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Advances in the management of alveolar soft part sarcoma

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ABSTRACT

Alveolar Soft Part Sarcoma is one of the less commonly diagnosed soft tissue sarcoma subtypes, an infrequent subtype within the already rare category of human malignancy of sarcoma. In this article we will summarize the histopathological features, natural history and distinct molecular and biological features that have become increasingly appreciated with newer technologies and precision oncology. We will discuss the contemporary management of this disease as well as emerging treatment options.

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Background

Alveolar Soft Part Sarcoma (ASPS) is an uncommon subtype of soft tissue sarcoma. Sarcomas are rare cancers, accounting for less than 1% of new adult malignancies; and the ASPS subtype is estimated to represent <1% of all soft tissue sarcoma (STS) diagnoses.

The first published description of ASPS was in 1952 as "malignant myoblastoma" or "granular cell myoblastoma."[1] The cell of origin of ASPS remains to be identified and has been a contentious topic: both a myogenic origin and a neural line of differentiation have been postulated.[2] More recently, transcriptomic data has suggested an undifferentiated mesenchymal stromal cell (MSC) phenotype,[3] a finding that offers a plausible explanation regarding the difficulty in pinpointing the origin of ASPS given that the MSC retains an undifferentiated state capable of adipogenic, chondrogenic, or osteogenic differentiation.

Clinical presentation and diagnosis

ASPS was defined histologically in the 1950s as consisting of cell "nests" loosely arranged along connective tissue containing sinusoidal vascular channels lined by flattened endothelium with characteristic intracytoplasmic rod-shaped crystals. These back-to-back "nests," separated by capillaries, classically appeared to resemble lung alveoli, hence the naming of the disease.[4] However, within the histologic classification of STS, ASPS is considered a sarcoma of uncertain differentiation (World Health Organization Classification for Sarcomas, 2013). ASPS also has been characterized by an unbalanced translocation that results from a gene fusion of the Transcription Factor 3 (*TFE3*) gene at Xp11 to the *ASPSCR1* gene at 17q25, creating an ASPL–TFE3 chimeric fusion protein[5]. Two variants of the *ASPSCR1-TFE3* fusion have been best described to date,[6] and through other non-canonical fusions have been more recently reported,[7] the clinical and prognostic implications of these fusion variants are yet to be determined.

ASPS most commonly occurs in the adolescent and young adult (AYA) age range (15-39 years), with the median age of presentation around 25 years of age, and affects females more than males.[8] ASPS often presents asymptomatically as a slow-growing tumor in the extremities, although it can arise from other sites, including the lungs, bone, female reproductive tract, and head and neck. Children have unique sites of involvement, including the tongue and the orbit, which are often hypervascular masses that are pulsatile[9] and often confused with vascular malformations.[10] As there is no associated functional impairment or other symptoms, ASPS patients tend to present with metastatic disease, with common sites including the lungs, bone, and brain. Although data are limited, brain metastases have been consistently associated with other sites of metastasis.[11]

Prognostic factors related to outcome

Metastatic disease at presentation is the most significant factor for overall survival (OS) in ASPS, with 5-year overall survival estimates compared to localized disease ranging from 20% to 46% vs 60% to 100%, respectively.[11-14] Stratification of ASPS by localized and metastatic disease to identify other prognostic factors has yielded clinically useful prognostic factors. For both localized and metastatic disease at diagnosis, complete surgical resection, if feasible, has been associated with higher overall survival and is considered the standard of care in localized disease.[8, 15] Younger age at diagnosis is associated with favorable outcomes, which can be partially attributed to children presenting with the more localized disease than adults.[16] Other risk factors that have been reported include sex (prognosis for males is worse than for females), tumor size in both localized (x>5 cm) and metastatic disease (x>10 cm), location (non-extremity worse than extremity), and incomplete surgical margins.[16]

Clinical Course

The natural history of ASPS has been well described, with a typically indolent course—even in the setting of metastatic disease—and marked by prolonged periods of disease stabilization.[11, 17] In contrast, ASPS is also characterized by a high likelihood of metastatic spread and late metastases.[17, 18] Although it is one of the rare solid tumor malignancies that is anecdotally associated with spontaneous regression (defined as partial or complete disappearance of a malignant tumor in the absence of treatment or in the presence of therapy considered inadequate to affect malignant disease behavior[19, 20]), data for this phenomena in ASPS come from a small number of published case reports that may not always meet the definition of regression.[21] However, prolonged progression-free intervals and spontaneous disease stabilization have been described for this disease, though the incidence and duration of these events are not well determined and are ascribed to the biology of the malignancy.

Contemporary management of ASPS

The mainstay of therapy for localized disease is surgical resection given the slow-growing nature of ASPS and retrospective data suggesting an improvement in overall survival for patients with a resected primary tumors who subsequently developed metastatic disease.[8] Expert recommendations suggest consideration of adjuvant radiation therapy in the setting of positive margins to reduce the risk of local recurrence, but adjuvant chemotherapy is not currently recommended Indeed, there is an increasing body of literature highlighting the poor response of ASPS tumors to conventional chemotherapy agents in the metastatic setting,[11, 15, 22] including newer agents approved for use in STS.[23] Although there are no FDA-approved drugs specifically for ASPS in the metastatic setting, anti-angiogenic multi-targeted tyrosine kinase inhibitors (TKIs) like pazopanib have demonstrated efficacy, with a median progression-free survival (PFS) of 13.6 months[23]. Other TKIs like sunitinib have also shown a similar median PFS of 17 months, with mostly grade 1-2 side effects[17]; both of these agents are recommended as therapeutic options for patients with ASPS. Recently, the use of single-agent pembrolizumab, a programmed cell death 1 (PD-1) inhibitor, has been recommended based on a retrospective analysis of a small number of patients with a high number of objective responses in an early clinical trial.[24]

Molecular characterization of ASPS

Angiogenesis modulation

ASPS is a highly vascular tumor for which pathological angiogenesis is believed to play an important role in promoting metastasis, and several groups have attempted to define the underlying molecular determinants driving this unique vascular biology associated with the malignant potential of ASPS. One study of three frozen tumor samples subjected to a focused angiogenesis cDNA array identified a unique panel of 18 angiogenesis-promoting genes that were upregulated compared to the normal tissue. In general, these angiogenesis-promoting genes were categorized into five groups: encoding growth factors and receptors (TGF-α, TGF-β), cytokines and/or chemokines, and adhesion molecules proteases, and transcription factors such as HIF-1α.[25] This angiogenesis profile based on the expression pattern of certain gene signatures was unique to ASPS and did not necessarily overlap with that of other STS. Similarly, others have reported prevalent upregulation of genes encoding angiogenesis-associated proteins, including HIF-1α and angiopoietin-like protein 2, in ASPS.[26, 27] Other angiogenesis-related molecules that have shown robust expression in this STS subtype include vascular endothelial growth factor receptor (VEGFR)1, VEGFR2, VEGFR3, epidermal growth factor (EGF), RET, platelet-derived growth factor (PDGF)B, PDGFRβ, and innate immunity-related receptors such as toll-like receptors (TLR)2 and

TLR9.[28] In ASPS tumors, the ASPL-TFE3 fusion protein is postulated to underlie the expression of some angiogenic factors. Limited data have shown certain angiogenic factors, such as angiogenin, JAG-1, and midkine, to have putative TFE3 binding sites in their promoter regions.[25]

Similarly, high expression of glycoprotein nmb (GPNMB), a downstream transcriptional target of the ASPL-TFE3 protein, has been measured at tumor intravasation sites. GPNMB overexpression is believed to be another key factor that is regulated by the fusion protein, and it induces properties of tumor invasiveness via transendothelial migration—a property that was lost with siRNA-mediated gene silencing.[29] GPNMB is crucial for the interaction between the tumor cells and endothelial cells to generate the metastatic intravascular potential commonly observed in ASPS.

Anti-angiogenic TKIs have been one of the more active treatment drug classes for ASPS, contrasting with the lack of activity of TKIs that do not target this pathway, such as dasatinib.[30] Better identification of the molecular determinants that represent mediators of angiogenesis and invasion in ASPS could offer opportunities to better understand and target the vascular histology in ASPS tumors.

MET/HGF pathway modulation

MET is one of the well-characterized genes known to be upregulated in ASPS. *MET* is a downstream target of TFE-3, which binds to the *MET* promoter[31]; given its role in cell survival and metastasis, MET has been postulated to forge a direct link between the ASPS-TFE3 fusion and disease pathogenesis of ASPS. Recently, a phosphoproteomic analysis of ASPS demonstrated expression of phosphorylated MET, a finding that indicates MET activation by its ligand, hepatocyte growth factor (HGF).[24] The same analysis revealed the expression of phosphorylated STAT3, which is thought to regulate HGF transcriptionally. These observations suggest the possibility of targeting these additional pathways to indirectly influence MET expression in ASPS by employing strategies that go beyond simple VEGF inhibition. In addition to *MET, CYP17A1,* and *UPP1* are some of the other genes that have been identified by integrated genomic approaches to be directly upregulated by the ASPL-TFE3 oncoprotein,[26] though clinical implications of this remain to be determined.

Epigenetic modulation

Hypermethylation-mediated gene silencing can lead to dysregulation of miRNAs, with subsequent influence on post-transcriptional regulation of oncogenes or tumor suppressor genes. Epigenetic evaluation of several STS, including one ASPS patient, using quantitative high-throughput analysis of DNA methylation patterns have been performed.[32] This evaluation demonstrated aberrant methylation of miR-34b/c CpG islands, with hierarchical clustering revealing 2 primary clusters that displayed different methylation patterns for normal tissue vs. STS, as well as variable patterns among the various STS. The ASPS sample, in particular, showed an 8.3% methylation level of miR-34b/c. Although the methylation pattern for ASPS did not overlap significantly with those of other STS, the biological implications of this are unclear due to the small sample size (a single ASPS patient). However, a broader investigation into the epigenetic landscape of ASPS may very well elucidate unique patterns of tumor suppressor transcriptional downregulation facilitated by fusion protein–mediated dysregulation of promoter methylation. Evaluating and understanding these methylation patterns could offer essential insights into the biological processes that drive ASPS.

The ASPL-TFE3 chimeric fusion and ASPS pathogenesis

The ASPL–TFE3 chimeric fusion protein in ASPS is believed to function as an aberrant transcription factor implicated in disease genesis.[5] The *ASPL* gene is joined in-frame upstream of

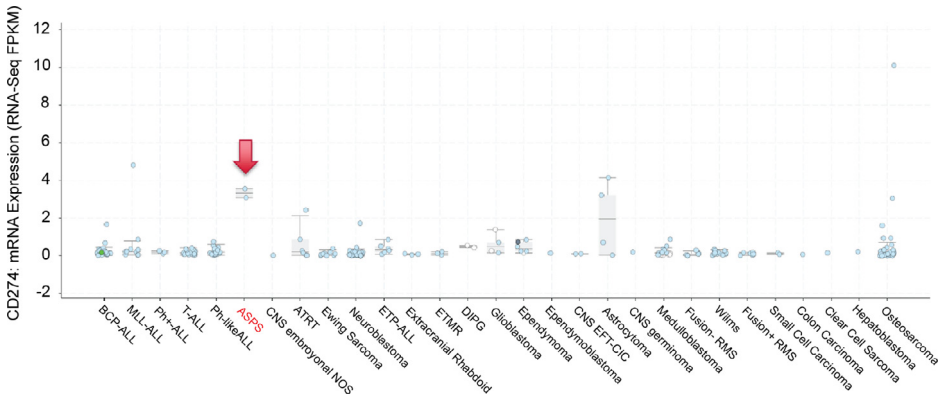

Fig. 1. PD-L1 expression in multiple tumor xenograft models. The red arrow indicates the high levels of PD-L1 mRNA expression noted in an ASPS model.

either the fourth or third exon of *TFE3*, resulting in two possible fusion transcripts, type 1 and type 2, respectively; the latter harbors an additional exon encoding the TFE3 activation domain.[26] Due to the rare nature of this STS, the prevalence of type 1 vs. type 2 fusion is not well established in the literature to date.

Comprehensive ASPS gene expression profiling studies have identified several potential targets of the ASPL-TFE3 fusion protein that are believed to influence angiogenesis, metastasis, and myogenic differentiation.[27] Some of these approaches have identified >100 genes that are likely dysregulated in the presence of the ASPL-TFE3 fusion protein, supporting its gain-of-function role.[26] Using pooled microarray readouts from immortalized ASPS cell lines harboring the ASPS type 1 fusion and individual patient tumor data, early studies identified aberrantly upregulated genes involved in cell cycle and tissue stroma-related cell adhesion control in response to the t(X;17)(p11;q25) translocation.[33] Notably, *CHEK1*, which encodes a kinase required for DNA damage checkpoint regulation, was overexpressed in ASPS—particularly in the ASPS cell line harboring the type 1 fusion. This can potentially explain the upregulation of cell cycle genes observed in ASPS tumor cells and raises the possibility of using agents targeting the DNA damage response, such as WEE1 and CHEK1 inhibitors, especially in patients harboring the type-1 fusion.

Immune modulation

An emerging body of literature has reported various observations that suggest ASPS presents targets susceptible to therapeutic immune modulation. TFE3, one of the fusion partners in ASPS, has a role in CD-40 ligand expression in activated CD4+ T-cells. TFE3 is also implicated in TGF-β signaling by synergizing with SMAD3/4, resulting in downstream activation of target genes.[34, 35] Furthermore, expression of class I HLA has been noted in ASPS, which is important in the context of immunogenic epitope recognition.[36] Moreover, the presence of PD-1–positive CD8+ T-cells juxtaposed to sarcoma cells expressing PD-L1 has been observed in some ASPS samples, further suggesting an immunosuppressive tumor immune microenvironment in ASPS.[37] Similarly, data from the Pediatric Preclinical Testing Consortium (PPTC) show that patient-derived xenograft models of ASPS express significantly higher PD-L1 compared to models of other high-risk childhood cancers (Fig 1). These findings strongly suggest that the PD-1/PD-L1 axis could affect anti-tumor immunity in these patients and support the use of anti-PD-L1 antibodies or other immunomodulatory agents to enhance anti-tumor immunity in ASPS.

Next-generation sequencing analysis in ASPS

The American Association for Cancer Research (AACR) developed Project GENIE (Genomics Evidence Neoplasia Information Exchange), an international, publicly accessible cancer registry to linking clinical-grade next-generation cancer genomic sequencing data to patient outcomes (AACR.org/Genie). Mutations in 40 unique ASPS-associated genes from 26 patients are shown in Figure 2. The majority of patients had a single mutation; 16 are potentially actionable; however, most are classified as non-pathogenic, variants of unknown significance. KMT2D, ERCC5, and PIK3CA, representing pathways of histone modification, DNA repair, and PI3KPI3K-Akt pathway, respectively, were amongst the three commonly mutated genes (Fig 2). Additionally, a higher number of mutations were seen with increasing age at diagnosis, suggesting that that most of these mutations are accumulated over time and may not be representative oncogenic drivers.[24]

Emerging treatment options

The growing understanding of the molecular and biological pathways in this disease is reflected in the focus of currently ongoing trials compiled from ClinicalTrials.gov, listed in Table 1. Search terms utilized were "alveolar soft part sarcoma" without additional restrictions and filtered by "active" and "recruiting." The identified elevated expression of angiogenesis target transcripts from array analysis, including VEGF targets, downstream MET signaling, as well as possible upregulation of immune modulation markers are represented in these studies.

Targeted therapies

Over the last couple of years, multiple TKI-targeting trials have reported results. Overall, these results have shown modest clinical activity, and have not improved on the efficacy reported for single-agents pazopanib (Votrient, Novartis, Basel, Switzerland)[23, 38] or sunitinib (Sutent, Pfizer, NY) in ASPS.[17, 39, 40] These agents remain the recommended standard-of-care as they are commercially available and are FDA-approved for the treatment of patients with STS in the second-line treatment setting. Cediranib, a targeted anti-VEGF and KIT inhibitor, has shown activity in both pediatric[41] and adult[18, 42] patients with ASPS, but this agent remains investigational only. A further randomized study of cediranib or sunitinib in patients with ASPS (NCT01391962) led by our team (Developmental Therapeutics Clinic at the National Cancer Institute [NCI], Bethesda, USA) has closed, and results are awaited.

Crizotinib

Targeting *MET* using investigational agents such as crizotinib (Xalkori, Pfizer, NY) has been explored due to its upregulation under the direct transcriptional activation by TFE3. The biomarker-enriched CREATE trial enrolled patients with advanced ASPS and MET positive or negative disease as determined by the presence of a detectable TFE3 rearrangement.[43] The primary endpoint of this study was not achieved (objective response in *MET-positive* ASPS patients in the first 12 enrolled patients) but patients with *MET-positive* tumors demonstrated a disease control rate of 90%. Adverse events (any grade) were reported in more than 50% of patients, and 20% of patients required at least one dose reduction. Given one of the objective responses was noted in a *MET-negative* patient, additional correlative studies may help predict how TFE3 rearrangements activate *MET*.

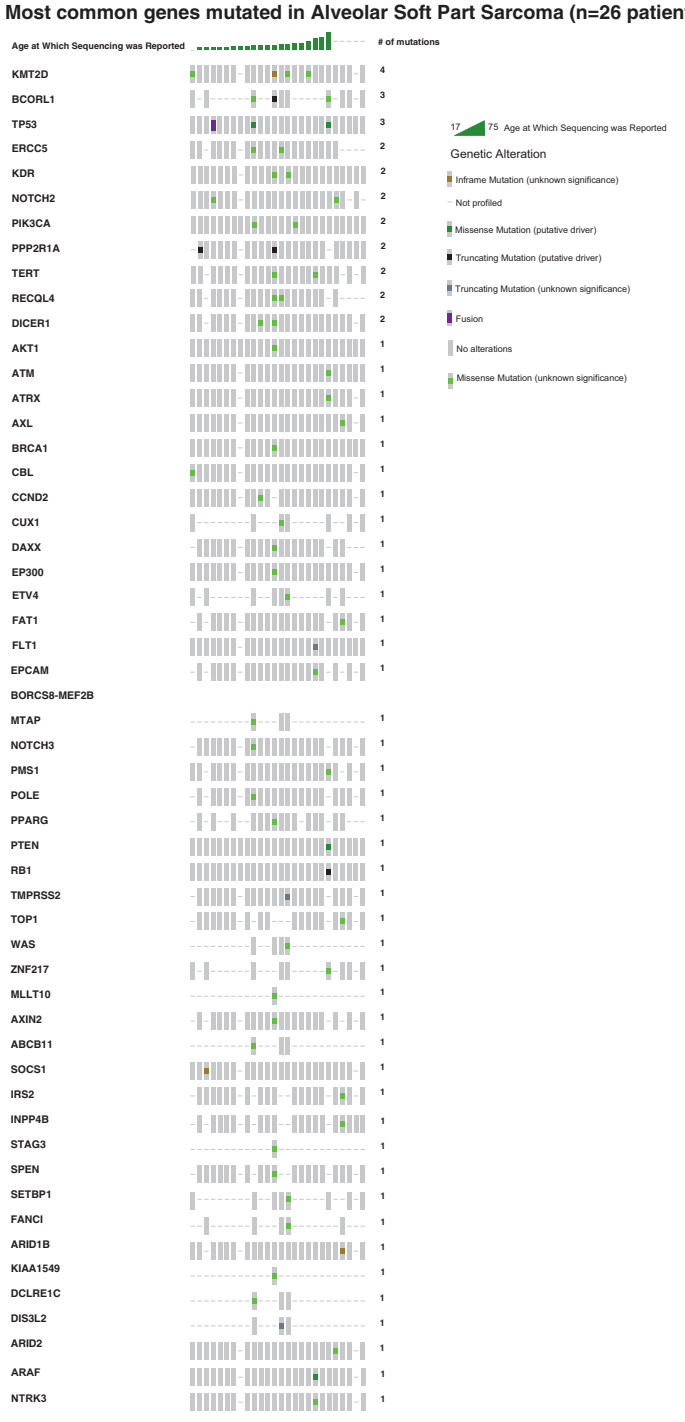

Fig. 2. Oncoplot in ASPS. Genomic data was downloaded from https://genie.cbioportal.org/ using GENIE Cohort v9.0-public. Patient level (n = 26) data of ASPS patients was visualized using the Oncoprint function in cBioPortal. As there are multiple sequencing assays, results are reported as number (#) of mutations in all patients.

Table 1
Selected ongoing international treatment trials for patients with alveolar soft part sarcoma.

Tumor type/eligibility	Experimental Agent(s)	Randomized	Phase	NCT number
ASPS (only)	atezolizumab atezolizumab+ bevacizumab*	No	Phase II	NCT03141684
STS† (ASPS, LMS, SS)	anlotinib (catequentinib)	Yes† (Not in ASPS)	Phase III	NCT03016819
STS‡ (myxofibrosarcoma, UPS, ASPS	pembrolizumab (melphalan and dactinomycin, ILP)‡	No	Phase II	NCT04332874

* Upon progression, patients will be able to enroll on the combination arm of the study (addition of bevacizumab). Targeted to open March 2021.

† Separate cohorts for ASS, LMS and SS. No randomization for ASPS patients, assigned to open label anlotinib. Comparator for randomized cohorts is dacarbazine.

‡ The study drug, pembrolizumab, is being evaluated in combination with melphalan and dactinomycin, delivered directly to the affected extremity using isolated limb infusion (ILI).

Anlotinib

Anlotinib (Catequentinib, Focus V, Chia-Tai Tianqing Pharmaceutical, China) is a novel TKI that inhibits VEGF/VEGFR signaling by inhibiting VEGFR-2,-3 and FGFR-1,-2,-3,-4 and also by selectively inhibiting the activity of PDGFRα/β, c-Kit, Ret, Aurora-B, c-FMS, and discoidin domain receptor 1 (DDR1).[44] Evaluation of the efficacy of this agent in ASPS has been carried mostly in China, where the agent is commercially available. More recently, a retrospective study of 22 patients with ASPS who received either anlotinib or sunitinib suggested an objective response rate (ORR) of 31.2% for the patient group treated with anlotinib (5 patients with a confirmed partial response (PR), compared to 35.5% in the pazopanib arm ($P = 0.772$).[45] Patients had not received prior antiangiogenic therapy, although 48.6% of the patients had received prior anthracycline-based chemotherapy. The anlotinib arm also had a reduced incidence of adverse events requiring dose reduction, which the authors theorized could explain the longer PFS on this arm: median PFS was 23.6 months [95% confidence interval (CI), 16.2-31.0 months] in patients treated with anlotinib, and 13.7 months (95% CI, 10.8–16.7 months) in those managed with pazopanib ($P = 0.023$). An earlier, prospective, Simon-2 stage phase II study of anlotinib in 4 separate STS subtypes that included an ASPS patient cohort evaluated a 12-week progression-free survival (PFS)-based assessment (specifically, 'three patients without disease progression at 12 weeks in the first 13 patients') as a primary endpoint. Patients in this study also could not have received prior antiangiogenic therapy. Twelve-week PFS for the ASPS cohort was reported as 77% with a median PFS of 21 months; OS was not reported due to insufficient events. No complete responses were reported in this study, but six patients with ASPS were reported to have a PR. Grade 3 and 4 toxicity events occurred in less than 5% of the study population. On the basis of this study, a double-blind placebo-controlled phase III trial in ASPS (as well as other STS subtypes) is ongoing (Table 1).

Cabozantinib

Cabozantinib (Cabometyx and Cometriq, Exilixis Inc., Alameda) inhibits multiple RTKs implicated in tumor growth, metastasis, and angiogenesis with MET and VEGFR2 being the primary targets. Our group has completed accrual of phase II trial of single-agent cabozantinib (60mg daily) in STS (https://www.ctos.org/Portals/0/PDF/2017%20CTOS%20Final%20Program.pdf,

CTOS 2017, no abstract available). Preliminary results have shown clinical activity in two of a total of six patients with ASPS, both of whom had progressed on prior anti-VEGF therapy. Additional data will be forthcoming from this study.

Selinexor

Selinexor (Xpovio®, Karyopharm Therapeutics, Massachusetts, USA) is a selective, orally available inhibitor of the nuclear export protein XPO1, which is responsible for the nuclear export of tumor suppressor transcription factor proteins and is associated with poor prognosis and chemotherapy resistance in several cancer types.[46-50] The phase Ib clinical trial of selinexor in advanced refractory bone or soft tissue sarcomas determined the treatment schedule and established modest preliminary anti-tumor activity (no objective responses but durable, stable disease; of note, only 1 patient with ASPS was enrolled in this study).[51] The most common $\geq$ grade 3 toxicities associated with selinexor in this study were lymphopenia, leukopenia, anemia, thrombocytopenia, and fatigue. Immunohistochemical analyses of tumor biopsies demonstrated selinexor-induced nuclear accumulation of the XPO-cargo tumor suppressor proteins p21, p53, and FOXO1, as well as increased tumor cell apoptosis following selinexor treatment. Selinexor has been shown to have activity as a single agent in various STS subtypes, including ASPS, both in cell lines and xenograft models.[52] Data describing the effects of selinexor on immune homeostasis are limited; however, *in vivo* data from Tyler et al. suggesting that treatment with selinexor can transiently modify circulating peripheral immune populations as well as enhance PD-L1 expression in several tumor cell lines, including ASPS has informed the rationale for the combination of selinexor with checkpoint inhibitors.[53] Several tumor models treated with combination therapy have suggested superior anti-tumor activity for this combination relative to either agent alone,[54, 55] and it is expected to enter clinical trials for ASPS patients (personal communication).

Immune checkpoint inhibitor therapies

A number of ASPS-specific immunotherapy trials have recently been designed due to reports of clinical activity with several single agent or combination checkpoint inhibitor trials in an unselected STS patient population with small or single-patient ASPS cohorts.

Single-agent therapies

Geptanolimab. This agent a fully humanized recombinant PD-1 antibody (GB226, Genor Biopharma), evaluated in patients with unresectable, recurrent, or advanced ASPS through a multicenter single-arm phase II study in China[56] (Table 1). Thirty-seven patients received intravenous (IV) geptanolimab (3 mg/kg) administered every 2 weeks for a maximum treatment duration of 1 year or disease progression. Published results indicate a 37.5% ORR[95% confidence interval (CI), 22.5-55.2] meeting the primary objective of the study; overall survival data were not published. Treatment was well tolerated, with no grade 4 or 5 events reported, though two patients discontinued therapy due to treatment-related side effects (hypophysitis and Mobitz type 1 atrioventricular block). Archival tumor tissue at baseline was evaluated for PD-L1 expression by combined positive score (CPS) $\geq$1, microsatellite instability (MSI), and tumor mutational burden (TMB); there were no differences in response between patients with CPS $\geq$1 (33.3%; 95% CI, 9.9-65.1) and CPS$<$1 (40.0%; 95% CI, 21.1-61.3), and all samples were MSS and TMB $<$1 mutation/Mb. The overall percentage of CD4+ T cells was significantly higher in nonresponders compared with responders based on flow cytometric analysis of peripheral blood T-cell subsets at baseline and on-study, with geptanolimab therapy reported causing a statistically significant decrease in peripheral CD4+ T-cell counts after 6 weeks.

Post hoc analysis confirmed responses were seen in this study in patients who had received prior VEGF therapy (36.8%; 95% CI, 16.3-61.6). However, the evaluated biomarker correlatives

were negative in this study, making it difficult to infer the mechanism of response in patients conclusively. To our knowledge, no approval has been requested for this agent either in the United States or China.

Atezolizumab. This anti-PD-L1 agent is currently being evaluated in a multicenter, open-label, Simon 2-stage phase II study as a single-agent through the Experimental Clinical Trials Network (ETCTN), led by our team (Table 1). In a pilot collaboration with the Clinical Center Pediatric Oncology Branch, co-localized at the at NCI, this trial permits enrollment of children from the age of 2 onwards at our site; there is no restriction on prior lines of treatment, including patients with asymptomatic, untreated metastases are eligible and HIV-positive patients. Atezolizumab (Tecentriqu, Genentech Inc., San Francisco) is administered IV every 3 weeks, utilizing a flat dose of 1200 mg in adults or 15 mg/kg (1200 mg max) in pediatric patients age ≥2, until progression or unacceptable toxicity. The primary objective of this study is the ORR. Correlative biomarker analysis from both blood and tumor specimens is also included.

Data for this trial were initially presented at the Annual Meeting of the Connective Tissue Oncology Society (CTOS) in 2018[57]and more recently at CTOS in 2019 after enrollment of 32 evaluable patients. Interim results show an estimated ORR of 32%, above the target ORR for this study of 25%, with durable responses measured in at least 50% of patients (duration of response: ≥15 months). No grade 4 or 5 events have been reported on the study, and no patient has discontinued therapy due to treatment. Data from this trial have contributed to the recent Orphan Drug designation for atezolizumab in patients with sarcoma.[58]

Patients who experience disease progression in this study will be considered for participation on a combination-drug arm of the study, which continues atezolizumab without dose or scheduling change together with the anti-VEGF inhibitor bevacizumab (Table 1).

Combination therapies

Despite the activity of single-agent checkpoint inhibitors in ASPS, both our group and other investigators and we have theorized that inhibition of the PD-1/PD-L1 pathway may not be sufficient to overcome an immunologically cold microenvironment. To our knowledge, only two immunotherapy combination trials, both conceptually similar with the use of an immunotherapy backbone together with an anti-angiogenic inhibitor, have reported to date evidence of clinical activity in ASPS cohort of patients.

Sunitinib and Nivolumab

This phase Ib/II trial enrolled previously treated patients with advanced STS; inclusion of ASPS patients was based on the sensitivity of this tumor to anti-VEGF therapy. The study design included a 14-day induction period of single-agent sunitinib (dose level 1= 37.5mg/day orally once daily, or dose level -1= 25mg/orally once daily). After induction, sunitinib was continued daily, and nivolumab was added (240 mg IV every 2 weeks) until disease progression. Dose de-escalation to level -1 was required during phase I due to 3 dose-limiting toxicities (DLTs) in 6 patients. A total of 7 patients with ASPS were enrolled, 3 patients on phase I and 4 patients on phase II, with partial responses reported in 4 patients (57%).[59] The 6-month PFS reported was 48% (95% CI 41%-55%), exceeding the 15% threshold for this primary objective on the study. Following dose reduction, toxicities were overall manageable [most common grade 3 or 4 adverse events reported included transaminitis (17.3%) and neutropenia (11.5%)]. Intriguingly, the authors pointed to earlier data hypothesizing that myelosuppression may be mediated by FLT3 inhibition by sunitinib.[59, 60]

Axitinib and pembrolizumab

Results from an STS trial combining the anti-VEGF agent axitinib and the anti-PD-1 inhibition pembrolizumab have been recently published[61]. This phase II study enrolled 36 patients, with 12 patients (36%) having a diagnosis of ASPS, with an initial run-in cohort receiving 5 mg of axitinib (Inlyta, Pfizer, NY) twice daily together with 200 mg of pembrolizumab (Keytruda, Merck and Co., NJ) once every 3, and subsequent patients receiving escalating doses of axitinib up to10

mg for a total of 2 years of therapy. Outcomes for the ASPS patients showed an ORR of 55%, and a 3-month PFS of 72.7% (95% CI 37.1-90.3). However, these results have come in the setting of overlapping toxicities, including severe autoimmune adverse events (21%). It remains to be determined if this combination shows superior clinical efficacy compared to either single agent alone.

The number of ASPS patients enrolled in these immunotherapy studies is small, likely to be in part due to the rarity of this disease. The enrollment of rare sarcoma subtypes in large heterogeneous STS studies also brings a number of limitations, including small numbers of patients with similar STS subtypes that precludes histology-specific statistical analysis that can overlook clinical efficacy, particularly in the setting of varying degrees of known biological aggressiveness. As highlighted by Martin-Boto et al. in their discussion, the distinct pathogenesis of ASPS can bias the endpoint of the of unselected STS studies that include ASPS patients, as outcomes for non-ASPS patient groups are not as frequent (in the case of objective responses) or durable. However, these outcomes confirm proof-of-therapeutic-concept and the clinical relevance of checkpoint inhibition in new therapeutic directions for this disease, even in the setting of low TMB levels and infiltrating tumor lymphocytes.[62, 63]

Conclusions

The rarity of ASPS and its unique biology and pathogenesis make it challenging to identify practice-changing therapeutic strategies. In recent years, the clinical activity in ASPS with checkpoint inhibitor therapies has been an exciting and therapeutically relevant finding, building on the activity of anti-angiogenic agents in this disease. From an epidemiological perspective, it will take a number of years to truly gauge the impact overall impact of novel molecularly targeted therapies and immune checkpoint inhibition, but we hope that future correlative studies that can evaluate possible predictive signatures will allow for better patient selection and rational drug combinations in this disease.

Author contributions

Geraldine O'Sullivan Coyne: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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