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Molecular targeted therapy in alveolar soft part sarcoma

Alveolar soft part sarcoma is a malignant and rare tumor that includes about 1% of all STS (soft tissue sarcoma), and usually occurs in adolescents and young adults. This type of cancer has tendency toward distant metastasis and invasion especially to brain and lungs. Alveolar soft part sarcoma (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. TFE3 is a potent regulator of tumor cell growth and metabolism pathways including (mTORC1, c-Met and HIF1α) (Fig. 1).

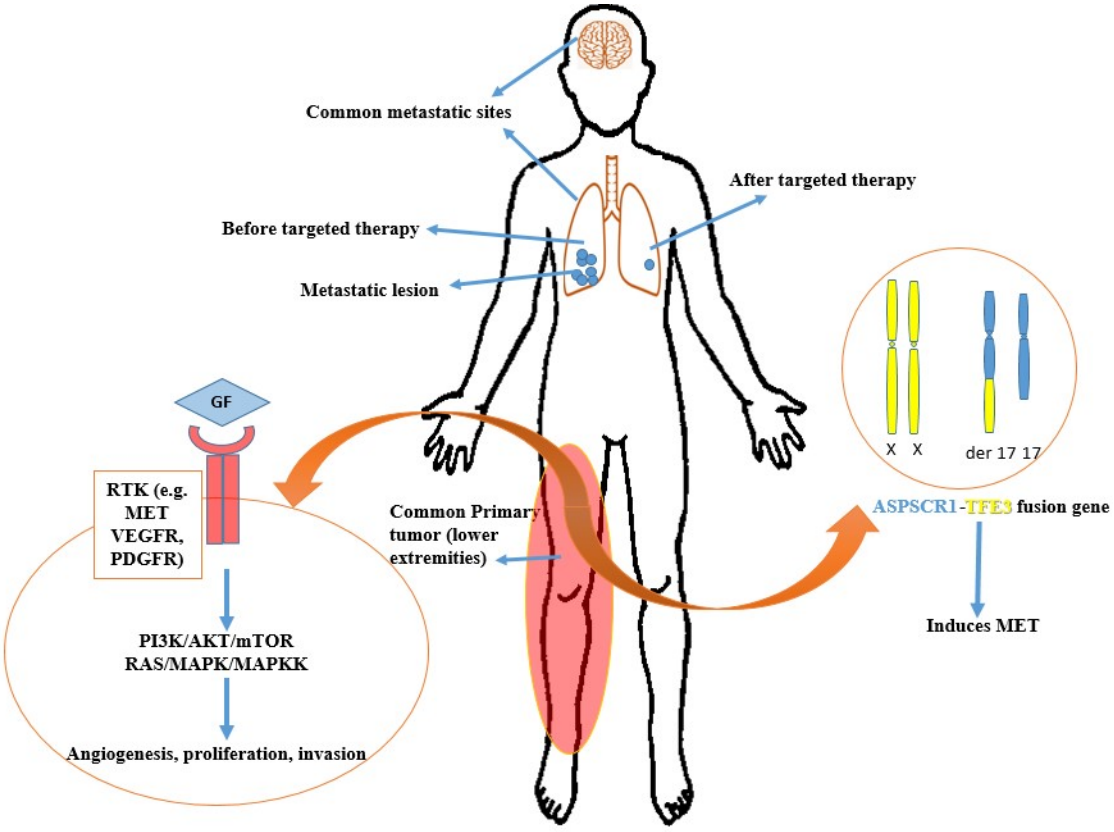

Fig. 1. Molecular features and targeted therapy of alveolar soft part sarcoma.

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. Many studies have shown that chemotherapy drugs are not effective in ASPS treatment and response to radiotherapy is controversial, but targeted therapy seems to be a good option for ASPS therapy (Fig. 2).

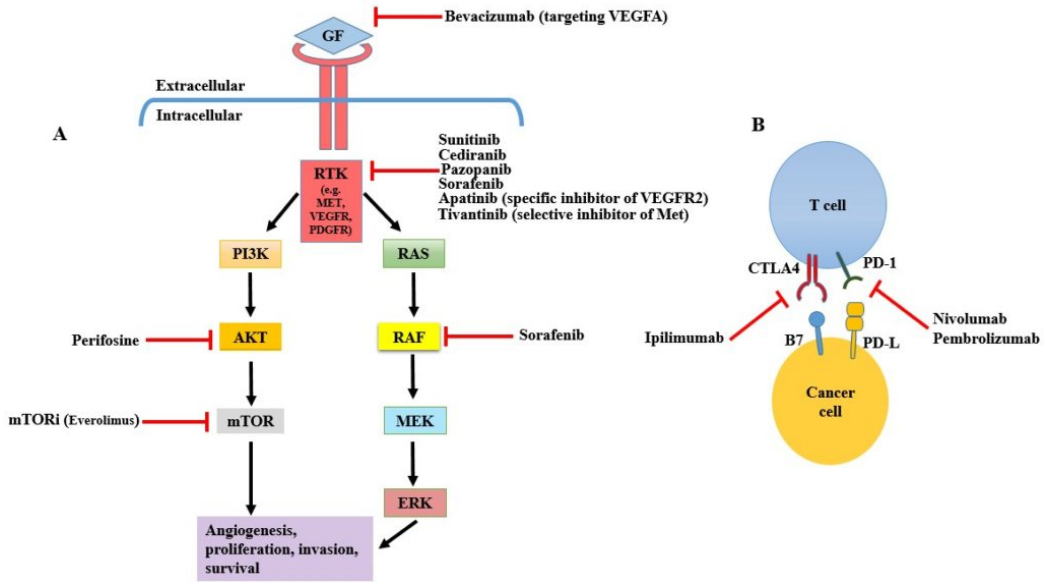

Fig. 2. Schematic representation of major deregulated oncogenic signaling pathways in ASPS and their inhibition by potential applicable molecular-targeting agents (A). Cancer immunotherapy could be as a salvage therapy approach for ASPS treatment (B). Some of these molecular-targeting agents such as perifosine, sunitinb, cediranib, pazopanib, everolimus and cabozantinib 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).

Transcriptomic analysis of ASPS has revealed upregulation of angiogenic and metastatic targets such as VEGF and c-Met suggesting that angiogenic and metastatic pathways are hallmarks of ASPS and could be used in ASPS therapy. Alveolar soft part sarcoma is a hyper vascular tumor, so use of angiogenesis inhibitors may be a suitable choice in controlling ASPS progression. Use of combined mulitargeted TKI (tyrosine kinase inhibitor) 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.

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