Cancer Control
Volume 28: 1–20
© The Author(s) 2021
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/10732748211038424
journals.sagepub.com/home/ccx
SAGE

Molecular targeted therapy for advanced or metastatic soft tissue sarcoma

Jin Yuan, MD[1], Xiaoyang Li, MD, PhD[1], and Shengji Yu, MD[1]

Abstract

Soft tissue sarcomas are a form of rare and heterogeneous neoplasms with high recurrence rate and mortality. Over the past decades, less progress has been achieved. Surgical management with or without adjuvant/neoadjuvant radiotherapy is still the first-line treatment for localized soft tissue sarcomas, and chemotherapy is the additional option for those with high-risk. However, not all patients with advanced or metastatic soft tissue sarcomas benefit from conventional chemotherapy, targeted therapy takes the most relevant role in the management of those resistant to or failed to conventional chemotherapy. Heterogeneous soft tissue sarcomas vary from biological behavior, genetic mutations, and clinical presentation with a low incidence, indicating the future direction of histotype-based even molecule-based personalized therapy. Furthermore, increasing preclinical studies were carried out to investigate the pathogenesis and potential therapeutic targets of soft tissue sarcomas and increasing new drugs have been developed in recent years, which had started opening new doors for clinical treatment for patients with advanced/metastatic soft tissue sarcomas. Here we sought to summarize the concise characteristics and advance in the targeted therapy for the most common subtypes of soft tissue sarcomas.

Keywords

soft tissue sarcoma, targeted therapy, molecular advance, clinical trials, tyrosine kinase inhibitors

Introduction

Soft tissue sarcomas (STS) are aggressive tumors that originate from mesenchyme, accounting for 1% of all adult cancers, with over 50 recognized histological subtypes according to the World Health Organization classification.[1] Despite the low incidence of STS, some subtypes are insensitive to traditional chemotherapy and progress rapidly with a high recurrence rate after resection, which results in the poor prognosis and high mortality.[2] Moreover, the prognosis of patients with STS has not improved markedly over the past few decades. According to the latest data reported by the American Cancer Society and the Surveillance, Epidemiology, and End Results Program from 2011 to 2017, there are approximately 5350 estimated deaths of STS in the United States for 2021, with a 5-year survival rate of 65.0% in recent years.[3,4] At present, surgery with optional perioperative chemotherapy is the standard treatment modality for localized STS.[5,6] For most subtypes of STS, palliative anthracycline-based chemotherapy alone or in combination with ifosfamide, is currently the first-line treatment for patients with advanced or metastatic STS. Owing to the rarity and the heterogeneity of STS, the lack of large scale data impedes the development of therapy in specific subtypes STS. In addition, STS are aggressive and commonly infiltrate deep tissue, with a high recurrence rate of 35%. 16% of all cases are found to develop metastasis at diagnosis, which is commonly involved in the lungs. However, the median overall survival (OS) of advanced or metastatic STS patients with conventional chemotherapy was just over a year.[7] Given the limitations of conventional chemotherapy in advanced STS, there is an urgent need to

[1]Departments of Orthopedics, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Corresponding Author:
Shengji Yu, Departments of Orthopedics, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China.
Email: shengjiyu@126.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (https://creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

develop novel therapeutic agents to improve patient's prognosis.

Targeted therapy may indicate a future direction for advanced STS. Preclinical researches on genomics and the molecular mechanisms of pathogenesis strongly support the therapeutic strategies for STS (Table 1).[8] Currently, drugs for targeted therapy have the advantage over conventional chemotherapy especially in patients with locally advanced or metastatic STS, with high efficiency, and confirmed safety (Table 2).[9] Vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) were demonstrated to be playing essential roles in tumor angiogenesis and growth and highly expressed in a variety of cancers.[10,11] Tyrosine kinase inhibitors (TKIs) targeting VEGFR and PDGFR were demonstrated to be effective in STS.[12] Mechanistic target of rapamycin (mTOR) and insulin-like growth factor type 1 receptor (IGF-1R) were all elucidated to be implicated in the signaling pathways which mediate cell proliferation and apoptosis, indicating the potential antitumor activity of the molecule inhibitors targeting these enzymes or signal transducers.[13,14] Such molecules include but not limit to c-Kit, MET, and cyclin-dependent kinases 4/6 (CDK4/6), and all have been studied as therapeutic targets.[15-17] Here, we summarize the recent preclinical studies and the advances of targeted therapy by major subtypes of STS according to the incidence.

Liposarcoma

Liposarcoma (LPS) is the most common histotype of STS, accounting for 20% of all STS and including 5 subtypes.[18] Well differentiated LPS (WDLPS) together with dedifferentiated LPS (DDLPS) account for the majority of LPS. Generally, liposarcoma exhibits relatively low malignancy compared to other subtypes of sarcomas. Advanced or metastatic patients with liposarcoma can reach a median OS of 15.6 months with eribulin, and median progression-free survival (PFS) of 4.2 months with trabectetin.[19,20] However, WDLPS/DDLPS presents indolent nature to chemotherapy. Specifically, these two subtypes were confirmed to be involved in CDK4 protein overexpression, resulting in cell cycle aberrations.[15,21,22] Locally advanced or metastatic WDLPS/DDLPS patients with CDK4 amplification and RB expression have a 12-week PFS (PFR12) of 66% (median PFS = 17.9 weeks) with CDK4 inhibitor palbociclib.[23] 57.2% PFS at 12 weeks (median PFS = 17.9 weeks) was observed in another clinical trial of palbociclib in patients with advanced WD/DDLPS.[24] More favorable PFR12 of 76% and median PFS of 30 weeks were observed with CDK4 inhibitor abemaciclib treatment in advanced progressive DDLPS.[25] Additionally, LPS responses to antiangiogenic therapy. Mahmood et al[26] reported that 82% patients with relapsed or refractory LPS with VEGFR and PDGFR inhibitor sunitinib malate achieved stable disease (SD) at 6 weeks, with a median PFS of 3.4 months, and PFR12 of 75% in the unpretreated LPS patient. 68.3% patients with unresectable or metastatic LPS remained progression-free at 12 weeks of 74.1% for DDLPS and 66.7% for myxoid/round cell liposarcoma (MRCLPS), with pazopanib targeting VEGFR, PDGFR, and KDR.[27] Anlotinib has been explored in patients with metastatic STS, and a PFR12 of 63% and a median PFS of 5.6 months were observed in LPS cohort.[9] However, similar multitargeted TKI regorafenib with targets including VEGFR-1, VEGFR-2, VEGFR3, c-Kit, and PDGFR, showed no improvement on PFS in treatment-refractory LPS.[28]

Though sensitive to chemotherapy and relatively low malignancy, it is also indispensable to investigate the potential targets of MRCLPSfor therapy. Recent study reported that JAK1/2 inhibitor combined with doxorubicin targeted both proliferating cells as well as cells with cancer stem cells features to circumvent chemotherapy resistance in treatment of myxoid cell liposarcoma.[29] Several drugs targeting receptor tyrosine kinases are under exploring for treating LPS, including sitravatinib (NCT02978859), lenvatinib (NCT03526679), and itacitinib (NCT03670069). Furthermore, continued exploration is encouraged due to the revealed specific amplification of CDK4 in WDLPS/DDLPS.

Synovial sarcoma

Synovial sarcoma (SS), characterized by a t (X; 18) reciprocal chromosomal translocation, is a rare, aggressive malignancy with high recurrent and metastatic rate.[30] About 50% patients with synovial sarcoma will develop metastasis, with a 5-year survival rate of 14.4%.[31] High-dose of ifosfamide has long been used to treat advanced synovial sarcoma for the relative sensitivity, with a best median PFS of 7.4 months.[7] However, more effective and less toxic agent is urgently needed. A phase 2 study of pazopanib treatment on patients with high- or intermediate-grade unresectable advanced STS reported a PFR12 of 49% and a median PFS of 161 days with treatment of pazopanib in SS cohort.[32] Later in a phase 3 study, pazopanib was observed to improve PFS notably in metastatic STS patients for most histologic types including SS.[33] Some other TKIs also achieved promising effect on SS. Olivier et al reported a phase 2 study of regorafenib in advanced and inoperable STS patients with intolerance or failure to first-line chemotherapy. They showed a significant longer median PFS (5.6 months) and a median duration (3.4 months) of treatment with regorafenib compared with placebo (1.0 month and 1.4 months, respectively), but there was no difference in OS.[34] The effect of BRAF and VEGFR inhibitor sorafenib on metastatic and/or locally advanced SS was reported to be limited.[35] A subsequent prospective research showed a patient affected by advanced SS who failed more than two regimens of chemotherapy achieved partial response (PR) with 6 months of time to progression and an OS of 11 months with sorafenib.[36] A phase 2 clinical trial reported that encouraging results were observed on patients with sorafenib plus dacarbazine.[37] Comfortingly, Chi et al[9] reported that patients

Table 1. Targeted therapies and genomic changes for STS.

Tumor	Genomic Alterations	Gene(s) related	Drugs
Liposarcoma			
Well-differentiated/dedifferentiated	12q14-15 amplification	MDM2, CDK4, HMGA2, SAS, GLI	Palbociclib Abemaciclib
Myxoid/round cell	t(12;16)(q13;p11); t(12;22)(q13;q12)	FUS-DDIT3; EWSR1-DDIT3	Sunitinib Pazopanib
Pleomorphic	13q14.2-5 loss	RB/TP53 loss	Anlotinib Regorafenib
Synovial sarcoma	t(X;18)(p11;q11)	SS18-SSX1 SS18-SSX2 SS18-SSX4	Pazopanib Regorafenib Sorafenib Anlotinib Apatinib Palbociclib
Leiomyosarcoma	del(10q11-21.2) del(13q14.3-21.1)	RB/PTEN loss	Pazopanib Sunitinib Sorafenib Regorafenib Anlotinib Cixutumumab+temsirolimus Ridaforolimus
Undifferentiated pleomorphic sarcoma	—	—	Pembrolizumab
Rhabdomyosarcoma			
Alveolar	t(2;13)(q35;q14) t(1;13)(p36;q14) t(X;2)(q13;q35)	PAX3-FOXO1 PAX7-FOXO1 PAX3-AFX	Cixutumumab+Temsirolimus Bevacizumab or temsirolimus +chemotherapy
Embryonal	Complex alterations	MYOD1 mutation	
Angiosarcoma	Complex alterations	MYC KIT TP53	Bevacizumab Sunitinib Sorafenib Pazopanib Everolimus
Solitary fibrous tumor	inv(12)(q13;q13)	NAB2 - STAT6	Sunitinib Sorafenib Bevacizumab + temozolomide Pazopanib Dasatinib
Ewing sarcoma	t(11;22)(q24;q12) t(21;22)(q22;q12) t(2;22)(q33;q12) t(7;22)(p22;q12)	EWSR1-FLI1 EWSR1-ERG EWSR1-FEV EWSR1-ETV1	Apatinib Cixutumumab + temsirolimus Cabozantinib
Alveolar soft parts sarcoma	der(17)t(X;17)(p11;q25)	ASPL-TFE3	Anlotinib Sunitibib Axitinib + pembrolizumab
Clear cell sarcoma	t(12;22)(q13;q12) t(2;22)(q33;q12)	EWSR1-ATF1 EWSR1-CREB1	Crizotinib Pazopanib Vemurafenib
Inflammatory myofibroblastic tumor	t(1;2)(q22;p23) t(2;19)(p23;p13) t(2;17)(p23;q23) t(2;2)(p23;q13) t(2;11)(p23;p15) inv(2)(p23;q35)	TPM3-ALK TPM4-ALK CLTC-ALK RANBP2-ALK CARS-ALK ATIC-ALK	Crizotinib Ceritinib
Perivascular epithelioid cell tumor		Loss of heterozygosity of TSC2	Sirolimus Everolimus Temsirolimus

(continued)

Table 1. (continued)

Tumor	Genomic Alterations	Gene(s) related	Drugs
Dermatofibrosarcoma protuberans	t(17;22)(q21;q13)	COL1A1-PDGFB	Imatinib
Epithetlioid sarcoma	Inactivation, deletion, or mutation of INI1 (SMARCB-1)	SMARCB-1/INI1	Tazemetostat
Malignant peripheral nerve sheath tumors		NF1, CDKN2A and EED or SUZ12	—
Desmoid tumor		CTNNB1 or APC mutation	Imatinib Sorafenib
Tenosynovial giant cell tumor/ pigmented villonodular synovitis	t(1;2)(p13;q35)	CSF1	Pexidartinib Imatinib Nilotinib

affected by refractory metastatic SS in treatment with anlotinib achieved the PFR12, median PFS, and OS of 75%, 7.7, and 12 months, respectively. A retrospective study of apatinib on patients with advanced sarcoma including SS conducted by Xie showed the 4-month and 6-month PFS rates were 46.3 and 36.5% for whole cohort, respectively, and 5.2 months for median duration of response (DR).[38] Another phase 2 trial of apatinib for metastatic sarcoma reported a PFR12 of 74% for the whole cohort, patients of whom with SS account for 9.4%.[39]

Yet some efforts did not lead to satisfactory results. Cixutumumab, an IGF-1R inhibitor, was reported to have unsatisfactory effect on patients with unresectable or relapsed/metastatic SS in a phase 2 study.[40] Therefore, researchers should put focus on preclinical studies to provide the basis for clinical trials. Continued SS18-SSX fusion genes induces the pathogenesis of SS. Preclinically, integrase interactor 1 (INI-1) deficiency was confirmed to allow Enhancer of Zeste Homologue 2 (EZH2) to become an oncogenic driver and specifically link to the presence of SS18-SSX1 fusion gene.[41,42] Thus, targeting SS18-SSX and related oncogenic pathways provides new direction for drug discovery,[43,44] and the clinical trials of EZH2 inhibitor tazemetostat in synovial sarcoma are already at the status of recruiting (NCT01897571; NCT02601950). Moreover, CDK4 inhibitor palbociclib was found to inhibit Rb-phosphorylation, inducing G1 arrest and proliferation block, which indicates palbociclib to be a potential agent for SS.[45]

Leiomyosarcoma

Leiomyosarcoma (LMS) arises from several locations, including the uterus, retroperitoneum, gastrointestinal tract, and vasculature, with an overall incidence ranging between 10% and 20% of all STS.[46] In an aforementioned study, PFR12 was 44% with median PFS of 91 days in the LMS cohort treated with pazopanib, and PR occurred in one patient with LMS.[32] Subsequent research of sunitinib on relapsed or refractory STS was carried out, reporting a median PFS and median OS of 3.7 and 9.2 months in LMS patients, respectively.[26] In another phase 2 study on patients with advanced STS after anthracycline-based regimens, the 6-month PFR was 35% with sorafenib in LMS group with the median PFS and OS of 4.9 and 12.5 months, respectively.[47] Moreover, sorafenib and dacarbazine combination present certain efficacy on pretreated STSs including LMS.[36] A significant longer median PFS of 3.7 months was achieved in LMS group with regorafenib in a placebo-controlled phase 2 trial.[34] In a phase 2 study of anlotinib on patients with refractory metastatic STS conducted by Chi et al, the PFR12 and median PFS was 75% and 11 months for LMS cohort.[9]

Leiomyosarcoma was characterized by the changes of losses in chromosomes 10q11 to 21.2 and 13q14.3 to q21.1, which leads to the deletion of tumor suppressor genes PTEN and the hyperactivation of phosphatidylinositol 3 kinase (PI3K)/AKT.[46] Preclinically, mTOR activation was seen in mice with PTEN-deficiency in the smooth cell muscle lineage, showing a critical role of AKT-mTOR pathway in LMS genesis.[48] Although mTOR inhibitor showed a significant effect on LMS preclinically, the clinical trials of single-agent temsirolimus or ridaforolimus on LMS was not inspiring.[49,50] Moreover, it is disappointing that the combination of an mTOR inhibitor with an IGF-1R inhibitor only showed effects mainly on bone sarcomas, with no significant activity in LMS.[51] Due to the complex and unbalanced karyotype of LMS, more efforts will be required to elucidate the underlying genetic mechanisms to guide targeted therapy.

Undifferentiated pleomorphic sarcoma

Undifferentiated pleomorphic sarcoma (UPS), previously classified as malignant fibrous histiocytoma (MFH), is a group of STS arising from fibroblasts. Although UPS accounts for one of the most common subtypes of STS, there are a few studies evaluating chemotherapy in patients with UPS. Anthracycline-based regimens are still the preferred regimens for UPS. However, the clinical outcomes of patients with advanced UPS were worst with the median OS of only 11 months.[52] Chi et al reported a PFR12 and median PFS of 58% and 4.1 months with anlotinib, respectively, in patients with

Table 2. Clinical trials about targeted therapy on STS.

Tumor	Drugs	Targets	Phase	Year	Population	Response	Clinical outcomes	NCT number
Liposarcoma (LPS)								
	Palbociclib	CDK4	II	2013	Advanced CDK4-amplified WDLPS/DDLPS	PR: 1/29	PFR12 66%; mPFS 17.9w	NCT01209598
	Abemaciclib	CDK4	II	2019	Adults with advanced DDLS	PR: 1/29	PFR12 76%; mPFS 30.4w	NCT02846987
	Sunitinib	PDGFR; VEGFR; c-Kit; FLT3	II	2011	Relapsed/refractory STS	SD:14/17	PFR12 75% for the untreated; 69.2% for the pretreated; mPFS 3.4m	NCT00400569
	Pazopanib	PDGFR; VEGFR	II	2017	Advanced intermediate-/high-grade LPS	PR: 1/41 SD: 17/41	PFR12 68.3%; mPFS 4.4m; mOS 12.6m	NCT01506596
	Anlotinib	VEGFR; FGFR; PDGFR; c-Kit; Ret; Aurora-B; c-FMS; DDR1	II	2018	Refractory metastatic STS	PR: 1/13 ORR: 13%	PFR12 63%; mPFS 5.6m; mOS 13m	NCT03016819
	Regorafenib	c-Kit; PDGFR; FGFR-1; RET; BRAF; VEGFR	II	2020	Advanced/Metastatic treatment-refractory LPS	No response	mPFS 1.87m; mOS 6.4m	NCT02048371
Synovial sarcoma (SS)								
	Pazopanib	VEGFR; PDGFR; c-Kit	II	2009	Relapsed/refractory advanced STS	PR: 5/37	PFR12 49%; mPFS 161d; mOS 310d	EORTC study 62043
	Pazopanib	VEGFR; PDGFR; c-Kit	III	2012	Metastatic STS	—	mPFS 4.6m; mOS 12.5m	NCT00753688
	Regorafenib	c-Kit; PDGFR; FGFR-1; RET; BRAF; VEGFR, Raf	II	2016	Advanced STS	PR: 1/13	PFR12 77%; mPFS 5.6m; mOS 13.4m	NCT01900743
	Sorafenib	BRAF; VEGFR	II	2009	Metastatic/recurrent STS	PR: 6/12 PD: 6/12	PFR12 42%	NCT00245102
	Sorafenib+dacarbazine	BRAF; VEGFR	II	2018	Advanced STS with zero to two prior lines of chemotherapy	PR: 1/11	PFR12 51%; mPFS 13.4w; mOS 13.2m*	NCT00837148
	Apatinib	VEGFR; c-Kit; PDGFR-β	R	2018	Advanced sarcoma not amenable to curative treatment	Best response PR DR:3.8m	4m-PFR 46.3%; 6m-PFR 36.5%*	—
	Apatinib	VEGFR-2	II	2019	Stage IV sarcomas failed prior chemotherapy	PR: 9/59[a] SD: 25/59[a] ORR:15.25%[a]	PFR12 74%; mPFS 7.93m; mOS 17.27m[a]	NCT03121846
	Cixutumumab	IGF-1R	II	2013	Previously treated advanced/metastatic STS	SD: 6/17	PFR12 21.4%; mPFS 6.4w; mOS 56.3w	NCT00668148

(continued)

Table 2. (continued)

Tumor	Drugs	Targets	Phase	Year	Population	Response	Clinical outcomes	NCT number
Leiomyosarcoma (LMS)								
	Pazopanib	VEGFR; PDGFR; c-Kit	II	2009	Relapsed/refractory advanced STS	PR: 1/41	PFR12 44%; mPFS 91d; mOS 354d	EORTC study 62043
	Sunitinib	PDGFR; VEGFR; c-Kit; FLT3	II	2011	Relapsed/refractory STS	SD:12/13	PFR12: 60% for the untreated, 62.5% for the pretreated; mPFS 3.7m	NCT00400569
	Sorafenib	BRAF; VEGFR	II	2013	Advanced STS patients pretreated with anthracycline-based chemotherapy	PR: 2/35 SD: 15/35 PD: 11/35	6-month PFR 35%; mPFS 4.9m; mOS 12.5m	—
	Regorafenib	c-Kit; PDGFR; FGFR-1; RET; BRAF; VEGFR, Raf	II	2016	Advanced STS	SD: 24/28	PFR12 57%; mPFS 3.7m; mOS 21m	NCT01900743
	Sorafenib+dacarbazine	BRAF; VEGFR	II	2018	Advanced STS with zero to two prior lines of chemotherapy	PR: 1/11	PFR12 51%; mPFS 13.4w; mOS 13.2m[a]	NCT00837148
	Anlotinib	VEGFR; FGFR; PDGFR; c-Kit; Ret; Aurora-B; c-FMS; DDR1	II	2018	Refractory metastatic STS	PR: 2/16	PFR12 75%; mPFS 11m; mOS 15m	NCT03016819
	Ridaforolimus	mTOR	II	2011	Advanced bone sarcoma and STS	CBR: 19/57	12-month PFR 20.2%; mPFS 16.1w	—
	Temsirolimus	mTOR	II	2011	Advanced STS with no prior chemotherapy for metastatic disease	PR: 1/9	PFR12 41%; mPFS 2m; mOS 7.6m[a]	—
	Cixutumumab+temsirolimus	IGF-1R; mTOR	II	2013	Metastatic/locally advanced of STS and bone sarcoma	—	mPFS 11.4w; mOS 14.6m[a]	NCT01016015
Undifferentiated pleomorphic sarcoma (UPS)								
	Anlotinib	VEGFR; FGFR; PDGFR; c-Kit; Ret; Aurora-B; c-FMS; DDR1	II	2018	Refractory metastatic STS	PR: 1/19 ORR: 5.3%	PFR12 58%; mPFS 4.1m	NCT03016819

(continued)

Table 2. (continued)

Tumor	Drugs	Targets	Phase	Year	Population	Response	Clinical outcomes	NCT number
Rhabdomyosarcoma (RMS)								
	Temsirolimus	mTOR	II	2013	Children with refractory/recurrent RMS	SD: 4/16 at 12w	PFR12 7%; mPFS 39d; mOS 7.6m	NCT00106353
	Cixutumumab	IGF-1R	II	2013	Previously treated advanced/ metastatic STS	SD: 4/17	PFR12 12%; mPFS 6.1w; mOS 23.6w	NCT00668148
	Cixutumumab+temsirolimus	IGF-1R; mTOR	II	2013	Metastatic/locally advanced of STS and bone sarcoma	—	mOS 18.9m	NCT01016015
	Cixutumumab+temsirolimus	IGF-1R; mTOR	II	2015	Pediatric patients and young adults with recurrent/refractory sarcomas	—	PFR12 12%[a]	NCT01614795
	Bevacizumab/temsirolimus +chemotherapy	VEGFR; mTOR	II	2019	Patients with RMS in first relapse with unfavorable prognosis	ORR: 28% for bevacizumab; 47% for temsirolimus	6-month EFS rate: 54.6% for bevacizumab; 69.1% for temsirolimus	NCT01222715
Angiosarcoma (AS)								
	Bevacizumab	VEGFR	II	2013	AS and epithelioid hemangioendotheliomas not surgically resectable	PR: 2/23 SD: 11/23	mPFS 11.4w; mOS 14.6m[a]	—
	Sorafenib	BRAF; VEGFR	II	2009	Metastatic/recurrent STS	PR: 5/37 PD: 6/12	PFR12 64%	NCT00245102
	Sorafenib	BRAF; VEGFR	II	2011	Advanced/metastatic AS patients	—	mPFS 1.8m; mOS 12m	NCT00874874
	Sorafenib	BRAF; VEGFR	II	2012	Recurrent/metastatic vascular sarcomas	PR: 1/8; SD: 5/8	mPFS 3m; mOS 17m[a]	—
	Everolimus	mTOR	II	2013	Metastatic/recurrent STS after failure of anthracycline and ifosfamide	PR: 1/3 SD: 1/3	PFR16 67% (2/3)	NCT01830153
Solitary fibrous tumors (SFT)								
	Sorafenib	BRAF; VEGFR	II	2013	Metastatic/advanced progressive SFT	No response	mOS 19.7m	NCT00874874
	Temozolomide + bevacizumab	VEGFR	R	2011	Advanced, recurrent and metastatic hemangiopericytoma and malignant SFT	—	6-month PFR 92.9%; mPFS 10.8m; mOS 24.3m	—
	Pazopanib	VEGFR; PDGFR; c-Kit	P	2015	Advanced SFT	PR: 1/11 SD: 8/11	6-month PFR 44.9%; mPFS 4.7m; mOS 13.3m	—
	Cixutumumab+temsirolimus	IGF-1R; mTOR	II	2013	Metastatic/locally advanced of STS and bone sarcoma	PR: 1/8	mPFS 89.6w for IGF-1R+	NCT01016015
	Pazopanib	VEGFR; PDGFR; c-Kit	R	2018	Recurrent/metastatic SFT	DCR: 88.95%	mPFS 6.2m	-
	Dasatinib	Src; PDGFR; c-Kit; BCR-ABL	II	2017	Advanced sarcoma including SFT	Objective tumor response: 5/25	6-month PFR 30%; mPFS 2m	NCT00464620

(continued)

Table 2. (continued)

Tumor	Drugs	Targets	Phase	Year	Population	Response	Clinical outcomes	NCT number
Ewing sarcoma (EWS)								
	Cixutumumab	IGF-1R	II	2013	Previously treated advanced/ metastatic STS	SD: 5/18	PFR12 11%; mPFS 6.4w; mOS 24.1w	NCT00668148
	Cixutumumab+temsirolimus	IGF-1R; mTOR	II	2013	Metastatic/locally advanced of STS and bone sarcoma	PR: 4/27	mPFS 6w; mOS 16.2m	NCT01016015
	Cabozantinib	VEGFR-2	II	2020	Advanced EWS or osteosarcoma	PR: 10/39	mPFS 4.4m; mOS 10.2m[a]	NCT02243605
	Apatinib	VEGFR; c-Kit; PDGFRB	R	2018	Advanced sarcoma not amenable to curative treatment	Best response PR DR: 2m	4m-PFR 46.3%; 6m-PFR 36.5%[a]	—
Alveolar soft part sarcoma (ASPS)								
	Cediranib	VEGFR; c-Kit	II	2014	Metastatic STS	PR: 4/6	—	NCT00385203
	Cediranib	VEGFR; c-Kit	II	2019	Metastatic STS	ORR: 45.5%	12m-PFR 38.7%; 12m-OS rate 90.3%	NCT01337401
	Crizotinib	MET; ALK; ROS1	II	2018	Locally advanced/metastatic ASPS	PR: 1/40	PFR12 85%; mPFS 8m for MET+	NCT01524926
	Axitinib+pembrolizumab	VEGFR; PD-L1	II	2019	Advanced/metastatic ASPS	PR: 6/11	PFR12 65.6%; mPFS 4.7m; mOS 18.7m	NCT02636725
	Anlotinib	VEGFR; FGFR; PDGFR; c-Kit; Ret; Aurora-B; c-FMS; DDR1	II	2018	Refractory metastatic STS	PR: 6/13	PFR12 77%; mPFS 21m	NCT03016819
Clear cell sarcoma (CCS)								
	Vemurafenib	BRAF	Case	2015	Soft tissue of left lumbar with lung metastases	CR	—	—
	Crizotinib	MET; ALK; ROS1	II	2017	Advanced CCS with MET alterations	PR: 1/26 SD: 17/26	mPFS 131 days; mOS: 277 days; PFR12 53.8%	NCT01524926
Inflammatory myofibroblastic tumor (IMT)								
	Crizotinib	MET; ALK; ROS1	II	2017	Pediatrics of unresectable IMT	PR: 5/14; SD: 7/14	—	NCT00939770
Perivascular epithelioid cell tumor (PEComa)								
	Sirolimus	mTOR	II	2020	Advanced malignant PEComa	ORR: 39%; DCR: 71%	—	NCT02494570
Dermatofibrosarcoma protuberans (DFSP)								
	Imatinib	PDGFRB	II	2012	Advanced/Metastatic DFSP	PR: 7/16; SD: 4/16	—	NCT00084630
	Imatinib	PDGFRB	II	2013	Advanced/Metastatic DFSP	PR: 4/8; SD: 2/8	—	NCT00085475
Malignant peripheral nerve sheath tumor (MPNST)								
	Pexidartinib+ sirolimus	CSF-1R; c-Kit; FLT3; mTOR	II	—	Unresectable MPNST	Recruiting	Recruiting	NCT02584647
	Sirolimus+Ganetespib	Mtor; Hsp90	II	2020	Unresectable/refractory MPNST	No response	No response	NCT02008877
Epithelioid sarcoma (ES)								
	Tazemetostat	EZH2	II	2020	Advanced ES with loss of INI1/ SMARCB-1	Objective response: 9/62	mPFS: 5.5m; mOS: 19m	NCT04204941

(continued)

Table 2. (continued)

Tumor	Drugs	Targets	Phase	Year	Population	Response	Clinical outcomes	NCT number
Desmoid Tumor (DT)								
	Imatinib	PDGFRB	II	2006	Advanced DT	PR: 3/19; SD: 4/19	—	—
	Imatinib	PDGFRB	II	2010	Progressive and recurrent aggressive DT	CR: 1/35; PR: 3/35	PFR12 91%; 2-year PFR 55%	—
	Sorafenib	BRAF; VEGFR	R	2012	DT patients	PR: 6/24; SD: 17/24	—	—
	Sorafenib	BRAF; VEGFR	III	2019	Progressive, symptomatic/ recurrent DT	ORR: 33%	2-year PFR 81%	NCT02066181
Tenosynovial giant cell tumor/pigmented villonodular synovitis (TGCT/PVNS)								
	Imatinib	PDGFRB; CSF1	R	2011	Advanced and/or metastatic TGCT/ PVNS	CR: 1/27; PR: 4/27	mPFS: 20.9m	—
	Nilotinib	CSF1; PDGFR; ABL	II	2018	Advanced TGCT/PVNS	PR: 3/51; SD: 46/51	PFR12: 92·6%	NCT01261429
	Pexidartinib	CSF-1R; c-Kit; FLT3	III	2020	Advanced TGCT	ORR: 53%	—	NCT02371369

SD, stable disease; PR, partial response; PD, progression disease; CBR, clinical benefit response; ORR, objective response rate; DR, duration of response; PFS, progression-free survival; PFR12, progression-free survival rate at 12 weeks; 6-month PFR, progression-free survival rate at 6 months, similarly 4-month, 12-month PFR; OS, overall survival; mPFS, median progression-free survival; mOS, median overall survival; R: retrospective study; P: prospective study.

[a]Means that the results were obtained from analysis of the whole cohort of multiple subtypes.

refractory metastatic UPS.[9] In addition, pembrolizumab exhibited meaningful clinical activity in UPS, with an objective response rate (ORR) of 40%.[53]

Rhabdomyosarcoma

Rhabdomyosarcoma (RMS), a malignant tumor of striated muscle origin, is the third most common extracranial solid tumor of childhood after Wilms tumor and neuroblastoma, accounting for approximately 4.5% of all childhood cancer.[54,55] There are three major subtypes of RMS, embryonal RMS (ERMS), alveolar RMS (ARMS), and pleomorphic RMS (PRMS). Adults are more likely to have PRMS which exhibits relative resistance to chemotherapy compared to ERMS and ARMS. Standard chemotherapy treatment is widely considered as the combination of vincristine, actinomycin D, and cyclophosphamide/ifosfamide. Localized RMS patients with integrated multidisciplinary treatment achieve a 5-year survival rate of 70%, whereas the prognosis of those with metastatic or recurrent RMS still remains poor.[54] Receptor tyrosine kinases, including the IGF-1R, anaplastic lymphoma kinase (ALK), PDGFR α and β, VEGFR, epidermal growth factor receptor (EGFR), and the fibroblast growth factor receptor 4 (FGFR4) have been demonstrated to be potential targets for therapy in RMS.[56] Increasing studies reported that only a small portion of patients with RMS benefit from single-agent targeted therapy. In a phase 2 study, mTOR inhibitor temsirolimus showed a poor efficacy in children with refractory or recurrent RMS.[57] Unsatisfactory result was also observed in patients with advanced or metastatic RMS with anti-IGF-1R antibody cixutumumab, with a PFR12 of 12% and median PFS of 6.1 weeks.[40] In contrast, Gary et al[51] reported that the combination of cixutumumab and temsirolimus had certain efficacy on patients with sarcoma, but clinical outcome of patients after treatment with this combination cannot be predicted by IGF-1R expression. However, another study reported that there was no improvement of activity but increased toxicity of this combination in pediatric patients and young adults with recurrent or refractory sarcoma including RMS.[58] Subsequently, a study of bevacizumab or temsirolimus in combination with chemotherapy demonstrated that RMS patients with temsirolimus had a superior event-free survival (EFS) compared with bevacizumab.[59] Till now, there are still not many suggested molecular targeted drugs for advanced or metastatic RMS. More efforts should be taken to reveal the pathogenesis and improve the outcome of advanced PRMS, and currently the targeted therapy for PRMS is hindered by two main factors, the rarity of PRMS with deficient clinical information and the undiscovered targets.

Angiosarcoma

Angiosarcoma (AS) is rare malignant endothelial-cell tumor of vascular or lymphatic origin, accounting for only 1% of all sarcomas.[60] For antiangiogenic therapy, Koontz et al[61] reported two pathological-complete response (CR) cases with nasal angiosarcomas with treatment of bevacizumab plus preoperative radiotherapy. Subsequently, single-agent bevacizumab showed significant activity in advanced AS patients with 2 PR and 11 SD observed in 32 patients.[62] Moreover, two successfully treated cases report of retroperitoneum and breast AS patients with sunitinib treatment indicated potential efficacy for further investigation.[63,64] The activity against AS was also seen with antiangiogenic molecule sorafenib, with PR rate of 14% and median PFS of 3.2 months.[35] However, sorafenib was reported to have limited antitumor activity in pretreated AS patients, and no response was seen in chemotherapy-naïve patients.[65] Similar results of limited efficacy of sorafenib were seen in vascular sarcoma patients including AS and solitary fibrous tumor in another trial.[66] Several retrospective studies analyzed the AS patients with pazopanib, and modest benefit was observed.[67-69] There is a multicenter phase 2 trial of mTOR inhibitor everolimus on patients with AS, reporting a highest PFR at 16 weeks of 67% (2/3) in previously anthracycline- and ifosfamide-containing chemotherapy treated AS patients.[70]

FLT4 gene co-amplification or KDR mutation was elucidated to be related to tumor genesis, and may play a critical role in therapeutic targeting.[71,72] Isabelle et al[65] reported that limited efficacy of sorafenib in AS patients may be implicated in the absence of KDR gene mutations. A case with advanced AS achieved a PR for three months with VEGFR-2 inhibitor apatinib, which may be attributable to KDR gene amplification.[73] All the demonstrations indicate the essential role of KDR in the targeted therapy for AS.

Solitary fibrous tumor

Solitary fibrous tumor (SFT), arising from submesothelial origin, is a rare mesenchymal malignancy that poorly responds to conventional chemotherapy.[74] Although SFT is rare, it is classified into three clinical-pathologic types: typical SFT, malignant SFT, and dedifferentiated SFT. Solitary fibrous tumor was long recognized to the rich vascular characteristics. Case reports showed IFN-α and/or thalidomide had certain efficacy in advanced SFT.[75,76] For potential targets, immunohistochemistry examination showed that upregulation of endothelial growth factors and receptors was implicated in the genesis of SFT.[77] Later, the efficacy of sunitinib on SFT was retrospectively confirmed, with 14 out of 29 patients achieved PR by Choi criteria.[78] Valentin et al reported a PFS of 9 months was observed in 2 out of 5 patients with progressive malignant SFT in treatment with sorafenib.[79] The efficacy of bevacizumab was retrospectively analyzed in advanced malignant SFT patients in combination with temozolomide, with an estimated PFS of 9.7 months and 6-month PFR of 78.6%.[80] Alice et al[81] reported that advanced SFT patients with sunitinib or pazopanib as 2nd, 3rd, or 4th line achieved median PFS of 5.1 months and 5 SD in 10 patients. Pazopanib also showed some activity as first-line treatment in patients with

advanced SFT in a single-institution.[82] A median PFS of 6.2 months achieved in 9 recurrent or metastatic SFT patients retrospectively in another study, demonstrating an effective treatment of pazopanib in both first- and second-line settings.[83] However, limited results were observed with another TKI dasatinib, indicating dasatinib not suggested for standard treatment.[84] Additionally, in an aforementioned study, 4 out of 8 patients with IGF-1R-positive SFT achieved a median PFS of 89.6 weeks and 16.1 weeks for those IGF-1R-negative, with the combination of the IGF-1R antibody cixutumumab and the mTOR inhibitor temsirolimus.[51] Since SFT can arise from anywhere in the body, and many studies did not have the specific subtypes as eligibility criteria, which may make the demonstration lack of precision.

Ewing sarcoma

Ewing sarcoma (EWS) is highly malignant small round cell mesenchymal sarcoma commonly with EWSR1-FLI1 fusion, accounting for less than 1% of all subtypes of STS.[85] Through decades probing, well-standardized treatment protocols was formed based on multidisciplinary care incorporating, with a reported long-term survival rates of 70%.[86,87] However, nearly 30% patients develops distant metastases, with 5-year survival rates of approximately 20%–30%.[88] Due to the high sensitivity to chemotherapy, several combinations of chemotherapy drugs exhibited promising responses in a variety of studies.[89-93] Of note, whether the benefit of the efficacy of these combinational agents overweighs toxicity is still under debate. Thus, new strategies for combining targeted therapy with chemotherapy is indispensable. The pathogenesis was demonstrated to be related to IGF-1, mTOR, and angiogenesis.[85] Cixutumumab showed an unsatisfactory result in patients with EWS, but showed a significant beneficial efficacy in combination with temsirolimus, and the expression of IGF-1R may indicate the clinical benefit.[40,51,94] Apatinib was reported to have an objective response rate(ORR) of 70% in Ewing sarcoma, with median duration of response of 2 months.[38] Moreover, antitumor effect of VEGFR-2 inhibitor cabozantinib has been confirmed in another study recently.[95] Recently Guenther et al demonstrated that dual targeting IGF-1R and CDK4/6 *in vitro* and *in vivo* promoted a synergistic response, suggesting further clinical investigation is warranted.[96]

Although EWS oncogenesis driven by EWS-FLI1 has long been proven, it is still difficult to use EWS-FLI1 protein as a therapeutic target. Novel peptide targeting EWS-FLI1 interaction with RNA helicase A was demonstrated to reduce the transcriptional activity of EWS-FLI1 with disruption of cell cycle kinetics in vitro.[97] Some other agents targeting Poly (ADP-ribose) polymerase 1, protein kinase C, RANKL, GD2, and CD99 also showed certain effects in EWS. In a word, new therapeutics are required to improve the clinical outcomes and prognosis of relapsed or metastatic EWS patients, mainly through developing new molecular targeted agents and new strategies with reduced toxicity.

Alveolar soft part sarcoma

Alveolar soft part sarcoma (ASPS) is a rare neoplasm representing < 1% of all STS, and usually presents early with metastases. Alveolar soft part sarcoma is highly angiogenic, typically insensitive to standard chemotherapy and radiotherapy, thus targeted therapy is urgent for the treatment of advanced/metastatic or unresectable ASPS.[98] Shivaani et al[99] reported metastatic ASPS patients with VEGFR-1, -2, and -3 inhibitor cediranib had a disease control rate (DCR) (PR+SD) of 84% at 24 weeks, and confirmed PR was observed in four of six patients with ASPS in another study.[100] Additionally, a recent study demonstrated an effective result of cediranib in ASPS patients with a median PFS of 10.1 months.[101] Clinical efficacy of sunitinib in patients with advanced ASPS was confirmed with a median PFS of 17 months.[102] The activity of crizotinib, MET, ALK, and ROS proto-oncogene 1 receptor tyrosine kinase (ROS1) inhibitor, was confirmed to have inspiring DCR and PFR in ASPS patients.[103] VEGFR inhibitor axitinib plus pembrolizumab were demonstrated to have preliminary activity in advanced ASPS patients, with a PFR12 of 72.7%.[104] Notably, ASPS patients benefit from anlotinib significantly with a median PFS of 21 months.[9] ASPSCR1-TFE3 in the MET signaling pathway has long been demonstrated to promote proliferation and angiogenesis in ASPS, with a confirmed activity of crizotinib reported in TFE3 rearranged ASPS MET+ patients.[103,105,106] All these findings indicate the angiogenesis molecules and MET kinase inhibitors to be the promising drugs for ASPS.

Clear cell sarcoma

Clear cell sarcoma (CCS), an extremely rare and aggressive form of sarcomas, approximately comprises 1% of all sarcomas.[107] The hallmark of CCS is the genetic aberration of t (12; 22) (q13; q12) translocation, leading to the creation of EWSR1-ATF1 fusion gene.[108] Chemotherapy is poorly effective for CCS, as a result, there is still no recognized treatment standards for advanced or metastatic CCS.[109] Another characteristic of CCS is the morphological and immunohistochemical profile of melanocytic differentiation. However, Yang et al[110] found that none of the 16 CCS harbored BRAF mutations, with a significantly higher IGF-1R expression in CCS compared to melanoma. Afterward, Protsenko et al[111] reported a metastatic relapse of BRAF-mutated CCS achieved CR in lung lesions with BRAF kinase inhibitor vemurafenib. No more studies of IGF-1R or BRAF inhibitors on CCS were carried out. Preclinically, the essential role of MET was confirmed for the viability and motility of CCS.[112] And then a phase 2 trial was carried out and demonstrated a beneficial effect of crizotinib on locally advanced or metastatic MET-positive CCS, with a median PFS of 131 days which was similar to the results achieved with pazopanib in previously treated sarcoma patients.[113] These aforementioned targets are all worth to further investigate.

Inflammatory myofibroblastic tumor

Inflammatory myofibroblastic tumor (IMT) is a rare mesenchymal neoplasm characterized by myofibroblastic and fibroblastic spindle cell proliferation with inflammatory infiltration. Inflammatory myofibroblastic tumor was considered as intermediate malignancies and rarely metastasizing by the World Health Organization, and half of all diagnosed cases were mutated with the presence of an ALK rearrangement.[114] Moreover, it is reported that ROS1 fusions were discovered in ALK-negative IMTs.[115] Crizotinib, an potent ALK and ROS1 inhibitor, showed an active antitumor effect on ALK-positive or ROS1-positive IMT even in adolescents, with no response to the ALK-negative IMT.[116,117] A literature review analyzed 30 crizotinib-treated patients with IMT and showed 12 out of 30 patients achieved CR or PR.[118] Although explorative data is promising, there is not many prospective studies about evaluating the efficacy of crizotinib on ALK-positive unresectable IMT. Of note, the clinical activity of crizotinib in pediatric IMT has been documented, with an ORR of 86%.[119]

Perivascular epithelioid cell tumors

Perivascular epithelioid cell tumor (PEComa) represents a family of rare mesenchymal tumors composed of distinctive perivascular epithelioid cells with expression of myomelanocytic markers.[120] Only a small subset of PEComas behave as malignancies. The characteristic genetic alteration is the loss of heterozygosity of TSC2 gene or more rarely of TSC1 gene which negatively regulates the mTOR complex 1, leading to the activation of the mTOR pathway. In recent years, a variety of case reports showed the activity of mTOR inhibitors in PEComas.[121-123] A most recent retrospective study aimed to clarify the activity of chemotherapy, and molecular targeted agents in advanced or metastatic PEComas showed a durable benefit of mTOR inhibitors.[124] Due to the promising efficacy of mTOR inhibitors observed in advanced PEComas, prospective studies are warranted. Recently, nab-sirolimus, nanoparticle albumin-bound mTOR inhibitor, was reported to be effective in advanced malignant PEComa with manageable toxicities, with an ORR and DCR of 39% and 71%, respectively, representing an important novel treatment option.[125]

Dermatofibrosarcoma protuberans

Dermatofibrosarcoma protuberans (DFSP), the most common dermal neoplasm, is a malignant fibroblastic tumor with a high rate of local recurrence and a low risk of metastasis.[126] The first option for localized DFSP is wide surgical resection or Mohs micrographic surgery (MMS), and the recurrence rates by MMS have been reported at 0% to 8.3%.[127] Conventional chemotherapy was ineffective in DFSP.[128] Hence, better treatment option is needed for those metastatic DFSP. The PDGFRB inhibitor imatinib showed a significant antitumor activity in locally advanced or metastatic DFSP.[129,130] A pooled analysis of two phase II clinical trials demonstrated that 11 of 24 DFSP patients with imatinib (45.9%) achieved PR, with median time to progression of 1.7 years.[131] Moreover, it was reported that a patient without t (17; 22) translocation did not respond to imatinib. Imatinib was approved as first-line therapy for advanced or metastatic DFSP, although primary resistance and secondary resistance could occur. Thus, more efforts should be taken to explore the resistance mechanisms and develop new therapeutic strategies for imatinib-resistant DFSP.

Malignant peripheral nerve sheath tumor

Malignant peripheral nerve sheath tumor (MPNST) is a rare neoplasm arising associated in a peripheral nerve or preexisting plexiform neurofibromas, accounting for approximately 5%–10% of all sarcomas.[132] Half of all MPNSTs are developed in patients with neurofibromatosis type 1 (NF1), with mutations of Neurofibromin 1 gene and TP53.[133] Kroep et al reported a response rate of 21%, with a median PFS and OS of 17 weeks and 48 weeks, respectively, in unresectable or metastatic MPNSTs with chemotherapy, which was similar with the outcomes of other histological subtype STSs.[134] Based on the preclinical findings that mTOR activation can be induced by NF1 inactivation, several mTOR inhibitors for MPNST has entered clinical trials and is currently ongoing (NCT02584647). Moreover, the antitumor effect of erlotinib on MPNST has been proven in vivo and in vitro, but there is no clinical activity observed (NCT00068367).[135,136] Despite promising preclinical activity of sirolimus in combination with ganetespib on MPNST, no responses were observed.[137] It is confusing that the clinical activity of mTOR inhibitors on MPNST did match the preclinical results, there is much more to discover potential targets.

Epithelioid sarcoma

Epithelioid sarcoma (ES) is a high-grade and highly aggressive STS of unknown histogenesis, displaying multidirectional differentiation that is predominantly epithelial.[138] Epithelioid sarcoma is prospectively treated with systemic therapy, and it was reported that the median PFS and OS for ES patients were lower as compared with STSs, indicating a poorer prognosis of ES than other STSs although the response to treatment was equivalent.[139] It was demonstrated that the interaction between inactivation of INI-1 and upregulation of EZH2 leads to ES tumorigenesis.[140] Tazemetostat, an oral selective inhibitor of the histone methyltransferase enhancer of EZH2, achieved a median PFS and median OS of 5.5 months and 19 months, respectively, in advanced epithelioid sarcoma with loss of INI-1/SMARCB-1.[141] Now, tazemetostat was approved as the first-line treatment for ES and identified to potentially enhance immune checkpoint

inhibition in combination preclinically.[142,143] Such combination is worthy of thorough exploring and investigation.

Desmoid tumor

Desmoid tumor (DT), also known as aggressive desmoid-type fibromatosis, is an invasive, non-metastasizing STS derived from mesenchymal progenitor cells.[144] There are two major types of DT based on etiology, sporadic DT and familial adenomatous polyposis-associated DT. Although the prognosis is relatively good, the clinical behavior of DT is highly variable, which requires constant multidisciplinary management. Imatinib was the first TKI utilized for treating progressive DT and showed a favorable result with an ORR of 10%–15% and a DCR of up to 70% at 6 months, especially effective on patients with S45F mutation of CTNNB1.[145,146] Sorafenib has a better efficacy than imatinib, with a response rate of 25% reported by a retrospective study of 26 DT patients.[147] More convinced results were observed in a double-blind phase 3 trial, reporting a 2-year PFR of 81% and ORR of 33%.[148] Given that DT is specifically driven by Wnt/β-catenin pathways, the inhibitors tegavivint are believed to be the expected therapeutic strategies, and the phase 1 trial currently is active (NCT03459469). Moreover, Notch-signaling pathway was also elucidated to be an essential regulator of embryonic development, and several Gamma-secretase inhibitors (GSIs) targeting Notch showed inspiring results in patients with DT.[149,150]

Tenosynovial giant cell tumor/pigmented villonodular synovitis

Tenosynovial giant cell tumor (TGCT), characterized by rearrangements of the macrophage colony-stimulating factor 1 (CSF1) gene, is a locally aggressive tumor arising from synovium of joints, bursae, or tendon sheaths.[151] Pigmented villonodular synovitis (PVNS), also known as diffuse type of this disease, is a synonym for the intra-articular form, and the extra-articular, localized variant is commonly called giant cell tumor of tendon sheath. Imatinib was reported to induce CRs in a relapsing PVNS/TGCT, providing a therapeutic option for advanced or unresectable PVNS/TGCT.[152] Another multicenter study of imatinib with 27 eligible advanced and/or metastatic TGCT/PVNS patients showed stable disease in 74% of patients, with one CR and 4 PRs.[153] Moreover, imatinib also showed an activity on patients with nilotinib-resistant PVNS.[154] In 2018, a phase 2, single-arm study with 51 advanced PVNS patients reported that 92.6% patients achieved stable disease with 12 week-treatment nilotinib.[155] Pexidartinib is a novel TKI targeting CSF1 receptor, and recently showed an overall response rate of 53% with a robust tumor response in advanced TGCT.[156] Although the mixed and cholestatic hepatotoxicity of pexidartinib was identified, it is manageable, and pexidartinib is the preferred regimens for TGCT/PVNS according to the latest NCCN guidelines for soft tissue sarcoma.

Future directions and conclusions

For the rarity and heterogeneities, the best treatment option for most subtypes of advanced sarcomas is still not clearly defined, and less attention was paid by researchers in this area. Thus, more efforts are required on the preclinical and clinical research for specific subtypes of STSs to investigate the appropriate treatment options. The inspiring results of targeted therapy in other solid tumors expand the studies utilizing this therapy for STS. Some TKIs for other disease indications were empirically tested in STS further in subtypes from basic research to clinical trials and achieved inspiring results, such as pazopanib and anlotinib which were used for treatment of renal cell carcinoma and non-small cell lung cancer, respectively. For this reason, the efficacy of some drugs for other indications were encouraged to be investigated in STS. An increasing body of researches reveal the pathogenesis and drug targets of STS, which strongly promote the investigation of drugs for targeted therapy. A great part of STS is involved in histotype-specific genetic or chromosome alterations, and their downstream molecules are mostly transcriptional factors which are difficult to be developed as therapeutic targets.

Furthermore, some molecule inhibitors in combination with chemotherapy or immunotherapy showed an enhanced efficacy in patients with STS compared to a single-agent therapy. In theory, targeted agents function on inducing rapid cancer cell death and the subsequent release of neoantigens, which in turn affects immune pathways and enhances the efficacy of checkpoint inhibitor treatment.[157] As the primary agents for targeted therapy, antiangiogenic agents improve the responsiveness with normalization of the abnormal vasculature and the increase of infiltration of immune effector cells, and then transform the immunosuppressive tumor microenvironment into the immunosupportive.[158] Moreover, pruning of vessels with antiangiogenic agents may worsen hypoxia, with the tumor progression via increased migration and inflammation, partially owing to the reduced delivery and efficacy of agents.[159,160] Thus, judicious dose of antiangiogenic agents can lead to the reduced vascular permeability, interstitial fluid pressure, and improved tumor perfusion, resulting in the enhanced antitumor immunity.[159-162] Recently, two combinations, nivolumab plus sunitinib and axitinib plus pembrolizumab, both showed an inspiring ORR in several subtype of advanced STS.[104,163] And now, combined targeted therapy with immunotherapy is the most promising treatment strategy. But most of all, the indications, standard protocol, time-window and appropriate dose of antiangiogenic agents for each type of STS still remain to be explored.

Aside from the combinational therapy, presurgical targeted therapy appears to be feasible. TKI was the most studied targeted agent for presurgical targeted therapy and applied in the treatment of renal cell carcinoma and breast cancer.[164-168] Favorable results were demonstrated by these case reports and retrospective studies, including tumor or thrombus shrinkage and lower recurrence rates, with deceased surgical difficulty.

Of note, in the aforementioned studies, presurgical targeted therapy was mostly utilized in the treatment of patients with advanced cancer, which was believed to be beneficial for both primary tumorectomy and metastasectomy. As for breast cancer, a systematic review illuminated that patients with HER2-positive breast cancer and HER2-negative breast cancer had significant increased pathologic and clinical CR, overall response with neoadjuvant treatment of trastuzumab and bevacizumab, respectively.[168] However, there is no obvious increase of breast conserving surgery rates was observed. Additionally, the risk for specific wound-related complications was reported to be increased but not severe complications. There are few studies about presurgical targeted therapy applied in sarcomas. Much remains to be explored, though, including but not limited to, about standardizing indications, protocols, the time-window for treatment.

In summary, targeted therapy in treatment of STS has achieved successes in a variety of subtypes. However, the clinical benefits are limited in some sarcomas with no specific therapeutic targets. Moreover, treatment resistance is still difficult to overcome, thus combinational therapy is a new approach to manage. The focal point should be on the investigation of critical molecules and driver oncogenes for the tumorigenesis to develop novel agents and guide therapy. Additionally, due to the difference of gene mutations between primary and metastatic lesions, more efforts should be made to clarify the mechanisms to guide therapy. Prospective and multicenter studies are required for the specific subtypes of STS for its important instruction significance. The targeted therapy currently cannot answer the expectations for the treatment of STS, there is much left to explore, both preclinically and clinically.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) (No. 2017-I2M-1-005); the Capital Characterized Clinical Application Research Fund of Beijing Municipal Science and Technology Commission of China (No. Z171100001017210); the Beijing Hope Run Special Fund of Cancer Foundation of China (No. LC2016L01); and the National Natural Science Foundation of China (No.82002848).

Ethical Approval

Our study did not require an ethical board approval because it did not contain human or animal trials.

ORCID iDs

Xiaoyang Li https://orcid.org/0000-0001-8316-3013
Shengji Yu https://orcid.org/0000-0002-8994-0562

References

1. Gamboa AC, Gronchi A, Cardona K. Soft-tissue sarcoma in adults: an update on the current state of histiotype-specific management in an era of personalized medicine. *CA Cancer J Clin*. 2020;70:200-229. doi:10.3322/caac.21605.
2. Meyer M, Seetharam M. First-line therapy for metastatic soft tissue sarcoma. *Curr Treat Options Oncol*. 2019;20:6. doi:1007/s11864-019-0606-9.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70:7-30. doi:10.3322/caac.21590.
4. Howlader NNA, Krapcho M, Miller D, et al, eds. *SEER Cancer Statistics Review*. Bethesda, MD: National Cancer Institute; 1975-2018. https://seer.cancer.gov/csr/1975_2018/ April, 2021.based on November 2020 SEER data submission, posted to the SEER web site
5. Issels RD, Lindner LH, Verweij J, et al. Effect of neoadjuvant chemotherapy plus regional hyperthermia on long-term outcomes among patients with localized high-risk soft tissue sarcoma: The EORTC 62961-ESHO 95 randomized clinical trial. *JAMA Oncol*. 2018;4:483-492. doi:10.1001/jamaoncol.2017.4996.
6. Gronchi A, Ferrari S, Quagliuolo V, et al. Histotype-tailored neoadjuvant chemotherapy versus standard chemotherapy in patients with high-risk soft-tissue sarcomas (ISG-STS 1001): an international, open-label, randomised, controlled, phase 3, multicentre trial. *Lancet Oncol*. 2017;18:812-822. doi:10.1016/s1470-2045(17)30334-0.
7. Judson I, Verweij J, Gelderblom H, et al. Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: a randomised controlled phase 3 trial. *Lancet Oncol*. 2014;15:415-423. doi:10.1016/s1470-2045(14)70063-4.
8. Tsimberidou AM. Targeted therapy in cancer. *Canc Chemother Pharmacol*. 2015;76:1113-1132. doi:10.1007/s00280-015-2861-1.
9. Chi Y, Fang Z, Hong X, et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. *Clin Cancer Res*. 2018;24:5233-5238. doi:10.1158/1078-0432.CCR-17-3766.
10. Zhao Y, Adjei AA. Targeting angiogenesis in cancer therapy: moving beyond vascular endothelial growth factor. *Oncol*. 2015;20:660-673. doi:10.1634/theoncologist.2014-0465.
11. Papadopoulos N, Lennartsson J. The PDGF/PDGFR pathway as a drug target. *Mol Aspects Med*. 2018;62:75-88. doi:10.1016/j.mam.2017.11.007.
12. Boudou-Rouquette P, Tlemsani C, Blanchet B, et al. Clinical pharmacology, drug-drug interactions and safety of pazopanib: a review. *Expert Opin Drug Metab Toxicol*. 2016;12:1433-1444. doi:10.1080/17425255.2016.1225038.
13. Hua H, Kong Q, Zhang H, Wang J, Luo T, Jiang Y. Targeting mTOR for cancer therapy. *J Hematol Oncol*. 2019;12:71. doi:10.1186/s13045-019-0754-1.

14. Janssen JA, Varewijck AJ. IGF-IR targeted therapy: past, present and future. *Front Endocrinol*. 2014;5:224. doi:10.3389/fendo.2014.00224.
15. Shapiro GI. Cyclin-dependent kinase pathways as targets for cancer treatment. *J Clin Oncol*. 2006;24:1770-1783. doi:10.1200/JCO.2005.03.7689.
16. Guo R, Luo J, Chang J, Rekhtman N, Arcila M, Drilon A. MET-dependent solid tumours - molecular diagnosis and targeted therapy. *Nat Rev Clin Oncol*. 2020;17:569-587. doi:10.1038/s41571-020-0377-z.
17. Abbaspour Babaei M, Kamalidehghan B, Saleem M, Huri HZ, Ahmadipour F. Receptor tyrosine kinase (c-Kit) inhibitors: a potential therapeutic target in cancer cells. *Drug Des Devel Ther*. 2016;10:2443-2459. doi:10.2147/DDDT.S89114.
18. Crago AM, Brennan MF. Principles in management of soft tissue sarcoma. *Adv Surg*. 2015;49:107-122. doi:10.1016/j.yasu.2015.04.002.
19. Schöffski P, Chawla S, Maki RG, et al. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2016;387:1629-1637. doi:10.1016/s0140-6736(15)01283-0.
20. Demetri GD, von Mehren M, Jones RL, et al. Efficacy and safety of trabectedin or dacarbazine for metastatic liposarcoma or leiomyosarcoma after failure of conventional chemotherapy: results of a phase III randomized multicenter clinical trial. *J Clin Oncol*. 2016;34:786-793. doi:10.1200/JCO.2015.62.4734.
21. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646-674. doi:10.1016/j.cell.2011.02.013.
22. Binh MB, Sastre-Garau X, Guillou L, et al. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. *Am J Surg Pathol*. 2005;29:1340-1347. doi:10.1097/01.pas.0000170343.09562.39.
23. Dickson MA, Tap WD, Keohan ML, et al. Phase II trial of the CDK4 inhibitor PD0332991 in patients with advanced CDK4-amplified well-differentiated or dedifferentiated liposarcoma. *J Clin Oncol*. 2013;31:2024-2028. doi:10.1200/JCO.2012.46.5476.
24. Dickson MA, Schwartz GK, Keohan ML, et al. Progression-free survival among patients with well-differentiated or dedifferentiated liposarcoma treated with cdk4 inhibitor palbociclib: a phase 2 clinical trial. *JAMA Oncol*. 2016;2:937-940. doi:10.1001/jamaoncol.2016.0264.
25. Dickson MA, Koff A, D'Angelo SP, et al. Phase 2 study of the CDK4 inhibitor abemaciclib in dedifferentiated liposarcoma. *Jco*. 2019;37:11004. doi:10.1200/JCO.2019.37.15_suppl.11004.
26. Mahmood ST, Agresta S, Vigil CE, et al. Phase II study of sunitinib malate, a multitargeted tyrosine kinase inhibitor in patients with relapsed or refractory soft tissue sarcomas. Focus on three prevalent histologies: leiomyosarcoma, liposarcoma and malignant fibrous histiocytoma. *Int J Cancer*. 2011;129:1963-1969. doi:10.1002/ijc.25843.
27. Samuels BL, Chawla SP, Somaiah N, et al. Results of a prospective phase 2 study of pazopanib in patients with advanced intermediate-grade or high-grade liposarcoma. *Cancer*. 2017;123:4640-4647. doi:10.1002/cncr.30926.
28. Riedel RF, Ballman KV, Lu Y, et al. A randomized, double-blind , placebo-controlled, phase II study of regorafenib versus placebo in advanced/metastatic, treatment-refractory liposarcoma: results from the sarc024 study.*The Oncol*. 2020;25:e1655-e1662. doi:10.1634/theoncologist.2020-0679.
29. Dolatabadi S, Jonasson E, Lindén M, et al. JAK-STAT signalling controls cancer stem cell properties including chemotherapy resistance in myxoid liposarcoma. *Int J Cancer*. 2019;145:435-449. doi:10.1002/ijc.32123.
30. Stacchiotti S, Van Tine BA. Synovial sarcoma: current concepts and future perspectives. *J Clin Oncol*. 2018;36:180-187. doi:10.1200/jco.2017.75.1941.
31. Guillou L, Benhattar J, Bonichon F, et al. Histologic grade, but not SYT-SSX fusion type, is an important prognostic factor in patients with synovial sarcoma: a multicenter, retrospective analysis. *J Clin Oncol*. 2004;22:4040-4050. doi:10.1200/JCO.2004.11.093.
32. Sleijfer S, Ray-Coquard I, Papai Z, et al. Pazopanib, a multikinase angiogenesis inhibitor, in patients with relapsed or refractory advanced soft tissue sarcoma: a phase II study from the European organisation for research and treatment of cancer-soft tissue and bone sarcoma group (EORTC study 62043). *J Clin Oncol*. 2009;27:3126-3132. doi:10.1200/jco.2008.21.3223.
33. van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2012;379:1879-1886. doi:10.1016/s0140-6736(12)60651-5.
34. Mir O, Brodowicz T, Italiano A, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol*. 2016;17:1732-1742. doi:10.1016/s1470-2045(16)30507-1.
35. Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. *J Clin Oncol*. 2009;27:3133-3140. doi:10.1200/jco.2008.20.4495.
36. Vincenzi B, Silletta M, Schiavon G, et al. Sorafenib and dacarbazine in soft tissue sarcoma: a single institution experience. *Expert Opin Investig Drugs*. 2013;22:1-7. doi:10.1517/13543784.2013.742886.
37. D'Adamo DR, Dickson MA, Keohan ML, et al. A phase ii trial of sorafenib and dacarbazine for leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors. *Oncol*. 2019;24:857-863. doi:10.1634/theoncologist.2018-0160.
38. Xie L, Guo W, Wang Y, Yan T, Ji T, Xu J. Apatinib for advanced sarcoma: results from multiple institutions' off-label use in China. *BMC Canc*. 2018;18:396. doi:10.1186/s12885-018-4303-z.
39. Liao Z, Li F, Zhang C, et al. Phase II trial of VEGFR2 inhibitor apatinib for metastatic sarcoma: focus on efficacy and safety. *Exp Mol Med*. 2019;51:1-11. doi:10.1038/s12276-019-0221-7.
40. Schöffski P, Adkins D, Blay JY, et al. An open-label, phase 2 study evaluating the efficacy and safety of the anti-IGF-1R

antibody cixutumumab in patients with previously treated advanced or metastatic soft-tissue sarcoma or Ewing family of tumours. *Eur J Cancer*. 2013;49:3219-3228. doi:10.1016/j.ejca.2013.06.010.
41. Wilson BG, Wang X, Shen X, et al. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. *Canc Cell*. 2010;18:316-328. doi:10.1016/j.ccr.2010.09.006.
42. Kadoch C, Crabtree GR. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. *Cell*. 2013;153:71-85. doi:10.1016/j.cell.2013.02.036.
43. Shen JK, Cote GM, Gao Y, et al. Targeting EZH2-mediated methylation of H3K27 inhibits proliferation and migration of synovial sarcoma in vitro. *Sci Rep*. 2016;6:25239-32016. doi:10.1038/srep25239.
44. Kawano S, Grassian AR, Tsuda M, et al. Preclinical evidence of anti-tumor activity induced by EZH2 inhibition in human models of synovial sarcoma. *PloS One*. 2016;11:e0158888. doi:10.1371/journal.pone.0158888.
45. Vlenterie M, Hillebrandt-Roeffen MH, Schaars EW, et al. Targeting cyclin-dependent kinases in synovial sarcoma: palbociclib as a potential treatment for synovial sarcoma patients. *Ann Surg Oncol*. 2016;23:2745-2752. doi:10.1245/s10434-016-5341-x.
46. Serrano C, George S. Leiomyosarcoma. *Hematol Oncol Clin N Am*. 2013;27:957-974. doi:10.1016/j.hoc.2013.07.002.
47. Santoro A, Comandone A, Basso U, et al. Phase II prospective study with sorafenib in advanced soft tissue sarcomas after anthracycline-based therapy. *Ann Oncol*. 2013;24:1093-1098. doi:10.1093/annonc/mds607.
48. Hernando E, Charytonowicz E, Dudas ME, et al. The AKT-mTOR pathway plays a critical role in the development of leiomyosarcomas. *Nat Med*. 2007;13:748-753. doi:10.1038/nm1560.
49. Chawla SP, Staddon AP, Baker LH, et al. Phase II study of the mammalian target of rapamycin inhibitor ridaforolimus in patients with advanced bone and soft tissue sarcomas. *J Clin Oncol*. 2012;30:78-84. doi:10.1200/jco.2011.35.6329.
50. Okuno S, Bailey H, Mahoney MR, et al. A phase 2 study of temsirolimus (CCI-779) in patients with soft tissue sarcomas: a study of the Mayo phase 2 consortium (P2C). *Cancer*. 2011;117:3468-3475. doi:10.1002/cncr.25928.
51. Schwartz GK, Tap WD, Qin LX, et al. Cixutumumab and temsirolimus for patients with bone and soft-tissue sarcoma: a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2013;14:371-382. doi:10.1016/s1470-2045(13)70049-4.
52. Savina M, Le Cesne A, Blay JY, et al. Patterns of care and outcomes of patients with METAstatic soft tissue SARComa in a real-life setting: the METASARC observational study. *BMC Med*. 2017;15:78. doi:78.2017/04/1110.1186/s12916-017-0831-7.
53. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017;18:1493-1501. doi:10.1016/s1470-2045(17)30624-1.
54. Dasgupta R, Fuchs J, Rodeberg D. Rhabdomyosarcoma. *Semin Pediatr Surg*. 2016;25:276-283. doi:10.1053/j.sempedsurg.2016.09.011.
55. Ruiz-Mesa C, Goldberg JM, Coronado Munoz AJ, Dumont SN, Trent JC. Rhabdomyosarcoma in adults: new perspectives on therapy. *Curr Treat Options Oncol*. 2015;16:27. doi:10.1007/s11864-015-0342-8.
56. Kashi VP, Hatley ME, Galindo RL. Probing for a deeper understanding of rhabdomyosarcoma: insights from complementary model systems. *Nat Rev Cancer*. 2015;15:426-439. doi:10.1038/nrc3961.
57. Geoerger B, Kieran MW, Grupp S, et al. Phase II trial of temsirolimus in children with high-grade glioma, neuroblastoma and rhabdomyosarcoma. *Eur J Cancer*. 2012;48:253-262. doi:10.1016/j.ejca.2011.09.021.
58. Wagner LM, Fouladi M, Ahmed A, et al. Phase II study of cixutumumab in combination with temsirolimus in pediatric patients and young adults with recurrent or refractory sarcoma: a report from the children's oncology group. *Pediatr Blood Cancer*. 2015;62:440-444. doi:10.1002/pbc.25334.
59. Mascarenhas L, Chi YY, Hingorani P, et al. Randomized phase II trial of bevacizumab or temsirolimus in combination with chemotherapy for first relapse rhabdomyosarcoma: a report from the children's oncology group. *J Clin Oncol*. 2019;37:2866-2874. doi:10.1200/JCO.19.00576.
60. Antonescu C. Malignant vascular tumors–an update. *Mod Pathol*. 2014;27 Suppl 1:S30-S38. doi:10.1038/modpathol.2013.176.
61. Koontz BF, Miles EF, Rubio MA, et al. Preoperative radiotherapy and bevacizumab for angiosarcoma of the head and neck: two case studies. *Head Neck*. 2008;30:262-266.
62. Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. *Ann Oncol*. 2013;24:257-263. doi:10.1093/annonc/mds237.
63. Yoo C, Kim JE, Yoon SK, et al. Angiosarcoma of the retroperitoneum: report on a patient treated with sunitinib. *Sarcoma*. 2009;2009:360875. doi:10.1155/2009/360875.
64. Silva E, Gatalica Z, Vranic S, Basu G, Reddy SK, Voss A. Refractory angiosarcoma of the breast with VEGFR2 upregulation successfully treated with sunitinib. *Breast J*. 2015;21:205-207. doi:10.1111/tbj.12380.
65. Ray-Coquard I, Italiano A, Bompas E, et al. Sorafenib for patients with advanced angiosarcoma: a phase II Trial from the French Sarcoma Group (GSF/GETO). *Oncol*. 2012;17:260-266. doi:10.1634/theoncologist.2011-0237.
66. von Mehren M, Rankin C, Goldblum JR, et al. Phase 2 southwest oncology group-directed intergroup trial (S0505) of sorafenib in advanced soft tissue sarcomas. *Cancer*. 2012;118:770-776. doi:10.1002/cncr.26334.
67. Kollár A, Jones RL, Stacchiotti S, et al. Pazopanib in advanced vascular sarcomas: an EORTC Soft Tissue and Bone Sarcoma Group (STBSG) retrospective analysis. *Acta Oncol*. 2017;56:88-92. doi:10.1080/0284186X.2016.1234068.

68. Ogata D, Yanagisawa H, Suzuki K, Oashi K, Yamazaki N, Tsuchida T. Pazopanib treatment slows progression and stabilizes disease in patients with taxane-resistant cutaneous angiosarcoma. *Med Oncol*. 2016;33:116. doi:10.1007/s12032-016-0831-z.
69. Yoo KH, Kim ST, Lee J, Park SH, Kim SJ, Kim HS. The role of pazopanib in various histologic subtypes of metastatic soft tissue sarcomas. *JCO*. 2014;32:10586. doi:10.1200/jco.2014.32.15_suppl.10586.
70. Yoo C, Lee J, Rha SY, et al. Multicenter phase II study of everolimus in patients with metastatic or recurrent bone and soft-tissue sarcomas after failure of anthracycline and ifosfamide. *Invest New Drugs*. 2013;31:1602-1608. doi:10.1007/s10637-013-0028-7.
71. Guo T, Zhang L, Chang NE, Singer S, Maki RG, Antonescu CR. Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. *Genes Chromosomes Cancer*. 2011;50:25-33. doi:10.1002/gcc.20827.
72. Antonescu CR, Yoshida A, Guo T, et al. KDR activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors. *Cancer Res*. 2009;69:7175-7179. doi:10.1158/0008-5472.CAN-09-2068.
73. Yang L, Liu L, Han B, Han W, Zhao M. Apatinib treatment for KIT- and KDR-amplified angiosarcoma: a case report. *BMC Canc*. 2018;18:618. doi:10.1186/s12885-018-4523-2.
74. Olson NJ, Linos K. Dedifferentiated solitary fibrous tumor: a concise review. *Arch Pathol Lab Med*. 2018;142:761-766. doi:10.5858/arpa.2016-0570-RS.
75. Kirn DH, Kramer A. Long-term freedom from disease progression with interferon alfa therapy in two patients with malignant hemangiopericytoma. *J Natl Cancer Inst*. 1996;88:764-765.
76. Lackner H, Urban C, Dornbusch HJ, Schwinger W, Kerbl R, Sovinz P. Interferon alfa-2a in recurrent metastatic hemangiopericytoma. *Med Pediatr Oncol*. 2003;40:192-194.
77. Hatva E, Böhling T, Jääskeläinen J, Persico MG, Haltia M, Alitalo K. Vascular growth factors and receptors in capillary hemangioblastomas and hemangiopericytomas. *Am J Pathol*. 1996;148:763-775.
78. Stacchiotti S, Negri T, Libertini M, et al. Sunitinib malate in solitary fibrous tumor (SFT). *Ann Oncol*. 2012;23:3171-3179. doi:10.1093/annonc/mds143.
79. Valentin T, Fournier C, Penel N, et al. Sorafenib in patients with progressive malignant solitary fibrous tumors: a subgroup analysis from a phase II study of the French sarcoma group (GSF/GETO). *Invest New Drugs*. 2013;31:1626-1627. doi:10.1007/s10637-013-0023-z.
80. Park MS, Patel SR, Ludwig JA, et al. Activity of temozolomide and bevacizumab in the treatment of locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor. *Cancer*. 2011;117:4939-4947. doi:10.1002/cncr.26098.
81. Levard A, Derbel O, Méeus P, et al. Outcome of patients with advanced solitary fibrous tumors: the centre Léon Bérard experience. *BMC Canc*. 2013;13:109. doi:10.1186/1471-2407-13-109.
82. Maruzzo M, Martin-Liberal J, Messiou C, et al. Pazopanib as first line treatment for solitary fibrous tumours: the Royal Marsden Hospital experience. *Clin Sarcoma Res*. 2015;5:5. doi:5.2015/02/1110.1186/s13569-015-0022-2.
83. Ebata T, Shimoi T, Bun S, et al. Efficacy and safety of pazopanib for recurrent or metastatic solitary fibrous tumor. *Oncology*. 2018;94:340-344. doi:10.1159/000486623.
84. Schuetze SM, Bolejack V, Choy E, et al. Phase 2 study of dasatinib in patients with alveolar soft part sarcoma, chondrosarcoma, chordoma, epithelioid sarcoma, or solitary fibrous tumor. *Cancer*. 2017;123:90-97. doi:10.1002/cncr.30379.
85. Balamuth NJ, Womer RB. Ewing's sarcoma. *Lancet Oncol*. 2010;11:184-192.
86. Esiashvili N, Goodman M, Marcus RB Jr. Changes in incidence and survival of Ewing sarcoma patients over the past 3 decades: surveillance epidemiology and end results data. *J Pediatr Hematol Oncol*. 2008;30:425-430. doi:2008/06/0610.1097/MPH.0b013e31816e22f3.
87. Subbiah V, Anderson P, Lazar AJ, Burdett E, Raymond K, Ludwig JA. Ewing's sarcoma: standard and experimental treatment options. *Curr Treat Options Oncol*. 2009;10:126-140. doi:10.1007/s11864-009-0104-6.
88. Cotterill SJ, Ahrens S, Paulussen M, et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from the European Intergroup Cooperative Ewing's sarcoma study group. *J Clin Oncol*. 2000;18:3108-3114. doi:10.1200/jco.2000.18.17.3108.
89. Hunold A, Weddeling N, Paulussen M, Ranft A, Liebscher C, Jürgens H. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. *Pediatr Blood Cancer*. 2006;47:795-800. doi:10.1002/pbc.20719.
90. Casey DA, Wexler LH, Merchant MS, et al. Irinotecan and temozolomide for Ewing sarcoma: the Memorial Sloan-Kettering experience. *Pediatr Blood Cancer*. 2009;53:1029-1034. doi:10.1002/pbc.22206.
91. Fox E, Patel S, Wathen JK, et al. Phase II study of sequential gemcitabine followed by docetaxel for recurrent Ewing sarcoma, osteosarcoma, or unresectable or locally recurrent chondrosarcoma: results of sarcoma alliance for research through collaboration study 003. *Oncol*. 2012;17:321. doi:10.1634/theoncologist.2010-0265.
92. Ferrari S, del Prever AB, Palmerini E, et al. Response to high-dose ifosfamide in patients with advanced/recurrent Ewing sarcoma. *Pediatr Blood Cancer*. 2009;52:581-584. doi:10.1002/pbc.21917.
93. Luksch R, Tienghi A, Hall KS, et al. Primary metastatic Ewing's family tumors: results of the Italian sarcoma group and scandinavian sarcoma group ISG/SSG IV study including myeloablative chemotherapy and total-lung irradiation. *Ann Oncol*. 2012;23:2970-2976. doi:10.1093/annonc/mds117.

94. Naing A, LoRusso P, Fu S, et al. Insulin growth factor-receptor (IGF-1R) antibody cixutumumab combined with the mTOR inhibitor temsirolimus in patients with refractory Ewing's sarcoma family tumors. *Clin Cancer Res*. 2012;18:2625-2631. doi:10.1158/1078-0432.CCR-12-0061.
95. Italiano A, Mir O, Mathoulin-Pelissier S, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2020;21:446-455. doi:10.1016/s1470-2045(19)30825-3.
96. Guenther LM, Dharia NV, Ross L, et al. A combination cdk4/6 and igf1r inhibitor strategy for Ewing sarcoma. *Clin Cancer Res*. 2019;25:1343-1357. doi:10.1158/1078-0432.CCR-18-0372.
97. Erkizan HV, Scher LJ, Gamble SE, et al. Novel peptide binds EWS-FLI1 and reduces the oncogenic potential in Ewing tumors. *Cell Cycle*. 2011;10:3397-3408. doi:10.4161/cc.10.19.17734.
98. Soheilifar MH, Taheri RA, Zolfaghari Emameh R, Moshtaghian A, Kooshki H, Motie MR. Molecular landscape in alveolar soft part sarcoma: implications for molecular targeted therapy. *Biomed Pharmacother*. 2018;103:889-896. doi:10.1016/j.biopha.2018.04.117.
99. Kummar S, Allen D, Monks A, et al. Cediranib for metastatic alveolar soft part sarcoma. *J Clin Oncol*. 2013;31:2296-2302. doi:10.1200/JCO.2012.47.4288.
100. Judson I, Scurr M, Gardner K, et al. Phase II study of cediranib in patients with advanced gastrointestinal stromal tumors or soft-tissue sarcoma. *Clin Cancer Res*. 2014;20:3603-3612. doi:10.1158/1078-0432.CCR-13-1881.
101. Judson I, Morden JP, Kilburn L, et al. Cediranib in patients with alveolar soft-part sarcoma (CASPS): a double-blind, placebo-controlled, randomised, phase 2 trial. *Lancet Oncol*. 2019;20:1023-1034. doi:10.1016/s1470-2045(19)30215-3.
102. Stacchiotti S, Negri T, Zaffaroni N, et al. Sunitinib in advanced alveolar soft part sarcoma: evidence of a direct antitumor effect. *Ann Oncol*. 2011;22:1682-1690. doi:10.1093/annonc/mdq644.
103. Schöffski P, Wozniak A, Kasper B, et al. Activity and safety of crizotinib in patients with alveolar soft part sarcoma with rearrangement of TFE3: European organization for research and treatment of cancer (EORTC) phase II trial 90101 'CREATE'. *Ann Oncol*. 2018;29:758-765. doi:10.1093/annonc/mdx774.
104. Wilky BA, Trucco MM, Subhawong TK, et al. Axitinib plus pembrolizumab in patients with advanced sarcomas including alveolar soft-part sarcoma: a single-centre, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20:837-848. doi:10.1016/s1470-2045(19)30153-6.
105. Lazar AJ, Lahat G, Myers SE, et al. Validation of potential therapeutic targets in alveolar soft part sarcoma: an immunohistochemical study utilizing tissue microarray. *Histopathology*. 2009;55:750-755. doi:10.1111/j.1365-2559.2009.03436.x.
106. Tsuda M, Davis IJ, Argani P, et al. TFE3 fusions activate MET signaling by transcriptional up-regulation, defining another class of tumors as candidates for therapeutic MET inhibition. *Cancer Res*. 2007;67:919-929. doi:10.1158/0008-5472.CAN-06-2855.
107. Ibrahim RM, Steenstrup Jensen S, Juel J. Clear cell sarcoma-A review. *J Orthop*. 2018;15:963-966. doi:10.1016/j.jor.2018.08.039.
108. Pellín A, Monteagudo C, López-Ginés C, Carda C, Boix J, Llombart-Bosch A. New type of chimeric fusion product between the EWS and ATFI genes in clear cell sarcoma (malignant melanoma of soft parts). *Genes Chromosomes Cancer*. 1998;23:358-360. doi:10.1002/(SICI)1098-2264.
109. Jones RL, Constantinidou A, Thway K, et al. Chemotherapy in clear cell sarcoma. *Med Oncol*. 2011;28:859-863. doi:10.1007/s12032-010-9502-7.
110. Yang L, Chen Y, Cui T, et al. Identification of biomarkers to distinguish clear cell sarcoma from malignant melanoma. *Hum Pathol*. 2012;43:1463-1470. doi:10.1016/j.humpath.2011.10.022.
111. Protsenko SA, Semionova AI, Komarov YI, et al. BRAF-mutated clear cell sarcoma is sensitive to vemurafenib treatment. *Invest New Drugs*. 2015;33:1136-1143. doi:10.1007/s10637-015-0280-0.
112. Davis IJ, McFadden AW, Zhang Y, et al. Identification of the receptor tyrosine kinase c-Met and its ligand, hepatocyte growth factor, as therapeutic targets in clear cell sarcoma. *Cancer Res*. 2010;70:639-645. doi:10.1158/0008-5472.CAN-09-1121.
113. Schöffski P, Wozniak A, Stacchiotti S, et al. Activity and safety of crizotinib in patients with advanced clear-cell sarcoma with MET alterations: European organization for research and treatment of cancer phase II trial 90101 'CREATE'. *Ann Oncol*. 2017;28:3000-3008. doi:10.1093/annonc/mdx527.
114. Gleason BC, Hornick JL. Inflammatory myofibroblastic tumours: where are we now? *J Clin Pathol*. 2008;61:428-437. doi:10.1136/jcp.2007.049387.
115. Lovly CM, Gupta A, Lipson D, et al. Inflammatory myofibroblastic tumors harbor multiple potentially actionable kinase fusions. *Cancer Discov*. 2014;4:889-895. doi:10.1158/2159-8290.CD-14-0377.
116. Butrynski JE, D'Adamo DR, Hornick JL, Dal Cin P, Antonescu CR, Jhanwar SC, et al. Crizotinib in ALK-rearranged inflammatory myofibroblastic tumor. *N Engl J Med*. 2010;363:1727-1733. doi:10.1056/NEJMoa1007056.2010/10/29
117. Gaudichon J, Jeanne-Pasquier C, Deparis M, et al. Complete and repeated response of a metastatic alk-rearranged inflammatory myofibroblastic tumor to crizotinib in a teenage girl. *J Pediatr Hematol Oncol*. 2016;38:308-311.
118. Theilen TM, Soerensen J, Bochennek K, et al. Crizotinib in ALK+ inflammatory myofibroblastic tumors-Current experience and future perspectives. *Pediatr Blood Cancer*. 2018;65:12-30. doi:10.1002/pbc.26920.
119. Mossé YP, Voss SD, Lim MS, et al. Targeting ALK With crizotinib in pediatric anaplastic large cell lymphoma and inflammatory myofibroblastic tumor: a children's oncology group study. *J Clin Oncol*. 2017;35:3215-3221. doi:10.1200/jco.2017.73.4830.
120. Armah HB, Parwani AV. Perivascular epithelioid cell tumor. *Arch Pathol Lab Med*. 2009;133:648-654. doi:10.1043/1543-2165-133.4.648.

121. Kenerson H, Folpe AL, Takayama TK, Yeung RS. Activation of the mTOR pathway in sporadic angiomyolipomas and other perivascular epithelioid cell neoplasms. *Hum Pathol*. 2007;38: 1361-1371. doi:10.1016/j.humpath.2007.01.028.
122. Wagner AJ, Malinowska-Kolodziej I, Morgan JA, et al. Clinical activity of mTOR inhibition with sirolimus in malignant perivascular epithelioid cell tumors: targeting the pathogenic activation of mTORC1 in tumors. *J Clin Oncol*. 2010;28:835-840. doi:10.1200/jco.2009.25.2981.
123. Dickson MA, Schwartz GK, Antonescu CR, Kwiatkowski DJ, Malinowska IA. Extrarenal perivascular epithelioid cell tumors (PEComas) respond to mTOR inhibition: clinical and molecular correlates. *Int J Cancer*. 2013;132:1711-1717. doi:10.1002/ijc.27800.
124. Sanfilippo R, Jones RL, Blay JY, et al. Role of chemotherapy, VEGFR inhibitors, and mtor inhibitors in advanced perivascular epithelioid cell tumors (PEComas). *Clin Cancer Res*. 2019;25: 5295-5300. doi:10.1158/1078-0432.CCR-19-0288.
125. Wagner AJ. Long-term follow-up for duration of response (DoR) after weekly nab-sirolimus in patients with advanced malignant perivascular epithelioid cell tumors (PEComa): Results from a registrational open-label phase II trial, AMPECT. In: Andrew J Wagner, Dana-Farber Cancer Institute BMA, The University of Texas Md Anderson Cancer Center DoSMOHTX, et al, eds. *ASCO Virtual Scientific Program*, 2020, American Society of Clinical Oncology.
126. Acosta AE, Vélez CS. Dermatofibrosarcoma protuberans. *Curr Treat Options Oncol*. 2017;18:56. doi:1007/s11864-017-0498-5.
127. Veronese F, Boggio P, Tiberio R, et al. Wide local excision vs. Mohs Tübingen technique in the treatment of dermatofibrosarcoma protuberans: a two-centre retrospective study and literature review. *J Eur Acad Dermatol Venereol*. 2017;31: 2069-2076. doi:10.1111/jdv.14378.
128. Wunder JS, Nielsen TO, Maki RG, O'Sullivan B, Alman BA. Opportunities for improving the therapeutic ratio for patients with sarcoma. *Lancet Oncol*. 2007;8:513-524. doi:10.1016/s1470-2045(07)70169-9.
129. Rubin BP, Schuetze SM, Eary JF, et al. Molecular targeting of platelet-derived growth factor B by imatinib mesylate in a patient with metastatic dermatofibrosarcoma protuberans. *J Clin Oncol*. 2002;20:3586-3591. doi:10.1200/JCO.2002.01.027.
130. Maki RG, Awan RA, Dixon RH, Jhanwar S, Antonescu CR. Differential sensitivity to imatinib of 2 patients with metastatic sarcoma arising from dermatofibrosarcoma protuberans. *Int J Cancer*. 2002;100:623-626. doi:10.1002/ijc.10535.
131. Rutkowski P, Van Glabbeke M, Rankin CJ, et al. Imatinib mesylate in advanced dermatofibrosarcoma protuberans: pooled analysis of two phase II clinical trials. *J Clin Oncol*. 2010;28: 1772-1779. doi:10.1200/JCO.2009.25.7899.
132. James AW, Shurell E, Singh A, Dry SM, Eilber FC. Malignant peripheral nerve sheath tumor. *Surg Oncol Clin N Am*. 2016;25: 789-802. doi:10.1016/j.soc.2016.05.009.
133. Uusitalo E, Rantanen M, Kallionpää RA, et al. Distinctive cancer associations in patients with neurofibromatosis type 1. *J Clin Oncol*. 2016;34:1978-1986. doi:10.1200/JCO.2015.65.3576.
134. Kroep JR, Ouali M, Gelderblom H, et al. First-line chemotherapy for malignant peripheral nerve sheath tumor (MPNST) versus other histological soft tissue sarcoma subtypes and as a prognostic factor for MPNST: an EORTC soft tissue and bone sarcoma group study. *Ann Oncol*. 2011;22:207-214. doi:10.1093/annonc/mdq338.
135. Mahller YY, Vaikunth SS, Currier MA, et al. Oncolytic HSV and erlotinib inhibit tumor growth and angiogenesis in a novel malignant peripheral nerve sheath tumor xenograft model. *Mol Ther*. 2007;15:279-286. doi:10.1038/sj.mt.6300038.
136. Holtkamp N, Malzer E, Zietsch J, et al. EGFR and erbB2 in malignant peripheral nerve sheath tumors and implications for targeted therapy. *Neuro Oncol*. 2008;10:946-957. doi:10.1215/15228517-2008-053.
137. Kim A, Lu Y, Okuno SH, et al. Targeting refractory sarcomas and malignant peripheral nerve sheath tumors in a phase I/II study of sirolimus in combination with ganetespib (SARC023). *Sarcoma*. 2020;2020:5784876. doi:5784876.2020/02/2510.1155/2020/5784876.
138. Thway K, Jones RL, Noujaim J, Fisher C. Epithelioid sarcoma: diagnostic features and genetics. *Adv Anat Pathol*. 2016;23: 41-49. doi:10.1097/pap.0000000000000102.
139. Touati N, Schöffski P, Litière S, et al. European organisation for research and treatment of cancer soft tissue and bone sarcoma group experience with advanced/metastatic epithelioid sarcoma patients treated in prospective trials: clinical profile and response to systemic therapy. *Clin Oncol*. 2018;30:448-454. doi:10.1016/j.clon.2018.02.065.
140. Weiss MC, Agulnik M. Tazemetostat as a treatment for epithelioid sarcoma. *Expert Opinion on Orphan Drugs*. 2020;8: 311-315. doi:10.1080/21678707.2020.1809377.
141. Gounder M, Schöffski P, Jones RL, et al. Tazemetostat in advanced epithelioid sarcoma with loss of INI1/SMARCB1: an international, open-label, phase 2 basket study. *Lancet Oncol*. 2020;21:1423-1432. doi:10.1016/s1470-2045(20)30451-4.
142. Zingg D, Arenas-Ramirez N, Sahin D, et al. The Histone methyltransferase Ezh2 controls mechanisms of adaptive resistance to tumor immunotherapy. *Cell Rep*. 2017;20:854-867. doi:10.1016/j.celrep.2017.07.007.
143. Zhou L, Mudianto T, Ma X, Riley R, Uppaluri R. Targeting EZH2 enhances antigen presentation, antitumor immunity, and circumvents anti-PD-1 resistance in head and neck cancer. *Clin Cancer Res*. 2020;26:290-300. doi:10.1158/1078-0432.CCR-19-1351.
144. Wu C, Amini-Nik S, Nik-Amini S, Nadesan P, Stanford WL, Alman BA. Aggressive fibromatosis (desmoid tumor) is derived from mesenchymal progenitor cells. *Cancer Res*. 2010;70: 7690-7698. doi:10.1158/0008-5472.Can-10-1656.
145. Heinrich MC, McArthur GA, Demetri GD, et al. Clinical and molecular studies of the effect of imatinib on advanced aggressive fibromatosis (desmoid tumor). *J Clin Oncol*. 2006;24: 1195-1203. doi:10.1200/JCO.2005.04.0717.
146. Penel N, Le Cesne A, Bui BN, et al. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): an FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up. *Ann Oncol*. 2011;22:452-457. doi:10.1093/annonc/mdq341.

147. Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of Sorafenib against desmoid tumor/deep fibromatosis. *Clin Cancer Res*. 2011;17:4082-4090. doi:10.1158/1078-0432.CCR-10-3322.
148. Gounder MM, Mahoney MR, Van Tine BA, et al. Sorafenib for advanced and refractory desmoid tumors. *N Engl J Med*. 2018; 379:2417-2428. doi:10.1056/NEJMoa1805052.
149. Messersmith WA, Shapiro GI, Cleary JM, et al. A Phase I, dose-finding study in patients with advanced solid malignancies of the oral γ-secretase inhibitor PF-03084014. *Clin Cancer Res*. 2015; 21:60-67. doi:10.1158/1078-0432.CCR-14-0607.
150. Kummar S, O'Sullivan Coyne G, Do KT, et al. Clinical activity of the γ-secretase inhibitor PF-03084014 in adults with desmoid tumors (aggressive fibromatosis). *J Clin Oncol*. 2017;35: 1561-1569. doi:10.1200/JCO.2016.71.1994.
151. Al-Ibraheemi A, Ahrens WA, Fritchie K, et al. Malignant tenosynovial giant cell tumor: the true "synovial sarcoma?" a clinicopathologic, immunohistochemical, and molecular cytogenetic study of 10 cases, supporting origin from synoviocytes. *Mod Pathol*. 2019;32:242-251. doi:10.1038/s41379-018-0129-0.
152. Blay JY, El Sayadi H, Thiesse P, Garret J, Ray-Coquard I. Complete response to imatinib in relapsing pigmented villonodular synovitis/tenosynovial giant cell tumor (PVNS/TGCT). *Ann Oncol*. 2008;19:821-822. doi:10.1093/annonc/mdn033.
153. Cassier PA, Gelderblom H, Stacchiotti S, et al. Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer*. 2012;118:1649-1655. doi:10.1002/cncr.26409.
154. Stacchiotti S, Crippa F, Messina A, et al. Response to imatinib in villonodular pigmented synovitis (PVNS) resistant to nilotinib. *Clin Sarcoma Res*. 2013;3:8. doi:10.1186/2045-3329-3-8.
155. Gelderblom H, Cropet C, Chevreau C, et al. Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2018;19: 639-648. doi:10.1016/s1470-2045(18)30143-8.
156. Tap WD, Gelderblom H, Palmerini E, et al. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet*. 2019;394:478-487. doi:10.1016/s0140-6736(19)30764-0.
157. Colli LM, Machiela MJ, Zhang H, et al. Landscape of combination immunotherapy and targeted therapy to improve cancer management. *Cancer Res*. 2017;77:3666-3671. doi:10.1158/0008-5472.CAN-16-3338.
158. Fukumura D, Kloepper J, Amoozgar Z, Duda DG, Jain RK. Enhancing cancer immunotherapy using antiangiogenics: opportunities and challenges. *Nat Rev Clin Oncol*. 2018;15: 325-340. doi:10.1038/nrclinonc.2018.29.
159. Jain RK. Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med*. 2001;7:987-989. doi:10.1038/nm0901-987.
160. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic Therapy. *Science*. 2005;307:58-62. doi:10.1126/science.1104819.
161. Huang Y, Goel S, Duda DG, Fukumura D, Jain RK. Vascular normalization as an emerging strategy to enhance cancer immunotherapy. *Cancer Res*. 2013;73:2943-2948. doi:10.1158/0008-5472.CAN-12-4354.
162. Ramjiawan RR, Griffioen AW, Duda DG. Anti-angiogenesis for cancer revisited: Is there a role for combinations with immunotherapy? *Angiogenesis*. 2017;20:185-204. doi:10.1007/s10456-017-9552-y.
163. Martin-Broto J, Hindi N, Grignani G, et al. Nivolumab and sunitinib combination in advanced soft tissue sarcomas: a multicenter, single-arm, phase Ib/II trial. *J Immunother Cancer* 2020; 8:e001561. doi:10.1136/jitc-2020-001561.
164. Kondo T, Hashimoto Y, Kobayashi H, et al. Presurgical targeted therapy with tyrosine kinase inhibitors for advanced renal cell carcinoma: clinical results and histopathological therapeutic effects. *Jpn J Clin Oncol*. 2010;40:1173-1179. doi:10.1093/jjco/hyq150.
165. Okamura Y, Terakawa T, Sakamoto M, et al. Presurgical pazopanib improves surgical outcomes for renal cell carcinoma with high-level IVC tumor thrombosis. *In Vivo*. 2019;33: 2013-2019. doi:10.21873/invivo.11698.
166. Peng C, Gu L, Wang L, et al. Role of presurgical targeted molecular therapy in renal cell carcinoma with an inferior vena cava tumor thrombus. *OncoTargets Ther*. 2018;11:1997-2005. doi:10.2147/OTT.S158114.
167. Guo G, Cai W, Li H, et al. Presurgical neoadjuvant targeted molecular therapy for kidney cancer with concomitant vena cava tumor embolus: a clinical study. *Oncol Lett*. 2017;14:369-375. doi:10.3892/ol.2017.6131.
168. Pathak M, Dwivedi SN, Deo SVS, Thakur B, Sreenivas V, Rath GK. Effectiveness of added targeted therapies to neoadjuvant chemotherapy for breast cancer: a systematic review and meta-analysis. *Clin Breast Cancer*. 2019;19:e690-e700. doi:10.1016/j.clbc.2019.06.001.