentially all people with ASPS examined so far. This finding cannot be passed on to children, however, as the finding occurs only in the tumour cells, not in the normal cells. In addition, there are no families in which multiple family members have the disorder.

ASPS grows even more slowly than clear cell sarcoma, but is definitely a malignant tumour that tends to spread inexorably if not completely removed by surgery. Many patients can live with disease for years and even decades. Although most patients with alveolar soft-part sarcoma can never be rid of their cancer completely, many can undergo repeated surgery over the years to keep it somewhat at bay.

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ASPS tends to occur more often in younger individuals, specifically adolescents and young adults.

Alveolar soft-part sarcoma is highly malignant, with a relatively indolent, yet relentless course. The overall prognosis is poor given the high frequency of metastatic (spread) disease.

Hagerty, B.L., Aversa, J., Diggs, L.P., Dominguez, D.A., Ayabe, R.I., Blakely, A.M., Davis, J.L., Luu, C. & Hernandez, J.M. 2020.
Background: Alveolar soft part sarcoma is a rare, histologic subtype of soft tissue sarcoma that remains poorly defined. We aimed to describe patient characteristics and treatment patterns and to examine factors associated with survival for patients with alveolar soft part sarcoma.
Methods: After identifying patients with alveolar soft part sarcoma in the National Cancer Database, we recorded their clinicopathologic characteristics. Univariable log-rank survival analysis and Cox proportional hazards model were employed. For context, survival comparisons were included for patients with other sarcoma subtypes.
Results: Overall, 293 patients with alveolar soft part sarcoma were identified. Interestingly, patients with head and neck tumors were least likely to present with distant disease (40%, P = .025). The majority of patients underwent resection (n = 183, 63%). Among those, no predictors of lesser survival were identified other than the presence of metastases (hazard ratio 6.04, P ≤ .001). Patients with stage IV alveolar soft part sarcoma who underwent resections experienced improved survival relative to similar patients with more common subtypes of soft tissue sarcomas (P ≤ .001).
Conclusion: Alveolar soft part sarcoma is exceedingly rare, and patients often present with metastases. Primary tumors can occur anywhere in the body, and location impacts the rates of metastases at presentation. Resection is associated with a favorable survival advantage when compared to other, more common histologic subtypes of soft tissue sarcomas.

Wang, L.Y., Jia, C., Zhang, M., An, H.B., Zhang, N., Wang, L., Fu, L.B. & He, L,J. 2020.
Objective: To investigate the clinicopathological manifestations, molecular genetic, diagnostic histology and differential diagnosis of alveolar soft part sarcoma (ASPS) in children.
Methods: A total of 13 cases of ASPS diagnosed at Beijing Children's Hospital from August 2009 to November 2018 were collected. HE staining, histochemical staining for PAS and D-PAS, immunohistochemical (IHC) staining for TFE3, INI1 and CD68 and florescence in situ hybridization (FISH) for TFE3 gene translocation were performed.
Results: There were four males and nine females, age ranged from 1 year and 2 months to 13 years and 8 months (mean 7.8 years); and four patients were under 5 years old. Histologically, the tumors showed a distinctive and characteristic nested or organoid growth pattern (11 cases) or solid, diffuse growth (2 cases). The tumor cells possessed abundant eosinophilic, or glycogen-rich and clear to vacuolated cytoplasm. The chromatin was relatively dispersed, with prominent and pleomorphic nucleoli; mitotic figures were rare. Vascular invasion was frequently seen. IHC staining showed specific nuclear TFE3 staining. The tumor cells were also positive for INI1,CD68 and vimentin; but were negative for MyoD1, Myogenin, CK and S-100 protein. Seven cases showed PAS and D-PAS staining, with fuchsia acicular or rod-shaped crystals in tumor cytoplasm. Nine cases showed TFE3 break-apart signals by FISH.
Conclusions: ASPS is a rare soft tissue sarcoma in children. Compared with ASPA in adults, it has both similarities and unique clinicopathologic characteristics. The diagnosis needs to be confirmed by combining clinical, pathologic, IHC and genetic testing.

Wang, Y., Min, L., Zhou, Y., Tang, F., Luo,Y., Zhang, W., Duan, H.& Tu. C. 2019.

Background: Evidence suggests that advanced or metastatic alveolar soft part sarcoma (ASPS) with high metastatic potential is chemo-resistant. However, the benefits of tyrosine kinase inhibitors have been demonstrated for the treatment of ASPS.

Purpose: This study aimed to investigate the efficacy and safety of apatinib, aspecific VEGFR-2 inhibitor, in ASPS patients. This retrospective analysis involved six patients with metastatic ASPS not amenable to curative treatment.

Patients and methods: Apatinib was administered at a dose of 500mg per day. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) guidelines. Survival analysis was performed using the Kaplan-Meier test, and a safety profile was recorded.

Results: The mean age of patients was 26.5 (range, 17-32) years. The median progression-free survival (PFS) was 18.53 months (95% CI, 12.23-NE). However, median overall survival (OS) has not been reached. Twenty-four month PFS and OS rates were 50.0% and 100.0%, respectively. One patient achieved a complete response, and the remaining patients achieved partial responses, with an objective response rate of 100%. Median follow-up was 20.6 (range, 12.43-34.13) months. The most common adverse events included gastrointestinal discomfort (4/6[66.7%]), hair hypopigmentation (4/6[66.7%]) and hand-foot skin reaction (3/6[50.0%]).

Conclusion: Apatinib shows beneficial activity in metastatic ASPS patients, and further studies are warranted with more cases and longer follow-up periods to fully characterize clinical efficacy and safety of apatinib in ASPS.

Incidence of Alveolar Soft-Part Sarcoma (ASPS)

The outdated South African National Cancer Registry (2017) does not provide any information regarding Alveolar Soft-Part Sarcoma (ASPS),

Causes and Risk Factors for Alveolar Soft-Part Sarcoma (ASPS)

There is no exposure or infection that is known to predispose to ASPS. It is known that two chromosomes break and rejoin is a certain way (unbalanced translocation) and bring together two genes, normally separated on chromosomes X (the sex chromosome) and 17.

Dickson, B.C., Chung, C.T., Hurlbut, D.J., Marrano, P., Shago, M., Sung, Y.S., Swanson, D., Zhang, L. & Antonescu, C.R. 2019.

"Alveolar soft part sarcoma (ASPS) is a rare malignancy that, since its initial description, remains a neoplasm of uncertain histogenesis. The disease-defining molecular event characterizing the diagnosis of ASPS is the ASPSCR1-TFE3 fusion gene. Following identification of an index case of ASPS with a novel TFE3 fusion partner, we performed a retrospective review to determine whether this represents an isolated event. We identified two additional cases, for a total of three cases lacking ASPSCR1 partners. The average patient age was 46 years (range, 17-65); two patients were female. The sites of origin included the transverse colon, foot, and dura. Each case exhibited a histomorphology typical of ASPS, and immunohistochemistry was positive for TFE3 in all cases. Routine molecular testing of the index patient demonstrated a HNRNPH3-TFE3 gene fusion; the remaining cases were found to have DVL2-TFE3 or PRCC-TFE3 fusion products. The latter two fusions have previously been identified in renal cell carcinoma; to our knowledge, this is the first report of a HNRNPH3-TFE3 gene fusion. These findings highlight a heretofore underrecognized genetic diversity in ASPS, which appears to more broadly molecularly overlap with that of translocation-associated renal cell carcinoma and PEComa. These results have immediate implications in the diagnosis of ASPS since assays

reliant upon ASPSCR1 may yield a false negative result. While these findings further understanding of the molecular pathogenesis of ASPS, issues related to the histogenesis of this unusual neoplasm remain unresolved."

Signs and Symptoms of Alveolar Soft-Part Sarcoma (ASPS)

Alveolar Soft-Part Sarcoma (ASPS) usually presents as a soft, painless, slow-growing mass that rarely causes functional impairment. In adults, the lower extremities are the most common location for this lesion, although it has been described in a variety of locations including the female genital tract, mediastinum, breast, urinary bladder, gastrointestinal tract, and bone. In children, ASPS most often occurs in the head and neck region. The tumours are extremely vascular, and occasionally present as a pulsatile mass with an associated bruit (a sound heard over an artery or vascular channel, reflecting turbulence of flow).

Most patients with alveolar soft-part sarcoma probably have had the cancer for some time before they come to medical attention. The reason is that the tumour grows so slowly that it at first causes few symptoms and does not form a large mass.

By the time the tumour is big enough that the patient feels a lump from the primary lesion and seeks out a physician for help, the tumour has frequently spread, establishing small metastatic colonies throughout the body, frequently found in the lungs and even the brain.

Diagnosis of Alveolar Soft-Part Sarcoma (ASPS)

In addition to a complete physical examination, doctors diagnose ASPS with:

- X-rays, which produce images of internal tissues, bones, and organs onto film
- Magnetic resonance imaging (MRI), which produces detailed images of the area where the tumour is located
- Computerized tomography scan (CT or CAT scan) to capture a detailed view of the body, in some cases
- Biopsy or tissue sample from the tumour to provide definitive information about the type of tumour; this is collected during surgery
- Bone scan to detect bone involvement
- Complete blood count (CBC), which measures size, number and maturity of different blood cells in a specific volume of blood
- Other blood tests, including blood chemistries

Leszczynska, M., Jodeh, D.S., Reed, D., Lynskey, E.M., Bittles, M.A., Mayer, J.L. & Rottgers, S.A. 2019.
BACKGROUND: Alveolar soft-part sarcoma (ASPS) is an uncommon malignancy that may present in a manner similar to benign vascular tumors.
METHODS: A 6-year-old boy with autism spectrum disorder was referred to the Johns Hopkins All Children's Hospital vascular anomalies clinic for the evaluation of a tongue mass.
RESULTS: Prior to the presentation, at 5 years of age, neck computed tomography (CT) was performed. This showed a well circumscribed, enhancing mass at the anterior aspect of the tongue. The radiologic impression was that this lesion was most likely a hemangioma. Two years later, the patient was evaluated in the vascular anomalies clinic. At that examination a 2-3 cm swelling was noted on the dorsal aspect of the tongue. The mass was fleshy and firm with discrete borders. Handheld Doppler examination indicated a

high-flow lesion. The patient underwent an excisional biopsy. The lesion was identified as an alveolar soft-part sarcoma based on pathologic characteristics.
CONCLUSION: Familiarity with common vascular tumors and malformations allows providers to diagnose the majority of these lesions on a combination of clinical history and physical examination. Atypical and combined lesions do benefit from imaging to help characterize and aid in the differential diagnosis. Biopsy enables definitive diagnosis but is necessary in the minority of cases. When in doubt, referral to a specialized, multidisciplinary vascular anomalies clinic will ensure that these patients receive management for this challenging collection of conditions.

Crombé, A., Brisse, H.J., Ledoux, P., Haddag-Miliani, L., Bouhamama, A., Taieb, S., Le Loarer, F. & Kind, M. 2019.
OBJECTIVES: To investigate the imaging features of alveolar soft-part sarcomas (ASPS) on pre-treatment MRI in order to identify relevant criteria to distinguish ASPS from other soft-tissue tumors.
METHODS: A series of 25 patients (mean age, 18.5 years old) with histologically proven ASPS from five French comprehensive cancer centers was compared to a control cohort of 292 patients with various histologically proven benign and malignant soft-tissue tumors representative of the 10-year long activity of one center. All had a baseline MRI with contrast-agent administration. Two radiologists independently reviewed the MRIs. Features assessing location, size, signal, architecture, periphery, and vascularization were reported. Their association with the histological diagnosis of ASPS was evaluated with chi-square or Fisher's test. Their prevalence, sensitivity, specificity, odds ratio, and reproducibility were calculated.
RESULTS: Eight MRI features were significantly associated with ASPS: deep location ($p < 0.001$), high signal intensities on T1-weighted imaging ($p < 0.001$), central area of necrosis ($p = 0.001$), absence of fibrotic component ($p = 0.003$), infiltrative growth pattern ($p = 0.003$), absence of tail sign ($p = 0.001$), presence of intra- and peritumoral flow-voids ($p < 0.001$), and number of flow-voids ≥ 5 ($p < 0.001$). Twenty out of the 25 (80%) ASPS showed at least 7 of these 8 features compared to only four out of 292 (1.4%) tumors of the control cohort (1 benign vascular tumor, 1 solitary fibrous tumor, 2 high-grade soft-tissue sarcomas). The five ASPS with less than 7 out of 8 features measured less than 40 mm.
CONCLUSION: The striking histological uniformity of ASPS translates into imaging. However, ASPS may be misdiagnosed as benign tumors or pseudo-tumors, notably intramuscular benign vascular tumors or vascular malformations.
KEY POINTS: • ASPS are rare aggressive mesenchymal tumors displaying recurrent MRI features highly reminiscent of the diagnosis. • Deep-seated tumors presenting with mainly high signal intensity on T1-weighted imaging, an absence of fibrotic component, ill-defined margins without aponeurotic extension, and more than five central and peripheral flow-voids are very likely to be ASPS. • ASPS may be misdiagnosed as intramuscular benign vascular tumor or vascular malformation, which occur in the same age group.

Xu, Y., Zhou, T., Tu, W., Sarrin-Khameh, N. 2019.
Alveolar soft part sarcoma is a rare highly malignant neoplasm of the soft tissue and usually occurs in the lower extremities of children and young adults. We report two cases of alveolar soft part sarcoma: a 24-year-old Latino man with a 10-cm neck mass and a 56-year-old Latino woman with a recurring thigh mass. Fine-needle aspiration and a core biopsy were performed on both, which was followed by tumor resection on the man. The smears displayed numerous loosely cohesive or single large cells with abundant granular cytoplasm, round nuclei, vesicular chromatin, and occasional prominent nucleoli. Periodic and Schiff (PAS)-positive, diastase-resistant rhomboid, or needle-shaped crystals were present. Both tumors had diffuse and strong nuclear TFE3 expression and aberrant cytoplasmic CD68 expression. Fluorescence in situ hybridization analysis was performed in the first case, which detected a characteristic translocation t(X;17)(p11;q25). The diagnosis of alveolar soft part sarcoma was rendered in both cases. Herein, we present the cytology, histology, immunohistochemistry, and molecular findings and discuss the differential diagnosis.

Treatment of Alveolar Soft-Part Sarcoma (ASPS)

A team of doctors from various specialties is best suited to work together to determine a course of treatment for alveolar soft-part sarcoma. The most common option may combine the following therapies:

- **Surgery**—A surgical oncologist (a cancer surgeon) removes the tumour and any surrounding tissues (margin). Since alveolar soft-part sarcoma often comes back after treatment, the surgeon may want to take a wide margin of tissue to get all of the cancer. If the tumour is in an arm or leg, this surgery might include removal of part or all of the arm or leg.
- **Radiation (radiotherapy)**—In this treatment, a radiation oncologist uses light energy such as high-energy X-rays to destroy or reduce the size of tumour cells. It is usually painless but can cause temporary side effects such as skin problems, diarrhoea, fatigue and stomach problems.
- **Targeted drug therapy**—Traditional chemotherapy (drugs that slow tumour cell growth or destroy it) usually is does not work well for alveolar soft-part sarcoma. In addition, the effects of chemo are severe and affect many parts of the body, making it a poor treatment choice for this cancer. Researchers have turned their focus to more targeted therapies that destroy the alveolar soft-part sarcoma cells without harming nearby healthy tissues.

Groisberg, R., Roszik, J., Conley, A.P., Lazar, A.J., Portal, D.E., Hong, D.S., Naing, A., Herzog, C.E., Somaiah, N., Zarzour, M.A., Patel, S., Brown, R.E. & Subbiah, V. 2020.

"Overexpression of transcription factor 3 in alveolar soft part sarcoma(ASPS) results in upregulation of cell proliferation pathways. No standard treatment algorithm exists for ASPS; multikinase inhibitors[tyrosine kinase inhibitor (TKI)] and immune checkpoint inhibitors (ICI) have shown clinical benefit. To date, no studies have reported on management strategies or sequencing of therapy. We evaluated ASPS treatment patterns and responses in an experimental therapeutics clinic. Genomic and morphoproteomic analysis was performed to further elucidate novel targets. We retrospectively reviewed patients with ASPS treated on clinical trials. Demographic and clinical next-generation sequencing (NGS) profiles were collected. AACR GENIE database was queried to further evaluate aberrations in ASPS. Morphoproteomic analysis was carried out to better define the biology of ASPS with integration of genomic and proteomic findings. Eleven patients with ASPS were identified; 7 received NGS testing and mutations in CDKN2A (*n* = 1) and hepatocyte growth factor (*n* = 1) were present. Ten patients were treated with TKIs with stable disease as best response and 4 patients with ICI (three partial responses). Within GENIE, 20 patients were identified harboring 3 called pathogenic mutations. Tumor mutation burden was low in all samples. Morphoproteomic analysis confirmed the expression of phosphorylated c-Met. In addition, fatty acid synthase and phosphorylated-STAT3 were detected in tumor cell cytoplasm and nuclei. Patients with ASPS have a quiescent genome and derive clinical benefit from VEGF-targeting TKIs. Morphoproteomic analysis has provided both additional correlative pathways and angiogenic mechanisms that are targetable for patients with ASPS. Our study suggests that sequential therapy with TKIs and immune checkpoint inhibitors is a reasonable management strategy."

Liu, J., Fan, Z., Li, S., Gao, T., Xue, R., Bai, C., Zhang, L., Tan, Z. & Fang, Z. 2020.

Background: Alveolar soft part sarcoma (ASPS) is a translocation-associated soft-tissue tumor resistant to conventional cytotoxic agents. This report aims to compare the efficacy of anlotinib versus pazopanib as targeted monotherapy in metastatic ASPS and to determine the impact of drug dosage reduction on disease control.

Methods: Sixteen and 31 patients with metastatic ASPS were respectively treated with anlotinib and pazopanib monotherapy at a single institution. Objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) were retrieved and compared between both therapeutic arms. Adverse events (AEs) within each group were recorded. Kaplan-Meier survivorship curves computed the impact of drug dosage reduction on PFS.

Results: The anlotinib group showed an ORR of 31.2%, compared to 35.5% in the pazopanib arm (P=0.772). Median PFS was 23.6 months [95% confidence interval (CI), 16.2-31.0 months] in patients treated with

anlotinib, but dropped to 13.7 months (95% CI, 10.8-16.7 months) in those managed with pazopanib (P=0.023). One (6.3%) patient on anlotinib and 11 (35.5%) on pazopanib developed AEs requiring drug dosage reduction (P=0.029), which significantly reduced patients' PFS in the latter setting (10.5 *vs*. 15.8 months, P=0.012). In patients without dosage reduction, anlotinib showed a bordering advantage than pazopanib on median PFS (24.5 *vs*. 15.8 months, P=0.112).
Conclusions: Compared to pazopanib, anlotinib yielded longer PFS and lower incidence of AEs in ASPS patients. Drug dosage reduction was more frequently encountered with the former agent and affected the disease control.

Brahmi, M., Vanacker, H. & Dufresne, A. 2020.
Purpose of review: Alveolar soft part sarcoma (ASPS) represent 0.5% of sarcomas, defining a rarest among rare malignancies. It affects young adults, displaying slow-growing mass of the thigh, head and neck, and trunk. Although quite indolent, a majority of cases displays an advanced disease with lung bone or central nervous system metastasis. Complete surgery is the cornerstone of localized ASPS, and advanced diseases poorly respond to chemotherapy. Here discuss recent progress in molecular characterization of ASPS and future prospects of therapeutic approaches.
Recent findings: ASPS is characterized by a specific oncogenic translocation ASPSCR1-TFE3 that induce hepatocyte growth factor receptor (MET) overexpression, angiogenesis, and immunosuppression in the tumor microenvironment. These specific biological features have encouraged the successful exploration of MET inhibitors, antiangiogenic drugs, and immunotherapy. We reviewed the main tracks of ASPS biology and recent insights from targeted therapies is ASPS mainly driven tyrosine kinase inhibitors (especially antiangiogenics), immune-checkpoint inhibitors, and their combinations.
Summary: Overall, antiangiogenics and anti Programmed cell death 1/Programmed cell death ligand 1 therapies showed a significant activity in ASPS that warrants additional investigation through randomized trials to validate those results and through ancillary biological studies to better understand resistance mechanisms and biomarkers of response.

Cohen, J.W., Widemann, B.C., Derdak, J., Dombi, E., Goodwin, A., Dompierre, J., Onukwubiri, U., Steinberg, S.M., O'Sullivan Coyne, G., Kummar, S., Chen, A.P. & Glod, J. 2019.
BACKGROUND: Alveolar soft-part sarcoma (ASPS), a rare vascular sarcoma with a clinically indolent course, frequently presents with metastases. Vascular endothelial growth factor (VEGF) is a promising therapeutic target. In a phase-II trial of the VEGF receptor inhibitor cediranib for adults with ASPS, the partial response (PR) rate (response evaluation criteria in solid tumors [RECIST] v1.0) was 35% (15/43; 95% confidence interval: 21-51%). We evaluated cediranib in the pediatric population.
PROCEDURE: Patients <16 years old with metastatic, unresectable ASPS received cediranib at the pediatric maximum tolerated dose of 12 mg/m^2 (≈70% of the fixed adult phase-II dose orally daily). Tumor response was assessed every two cycles (RECIST v1.0). A Simon two-stage optimal design (target response rate 35%, rule out 5%) was used.
RESULTS: Seven patients (four females), with a median age of 13 years, (range 9-15), were enrolled on stage 1. The most frequent grade 2 or 3 adverse events were neutropenia, diarrhea, hypertension, fatigue, and proteinuria. The best response was stable disease (SD) (median cycle number = 34). Three patients were removed from the study treatment for disease progression (cycles 4, 5, and 36). Five of seven patients had SD for ≥14 months. Two patients with SD remain on study (34-57+ cycles).
CONCLUSIONS: Cediranib did not reach the target response rate in this small pediatric cohort, in contrast to the adult 35% PR rate. The pediatric dosing was 30% lower compared to the adult dosing, which may have contributed to response differences. Prolonged SD was observed in five patients, but given the indolent nature of ASPS, SD cannot be clearly attributed to cediranib. Cediranib has an acceptable safety profile.

Judson, I., Morden, J.P., Kilburn, L., Leahy, M., Benson, C., Bhadri, V., Campbell-Hewson, Q., Cubedo, R., Dangoor, A., Fox, L., Hennig, I., Jarman, K., Joubert, W., Kernaghan, S., López Pousa, A., McNeil, C., Seddon, B., Snowdon, C., Tattersall, M., Toms, C., Martinez Trufero, J. & Bliss, J.M. 2019.

BACKGROUND: Alveolar soft-part sarcoma (ASPS) is a rare soft-tissue sarcoma that is unresponsive to chemotherapy. Cediranib, a tyrosine-kinase inhibitor, has shown substantial activity in ASPS in non-randomised studies. The Cediranib in Alveolar Soft Part Sarcoma (CASPS) study was designed to discriminate the effect of cediranib from the intrinsically indolent nature of ASPS.

METHODS: In this double-blind, placebo-controlled, randomised, phase 2 trial, we recruited participants from 12 hospitals in the UK (n=7), Spain (n=3), and Australia (n=2). Patients were eligible if they were aged 16 years or older; metastatic ASPS that had progressed in the previous 6 months; had an ECOG performance status of 0-1; life expectancy of more than 12 weeks; and adequate bone marrow, hepatic, and renal function. Participants had to have no anti-cancer treatment within 4 weeks before trial entry, with exception of palliative radiotherapy. Participants were randomly assigned (2:1), with allocation by use of computer-generated random permuted blocks of six, to either cediranib (30 mg orally, once daily) or matching placebo tablets for 24 weeks. Treatment was supplied in number-coded bottles, masking participants and clinicians to assignment. Participants were unblinded at week 24 or sooner if they had progression defined by Response Evaluation Criteria in Solid Tumors (version 1.1); those on placebo crossed over to cediranib and all participants continued on treatment until progression or death. The primary endpoint was percentage change in sum of target marker lesion diameters between baseline and week 24 or progression if sooner, assessed in the evaluable population (all randomly assigned participants who had a scan at week 24 [or sooner if they progressed] with target marker lesions measured). Safety was assessed in all participants who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01337401; the European Clinical Trials database, number EudraCT2010-021163-33; and the ISRCTN registry, number ISRCTN63733470 recruitment is complete and follow-up is ongoing.

FINDINGS: Between July 15, 2011, and July 29, 2016, of 48 participants recruited, all were randomly assigned to cediranib (n=32) or placebo (n=16). 23 (48%) were female and the median age was 31 years (IQR 27-45). Median follow-up was 34·3 months (IQR 23·7-55·6) at the time of data cutoff for these analyses (April 11, 2018). Four participants in the cediranib group were not evaluable for the primary endpoint (one did not start treatment, and three did not have their scan at 24 weeks). Median percentage change in sum of target marker lesion diameters for the evaluable population was -8·3% (IQR -26·5 to 5·9) with cediranib versus 13·4% (IQR 1·1 to 21·3) with placebo (one-sided p=0·0010). The most common grade 3 adverse events on (blinded) cediranib were hypertension (six [19%] of 31) and diarrhoea (two [6%]). 15 serious adverse reactions in 12 patients were reported; 12 of these reactions occurred on open-label cediranib, and the most common symptoms were dehydration (n=2), vomiting (n=2), and proteinuria (n=2). One probable treatment-related death (intracranial haemorrhage) occurred 41 days after starting open-label cediranib in a patient who was assigned to placebo in the masked phase.

INTERPRETATION: Given the high incidence of metastatic disease and poor long-term prognosis of ASPS, together with the lack of efficacy of conventional chemotherapy, our finding of significant clinical activity with cediranib in this disease is an important step towards the goal of long-term disease control for these young patients. Future clinical trials in ASPS are also likely to involve immune checkpoint inhibitors.

FUNDING: Cancer Research UK and AstraZeneca.

Malouf, G.G., Beinse, G., Adam, J., Mir, O., Chamseddine, A.N., Terrier, P., Honore, C., Spano, J.P., Italiano, A., Kurtz, J.E., Coindre, J.M., Blay, J.Y. & Le Cesne, A. 2019.

BACKGROUND: Alveolar soft part sarcoma (ASPS) is a rare sarcoma characterized by a slow evolution, brain metastasis (BM), and resistance to doxorubicin. Antiangiogenic therapies (AAT) have shown clinical activity, but little is known about the optimal therapeutic strategy, specifically considering BM.

SUBJECTS, MATERIALS, AND METHODS: We performed a retrospective analysis of all patients with ASPS treated in three referral centers of the French Sarcoma Group. We aimed to describe factors associated with overall survival (OS) and the impact of BM on outcome of patients treated by AAT.
RESULTS: We identified 75 patients between 1971 and 2012 (median age = 23, range: 5-96 years). Median follow-up was 74 months. Patients with localized (*n* = 44, 59%) and metastatic (*n* = 31, 41%) diseases had a 10-year OS of 69% and 25%, respectively. Only surgical incomplete resection was associated with shorter OS in localized disease (hazard ratio [HR] = 5.2, 95% confidence interval [CI] 1.2-22.4, *p* = .02). Fifty-two (69%) patients developed lung metastasis (LM; baseline: *n* = 31, [41%]; de novo: *n* = 21, [28%]). Thirteen patients developed BM, all occurring after LM. Tumor size ≥5 cm was associated with poorer BM-free survival (HR = 8.4, 95% CI 2.1-33.9, *p* = .002). Median OS post-BM was 17 months (95% CI 15 to not assessable). Overall, 12 patients were treated with AAT (sunitinib *n* = 10): 5 patients had BM and achieved poor outcomes compared with patients without, with median progression-free-survivals of 2 versus 11 months, respectively.
CONCLUSION: Baseline larger tumors were associated with increased risk of brain metastasis in patients with ASPS. Patients with BM seem to have little benefit from AAT, suggesting the need to develop antineoplastic agents with high central nervous system penetrance in this setting.
IMPLICATIONS FOR PRACTICE: Alveolar soft part sarcoma (ASPS) is an extremely rare subtype of sarcoma that is particularly resistant to conventional therapies. Antiangiogenic therapies (AAT) have shown promising results. However, patients with ASPS still die of tumor evolution. This study highlights the prognostic shift induced by brain metastasis (BM), identifying this event as a major contributor to the death of patients with ASPS, and observes a striking lack of effectiveness of AAT in patients who had previously developed BM. This observation is of interest for the therapeutic development in ASPS, highlighting the need to develop strategies dedicated to BM, such as radiosurgery or high-central nervous system penetrance tyrosine kinase inhibitors.

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.
Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The **South African National Clinical Trials Register** provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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Sources and References Consulted and/or Utilised

Alveolar Soft-Part Sarcoma
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