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REVIEW

Molecular Landscape in Alveolar Soft Part Sarcoma: Implications for Molecular Targeted Therapy

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ABSTRACT

Alveolar soft part sarcoma (ASPS) is a highly aggressive rare soft tissue sarcoma (STS) with poor prognosis especially in the metastatic form. ASPS is resistant to standard chemotherapy. Although, early diagnosis and surgical resection of operable tumor could lead to improved patient survival but novel treatment options are needed for advanced (metastatic) ASPS. This malignancy exhibits highly angiogenic behavior which reflects hyper-activation and over expression of angiogenic factors. Understanding the molecular events in this type of sarcoma is important in finding novel molecular based targeted therapies. We aim to review molecular aspects of ASPS growth and treatment.

1. Introduction

ASPS is a malignant and rare tumor that includes about 1% of all STS, and usually occurs in adolescents and young adults [1,2]. ASPS generally arises in skeletal muscles of lower limbs [3]. For the first time, Christopherson and colleagues discovered ASPS and described features of this type of cancer [4]. ASPS is usually painless and an asymptomatic mass [5,6]. ASPS usually affects the head and neck in children [7], but in adults, ASPS is rare in these positions [8] and usually occurs in the lower extremities [9]. ASPS is composed of cells with granular cytoplasm arranged along delicate fibrous septa and has alveolar or organoid pattern [10]. Although histological origin of ASPS is uncertain [11], but skeletal muscle and neural origin have been proposed in different studies [12,13]. There is a nonreciprocal chromosomal translocation der(17)t(X;17)(p11;q25) in the ASPS that results in oncogenic fusion gene, ASPSCR1-TFE3 [14]. In this chromosomal translocation, the transcription factor E3 gene (TFE3) of X chromosome fuses with ASPSCR1 (alveolar soft part sarcoma critical region 1) gene in chromosome 17 and results in aberrant fusion protein. This aberrant protein can be used as diagnostic marker but because of the presence of TFE3 in granular cell tumor, antibody against TEF3 is not specific for ASPS in spite of high sensitivity [15]. Females have more tendencies to ASPS because they have two X chromosomes. So, the translocation rate related to ASPS is more likely in females [16]. Tumor resection is the most effective treatment intervention for operable ASPS and could result in complete remission, but if complete excision of tumor through surgery is not possible, poor prognosis is predictable [17]. Many studies have shown that chemotherapy drugs are not effective in ASPS treatment and response to radiotherapy is controversial [18], but targeted therapy seems to be a good option for ASPS therapy [19]. In the present review, molecular aspects and targeted therapy strategies were investigated and discussed in ASPS.

2. ASPS has metastatic behavior

The number of ASPS recorded articles in PubMed has grown gradually over last 20 years (since 1997 to 2017) (Fig. 1). Unlike most sarcomas, ASPS has high tendency for metastasis [20]. This type of cancer has tendency toward distant metastasis and invasion especially to brain and lungs [21]; However uncommon sites of metastasis such as distal phalanx of hand has been reported [22]. Survival rate of patients with metastatic ASPS is from 3 to 3.3 years and the time interval between metastasis detection and death varies from 10 months to 6.2 years [23]. Some studies have shown that although ASPS growth rate is

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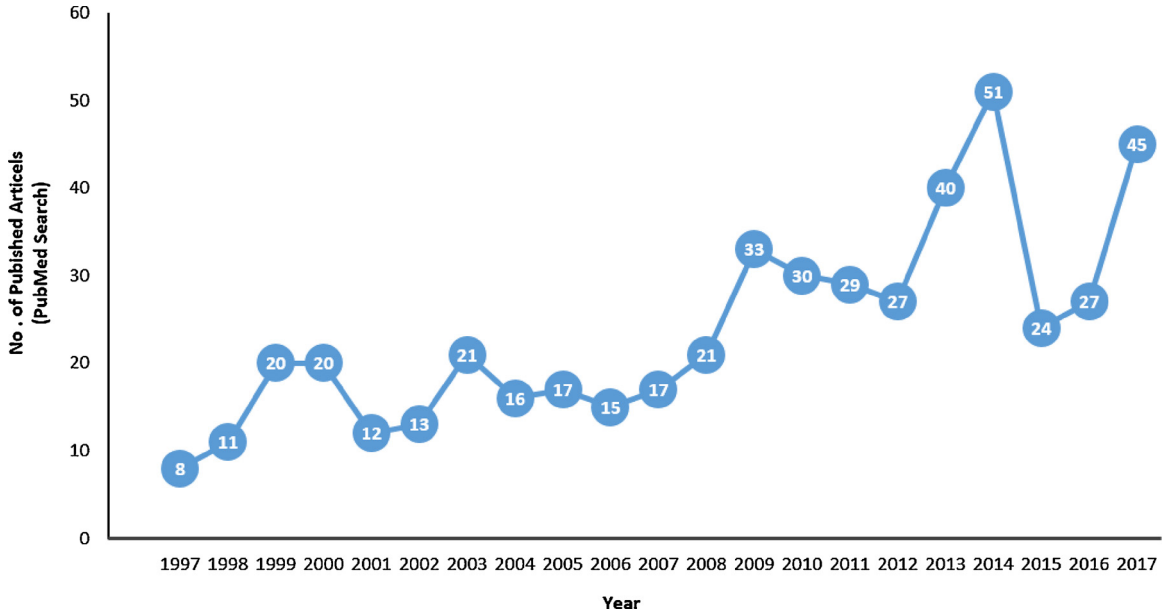

Fig. 1. The number of ASPS related articles in PubMed *published* every *year since 1997.*

slow and asymptomatic, but metastatic rate and vascular invasion are very high [17]. The larger ASPS tumor mass, the more systemic spread [1]. In the other words, there is a significant relationship between tumor size and the probability of metastasis occurrence in ASPS. There is a high occurrence (about 30%) of brain metastasis in ASPS in comparison to other STS [24]. In most patients with advanced stage disease, pulmonary metastases were seen [25]; However lymph node affection in ASPS has not been found routinely [26].

3. Molecular features of ASPS

ASPS belongs to microphthalmia transcription factor (MiT)-associated tumors [27]. The MiT gene family includes (TFE3, *TFEB, TFEC,* and MiTF) which are basic helix-loop-helix leucine zipper transcription factors and are deregulated in different types of cancer such as renal cell carcinoma (RCC), melanoma and ASPS [27,28]. ASPS is characterized by unbalanced non-reciprocal translocation between X and 17 chromosomes, t(X; 17) (p11.2; q25) which leads to ASPSCR1-TFE3 fusion gene [29]. TFE3 is a potent regulator of tumor cell growth and metabolism pathways including (mTORC1, c-Met and HIF1α) [30]. TFE3 promotes cell cycle progression through desensitization inhibitory role of retinoblastoma protein (pRB) [31]. ASPSCR-1 gene is highly expressed in skeletal muscle and heart which physiologically regulates glucose transporter GLUT4 and could increase oncogenic potential and activity of TFE3 as a partner fusion gene in cancer [29,32]. ASPSCR1-TFE3 induces MET expression which leads to MET mediated downstream signaling pathways activation such as PI3K/AKT and MAPK[33] (Fig. 2). Pathological angiogenesis plays important role in tumor progression by facilitating metastasis and providing supply of nutrient and oxygen [34]. ASPS is highly vascular. Different approaches including gene expression profiling, western blotting and immune profiling have revealed robust expression of angiogenic associated molecules including vascular endothelial growth factor receptor (VEGFR)1, VEGFR2, VEGFR3, epidermal growth factor (EGF), MET, RET, platelet-derived growth factor (PDGF)B, PDGFRB and innate immunity related receptors such as toll-like receptors (TLR)2 and TLR9 in ASPS [35–38].

Investigation of interaction between cells and their microenvironment is an interesting field in cancer molecular pathogenesis. TFE3 may act as a modulator of immune response in tumor microenvironment through transforming growth factor beta (TGF-β) and CD40 ligand (CD40L) activation, which finally could lead to inflammation [39]. By focusing on genetic mouse model of ASPS, Goodwin et al. have indicated that lactate could promote angiogenesis and proliferation as an important metabolite in the tumor microenvironment. Moreover, this phenomenon might be link to high prevalence of ASPS cases arise in skeletal muscles which produce and uptake lactate [40]. Although more investigations should be done for tracing of the cell origin of ASPS, it has been shown that cancerous cells in some ASPS patients express nuclear myogenic differentiation 1 (MyoD1) that is a marker of skeletal muscle differentiation[41]. Epithelial markers like cytokeratin and epithelial membrane antigen (EMA) have not been found in ASPS cells that eliminates the possibility of epithelial origin [42]. Furthermore, upregulation of Pax6 gene in ASPS cells suggests neural origin of ASPS [38]. In another ASPS mouse model has been revealed glycoprotein nmb (GPNMB) as a downstream transcriptional proteoglycan target of ASPSCR1-TFE3, is upregulated in ASPS and involves in intravasation step of metastasis [43], hence, the role of proteoglycans in tumor progression is confirmed. Recently, it has been demonstrated that human cytomegalovirus proteins and genes could be identified in ASPS cases, which implies the role of this oncovirus in ASPS molecular pathogenesis [44].

Examination of tissue pattern, immunohistochemical markers expression and determination of ASPSCR1-TFE3 by fluorescence in situ hybridization (FISH) are being used in ASPS diagnosis [45]. Detection of circulating tumor DNA (ctDNA) or circulating tumor cells CTC in the blood is potential less-invasive biomarker for cancer diagnosis [46,47]. Because of highly metastatic nature of ASPS, CTC could be detected in patient blood sample. On the other hand, it has been reported that ASPSCR1–TFE3 chimeric transcripts can be detected in peripheral blood of metastatic ASPS patients by reverse transcriptase-polymerase chain reaction (RT-PCR) [48].

Bioinformatics analysis is a fast and informative approach for identification of crucial targets and pathways that are involved in various pathological conditions including cancer [49]. Through bioinformatics analysis of ASPS-1 cell line and ASPS patients, Covell et al. have identified important targets in cell cycle and cell adhesion related pathways such as FLT1, MET, CHK1, ARHGD1A, CDC6, RAD51L3, BIRC5, and CCL4 [50]. E-selectin is a metastasis mediator which identified by protein-protein interaction (PPI) network in ASPS [51]. Therefore, exploring and analysis of molecular data could be an opportunity for finding novel and efficient treatment.

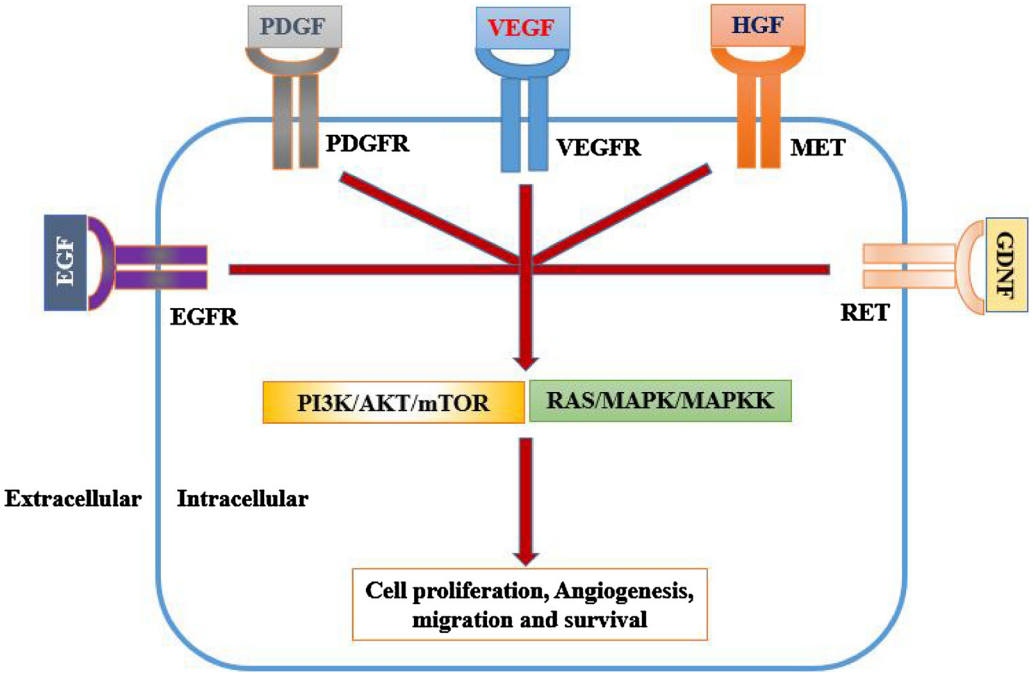

Fig. 2. Important signaling pathways involved in ASPS tumorigenesis. (PDGF: platelet-derived growth factor, PDGFR: platelet-derived growth factor receptor, VEGF: vascular endothelial growth factor VEGFR: vascular endothelial growth factor receptor, HGF: hepatocyte growth factor, GDNF: glial cell-*derived* neurotrophic factor, EGFR: epidermal growth factor receptor).

4. ASPS targeted therapy

ASPS is resistant to conventional cytotoxic chemotherapy. Recently it has been shown that autophagic genes play a key role in developing resistance to chemotherapy in ASPS [52]. The effectiveness of gold nanoparticles has been shown in diagnosis and therapy of cancer [53]. Moreover, targeted gold nanoparticles could enhance chemoradiotherapy response in STS [54,55]. Some studies have shown that radiotherapy has beneficial effects in controlling local recurrence and slowing metastasis [56,57], but other studies have indicated radiotherapy resistance in ASPS [58]. Total resection of this tumor could lead to enhanced survival and remission but recurrence maybe occur after surgery [59]. Exploring novel therapeutic strategies including immunotherapy and targeted therapy is still necessary for this type of sarcoma especially in advanced (metastatic) form. Transcriptomic analysis of ASPS has revealed upregulation of angiogenic and metastatic targets such as VEGF and c-Met [36] suggesting that angiogenic and metastatic pathways are hallmarks of ASPS and could be used in ASPS therapy. ASPS is a hyper vascular tumor, so use of angiogenesis inhibitors may be a suitable choice in controlling ASPS progression. In this regard, we review various novel multi-targeted tyrosine kinase inhibitors (TKI) that are in clinical development for ASPS targeted therapy (Fig. 3).

4.1. Sunitinib (Sutent®)

Sunitinib is an oral anti-angiogenic multi-targeted receptor TKI that was approved for RCC, gastrointestinal stromal tumors (GIST) and pancreatic neuroendocrine tumors [65,66]. VEGFR1, 2, 3, PDGFR-α, PDGFR-β, fibroblast growth factor receptor 1 (FGFR1), fms-related tyrosine kinase 3 (FLT3), stem cell factor receptor (c-Kit), ret proto-oncogene (RET), MET proto-oncogene and colony stimulating factor 1 receptor (CSF1R) are proangiogenic and oncogenic targets of sunitinib [67]. Sunitinib has been introduced as first line therapy for ASPS [68]. Antigrowth capability of sunitinib in ASPS primary culture has been shown by anti-proliferative assay [35]. Sunitinib side effects and interactions have been shown in various studies. Nausea, diarrhea, anorexia, hypothyroidism, thrombocytopenia, neutropenia, hypertension and hand-foot syndrome are sunitinib adverse effects [69,70]. Epigallocatechin-3-gallate has anti-tumoral activity in cancer [71] but its interaction with sunitinib may reduce bioavailability of sunitinib in metastatic RCC [72]. The effects of sunitinib for ASPS treatment in various clinical study reports are summarized in Table1.

4.2. Bevacizumab (Avastin®)

Bevacizumab is an antiangiogenic monoclonal antibody that targets VEGFA [77]. Intravenous administration of bevacizumab is used in the first-and/or second-line treatment of different types of cancer including metastatic colorectal cancer, advanced nonsquamous non-small cell lung cancer, metastatic RCC, ovarian epithelial cancer, fallopian tube cancer, primary peritoneal cancer and metastatic breast cancer [78]. ASPS mouse model was established for the first time in Vistica et al study. They have shown that combination therapy using bevacizumab and topotecan in ASPS treatment is more effective than monotherapy [79]. In a case report study, it has been revealed that eight courses of cytotoxic chemotherapy was ineffective in a metastatic ASPS but treatment with bevacizumab in combination with interferon alfa-2b (IFNα-2b) improved patient outcome, especially regression of metastatic lesions was achieved; however, due to loss of efficacy, it was identified that bevacizumab leads to tumor progression [80]. Although IFNα-2b has antiangiogenic activity but ASPS treatment failure with IFNα-2b has been reported in some studies [81]. Another case-based study has shown that treatment of 5 year-old child with metastatic ASPS with bevacizumab leads to 30% decrease in tumor size after 2 months [82].

4.3. Pazopanib (Votrient®)

Pazopanib has been approved for RCC and STS [83]. Pazopanib and sunitinib are two TKI with similar targets[68]. For the first time, Shido and Matsuyama have indicated that Pazopanib could be a suitable drug in first line therapy of unresectable ASPS [45]. It has been shown that pazopanib might not pass across blood brain barrier [84]. Therefore, pazopanib might not act effectively in ASPS patients with brain metastases. Pazopanib and trabectedin are two approved drugs stand in second-line therapy of STS [85]. Trabectedin breaks DNA double helix by binding to minor groove and stops cell cycle progression from G2 to M phase [86]. In a retrospective study concluded from world reference centers for sarcoma has been shown that pazopanib could be a

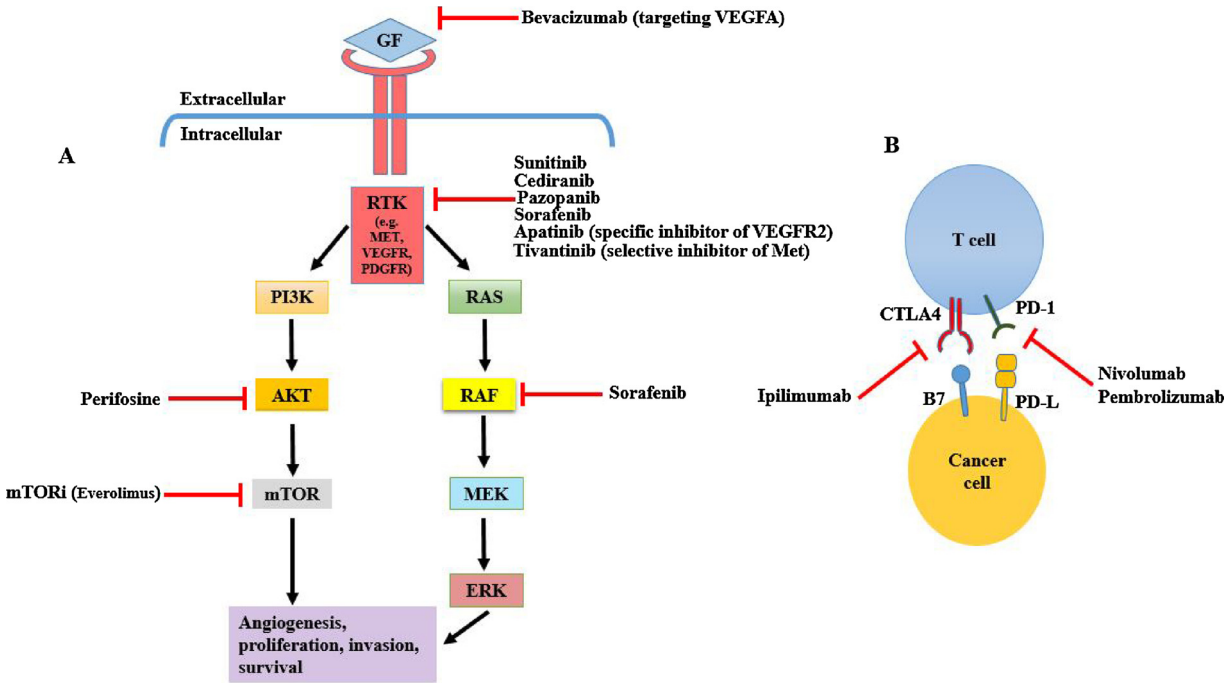

Fig. 3. Schematic representation of major deregulated oncogenic signaling pathways in ASPS and their inhibition by potential applicable molecular-targeting agents (A). Cancer immunotherapy could be as a salvage therapy approach for ASPS treatment (B). Some of these molecular-targeting agents such as perifosine[60], sunitinb, cediranib[61], pazopanib[62], everolimus[63] and cabozantinib[64] are under clinical trial for ASPS and/or STS treatment. More investigations are needed to better assess the efficacy of these drugs in ASPS treatment. (GF: growth factor, RTK: receptor tyrosine kinases, PI3K: phosphatidylinositol-3 kinase, mTOR: the mammalian target of rapamycin, MEK: mitogen-activated protein kinase kinase, ERK: extracellular signal–regulated kinase, PD-1: programmed cell death protein 1, PD-L: programmed death-ligand 1, CTLA4: cytotoxic T-lymphocyte-associated protein 4).

favorable choice in first-line treatment of advanced ASPS but trabectedin seems to have low effect in clinical practice [87]. However, some reports have shown that trabectedin could stabilize tumor progression without grade 3/4 toxicity [88]. The effects of pazopanib on ASPS treatment in various clinical studies are summarized in Table 2.

4.4. Cediranib (Recentin®)

Cediranib is a small molecule inhibitor that suppresses VEGFR1, 2 and 3[91]. It has been demonstrated through gene expression analysis that angiopoietin-2 (ANGPT2) and FLT1 were downregulated after treatment with cediranib [92]. Tumor infiltrating myeloid cells have involved in ASPS tumor vasculature and cediranib could inhibit this phenomenon [87]. Investigation of the molecular mechanisms underlying treatment of ASPS with cediranib through analysis of microarray data have shown the importance of MAPK signaling pathway, VEGFR1, VEGFR2, PDGFR and E-selectin in ASPS growth and invasion. However, these results need to be validated [51]. In another study of 43 ASPS cases, partial response (PR) and stable disease (SD) were 84% at 6 months and downregulation of vascular genesis targets due to cediranib has been confirmed [92]. In another study four PR and two SD were observed among six ASPS cases who received cediranib [93].

4.5. Apatinib (Aitan®)

Apatinib is a specific inhibitor of VEGFR2 that was used for treatment of metastatic gastric cancer and some types of sarcoma [94–96]. Apatinib could reverse multi-drug resistance in cancer and leads to increase intracellular concentrations of chemotherapeutic drugs [97], suggesting that it would be effective for treatment of chemoresistant cancers such as ASPS. It has been reported apatinib could significantly reduce lung metastatic lesions after one month with non-hematological side effects in metastatic ASPS [98].

4.6. Tivantinib (ARQ 197)

Tivantinib is a selective inhibitor of c-*Met tyrosine kinase receptor (MET)* [99]. Angiogenic effects of MET mediated by reduced THBS1 expression as an antiangiogenic factor and increased VEGF expression [100,101]. Furthermore, MET activity and expression is induced by upregulated TFE3 [102]. So, MET is a suitable target of TKI. A case report study has demonstrated that tumor growth was reduced in two patients after prescribing tivantinib in spite of low expression level of MET. In another study, it has been shown that MET inhibitor alone did not lead to reduction in tumor size in ASPS and most of the patients showed SD [103].

4.7. Cabozantinib (Cabometyx®) and Dasatinib (Sprycel®)

Cabozantinib is a small molecule TKI which targets MET, RET, VEGFR2, FLT3, c-kit and can be used in RCC and thyroid cancer treatment [104,105]. Dasatinib is an oral small molecule inhibitor of multiple tyrosine kinases that is used for chronic myeloid leukemia (CML) and philadelphia chromosome–positive acute lymphoblastic leukemia (ph+ ALL) [106]. Mukaihara et al. by in vitro and in vivo experiments have shown that cabozantinib and dasatinib suppress significantly tumor growth and invasion rather than pazopanib in ASPS and they have proposed cabozantinib as an alternative appropriate drug in pazopanib resistant ASPS; Moreover, they have confirmed antitumoral effect of suntinib and cediranib[107].

4.8. Nivolumab, Sorafenib and Imatinib

Nivolumab, sorafenib and imatinib are angiogenesis inhibitors. Kue et al. have shown that the best response to sorafenib was PR and in another study, PD was reported [108]. Similar to sorefenib, therapeutic effects of nivolumab and imatinib were not favored in ASPS therapy [109].

Table 1
Sunitinib in the treatment of ASPS. Response to chemotherapy was very poor or ineffective in all reports (PFS: Progression Free Survival, OS: Overall Survival). (Y, yes; N, no; ND, not determined; PD, progressive disease; PR, partial response; SD, stable disease).

# of Patient received Suintinb	Surgery	Radiotherapy	Chemotherapy	Additional targeted therapy	PFS and/or OS (months)	Best response and/or main treatment result	Ref.
15	N	N	5 patients	N	19/56	6 PR, 8 SD, 1 PD, despite side effects in all patients long term clinical benefits were confirmed	[73]
14	2 patients after neoadjuvant therapy with Sunitinib	4 patients	4 patients	N	41	Sunitinib as a suitable option in neoadjuvant therapy of unrespectable ASPS	[74]
2	Y	Y	Y	Bevacizumab (1 patient)	-	PR, regression of metastatic lung lesions	[75]
9	Y	7 patients	6 patients	N	17/19	5 PR, 3 SD, 1 PD	[35]
1	Y	Y	Y	No response to Foretinib (XL880)	-	complete regression of the local tumor and bone metastases stabilization	[57]
1	tumor resection and pulmonary metastasectomy	Y	Y	N	-	Sunitinib causes skin necrosis in patient with pre-existing skin necrosis	[76]
4	Y (biopsy)	N	Y	N	-	2 PR, 1 SD, 1 PD, acceptable drug response was achieved in all patients except one	[37]

5. Anti-angiogenesis drug resistance and the other novel treatment options

Various mechanism of resistance to antiangiogenics have been described in cancer [110]. Anti-angiogenesis drug resistance might be due to cross talk between different signaling pathways. For example, MET signaling has cross talk with EGFR, insulin like growth factor 1 receptor (IGF-1) and wnt pathways which involved in drug resistance [111]. The other anti-angiogenesis inhibitors in a same class may compensate anti-angiogenesis drugs resistance in some patients by targeting different targets. According to salvage treatment for RCC, combination of lenvatinib with mTOR inhibitor (mTORi) could improve outcome in patients who are resistant to anti-VEGF drugs such as sunitinib or pazopanib [112]. Because of similarity between RCC and ASPS, combination of the above-*mentioned drugs* could be useful in ASPS patients who are resistant to pazopanib as a possible salvage treatment [68]. Metabolic symbiosis between tumor cells is another resistance mechanism, which has been demonstrated in various cancer types such as sunitinib resistant RCC. This type of resistance mechanism could be blocked by mTORi such as everolimus [113]. Genetic and epigenetic alterations might be involved in antiangiogenic drugs resistant tumor cells [80,114]. Micro-RNAs (miRNA)s are small non-coding RNAs which function as tumor suppressors or oncogenes in various types of cancer [115]. Xie et al. have shown DNA hypermethylation of the miR-34b/c as a potential prognostic biomarker in STS including ASPS [116]. To best of our knowledge, there is no study on miRNA profiling in ASPS. Besides unraveling novel non-invasive biomarker, exploring miRNA expression profile of ASPS could provide better understanding of molecular mechanism of anti-cancer drugs resistance due to miRNA dysregulation [117–119]. Cancer stem cells (CSC)s have self-renewal and pluripotency properties which are similar to stem cells and are involved in tumorigenesis, metastasis, chemoradiotherapy resistance and tumor relapse [120,121]. High expression of CSC markers such as CD44 and aldehyde dehydrogenases (ALDH) has been observed in STS [122,123]. Enrichment of CSC after sorafenib treatment despite anti-proliferative effects of sorafenib may be a possible mechanism of TKI resistance in STS[124].

Cancer immunotherapy could be considered as a salvage therapy approach [125]. For the first time in a case report study it has been reveled combined check point inhibitors such as ipilimumab (anti CTLA4), pembrolizumab and nivolumab (anti PD-1) would be one of the effective therapy for anti-angiogenic resistant ASPS (Fig. 3B) [39] which could boost immune responses against tumor. Metastatic melanoma patients vaccination with irradiated tumor cells expressing granulocyte-macrophage colony-stimulating factor (GM-CSF) stimulates antitumor immunity; according to similar aspects between ASPS and melanoma, autologous immunotherapy approach can be highlighted as a treatment option for ASPS [126].

6. Conclusion

Surgery of local and metastatic ASPS could be an appropriate treatment option, but the risk of tumor recurrence would remain. Nowadays, majority of studies have confirmed that conventional chemotherapy is an ineffective approach for treatment of ASPS. Molecular targeted therapy have been highlighted as a novel and promising treatment strategy for ASPS. Use of combined mulitargeted TKI and immunotherapeutic can improve patient outcomes in ASPS; however, more translational and clinical researches are necessary to demonstrate efficacy and safety of these treatment approaches. Altogether surgical resection of operable tumor with targeted therapy is suggested for ASPS patients.

Conflicts of interests

There is no conflict of interest to declare.

Table 2
Pazopanib in ASPS treatment. Chemotherapy response was very poor or ineffective in all reports.)Y, yes; N, no; ND, not determined; PD, progressive disease; PR, partial response; SD, stable disease(.

# of Patient received Pazopanib	Surgery	Radiotherapy	Chemotherapy	Additional targeted therapy	Best response and/or main treatment result	Ref.
1	decompression-surgery	Y	Y	N	a newly developed brain metastasis was detected	[45]
2	One of the 2	Y	One of the 2	Bevacizumab & Pazopanib	SD, Pazopanib is recommended in second line of therapy of patients who obtain disease progression in first line of therapy	[68]
1	Y	ND	Y	N	Tumor regrowth	[89]
30	ND	ND	In some cases	Crizotinib, Sunitinib for some cases	Clinical value of Pazopanib is confirmed, PFS was 13.6 months	[87]
1	Y	ND	Y	N	PR, Improvement multiple pulmonary metastatic lesion	[90]

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