Review Article



# Next frontiers in systemic therapy for soft tissue sarcoma

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**Abstract:** Soft tissue sarcoma (STS) is a heterogeneous disease with more than 50 subtypes. Once the disease reached locally advanced or metastatic status, the standard treatment remains to be chemotherapy. Current understanding of the underlying molecular and genomic mechanisms of different histology subtypes have led to encouraging development of new drugs in treating STS. Besides molecular targeted therapy, immunotherapy have also shown promising advancement in solid tumor treatments. This review will be in two parts. The first part will focus on the molecular targeted agents aiming at molecular or genetic alterations that are more specific in STS, including antiangiogenic molecules, plate-derived growth factor receptor alpha (PDGFRA) monoclonal antibody, colony-stimulating factor-1 receptor (CSF-1R), selective inhibitors of nuclear export (SINE), cyclin-dependent kinase 4/6 (CDK 4/6), mdm2, and epigenetic regulators. We also discussed in depth about how current precision medicine influences the treatment paradigm in STS. In the second part, we focus on the landscape of immunotherapy in STS including immune checkpoint inhibitors (ICIs) and the combinations of immunotherapies or with other molecules that could modulate the tumor microenvironment. These included the program cell death-1 receptor and its ligand (PD-1/PD-L1), cytotoxic T lymphocyte associated protein-4 (CTLA-4) and the combination with anti-angiogenic agents that could facilitate the trafficking of T cells. Strategies targeting the tumor-associated antigen NY-ESO-1, which is commonly observed in synovial sarcoma and myxoid round cell liposarcoma, via viral vaccines and adoptive T cells will also be discussed. These new frontiers of treatment that are developed with better insights into sarcoma and immune biology hopefully will change the treatment paradigm of advanced STS in the future.

**Keywords:** Soft tissue sarcoma (STS); molecular targeted therapy; precision medicine; immunotherapy

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## Introduction

Soft tissue sarcomas (STSs) accounts for less than 1% of all cancer, but are highly heterogeneous in terms of anatomical location, histology, molecular characteristics and prognosis (1). Approximately 50% to 60% of cases occur in the extremities. Neoadjuvant and/or adjuvant chemotherapy or radiotherapy can be given, depending on the tumor histological subtype, grade, and margin status (2,3). A 5-year distant metastasis-free survival of over 60% can be achieved (4,5). On the other hand, retroperitoneal sarcoma (RS) accounts for 15% of all STSs. Complete surgical resection with a negative margin is hard to achieve mostly because the tumor is deeply seated in the retroperitoneum adjacent to many vital organs, and oftentimes presents as multifocal disease (6). Local recurrence is the major cause of treatment

failure in RS patients, and although retrospective study suggested radiation may play a role in disease control (7), the result of the prospective clinical trial [Surgery With or Without Radiation Therapy in Untreated Nonmetastatic Retroperitoneal Sarcoma (STRASS); NCT01344018] to understand the role of radiotherapy in improving local control of RS patients is highly anticipated.

For metastatic disease, chemotherapy is still the mainstream therapy. Single agent anthracycline is the standard first-line therapy, with a median overall survival around 12 to 14 months. Combination with ifosfamide may improve response rate but is associated with excessive toxicities (8). Gemcitabine plus docetaxel may be an alternative option (9). For the second line treatment, eribulin and trabectedin have demonstrated efficacy in liposarcoma (LPS) and leiomyosarcoma (LMS) (10,11).

Progress of the treatment of advanced STS mainly comes from the understanding of driver oncogenes. Most of the gastrointestinal stromal tumors (GISTs) contained either *c-KIT* or *PDGFRA* mutation, which can be effectively inhibited by tyrosine kinase inhibitors (TKIs) such as imatinib, sunitinib or regorafenib (12-14). On the other hand, more than 85% of inflammatory myofibroblastic tumors (IMT) harbored kinase fusions involving *ALK*, *ROS1*, or *PDGFRβ* (15). ALK inhibitor, such as crizotinib, has shown potent efficacy in this disease (16). Other examples include imatinib or sunitinib for dermatofibrosarcoma protuberans harboring t (17;22) (q22;q13.1) translocation with resultant fusion gene *COL1A1-PDGFB* (17), or mTOR inhibitor for perivascular epithelioid cell tumor (PEComa) family with deletion or under-expression of TSC1 or TSC2 (18). The new frontiers of systemic treatments in advanced STS will come from not only the search of driver oncogenes in different STS histology but also the insight of other genomic, epigenetic, and immunological niches in STS. In this review, we will discuss recently identified novel treatments in STS based on different molecular and immune system pathways (*Table 1*).

## The molecular targeted therapies

### *Anti-angiogenic therapies*

Angiogenesis is one of the important hallmarks in cancer (44). Vascular endothelial growth factor (VEGF) is considered one of the main driving molecular for angiogenesis, and thus the main target for drug development. VEGF is found to be highly expressed in many types of STS (45), and the increased VEGF or other angiogenic factors are associated with a poor prognosis (46-48). Moreover, in comparison with healthy individuals, STS patients were found to have significantly elevated VEGF serum levels (49,50). These studies hence provided the rationale for developing anti-angiogenesis therapy for STS.

The small-molecule VEGF inhibitor pazopanib is a multi-targeted TKI, with significant activity against receptor of VEGF type 1, 2, and 3 (VEGFR-1, -2, and -3), and platelet-derived growth factors (PDGFR) (51). In a stratified phase 2 clinical trial in relapsed or metastatic STS, except for LPS, it achieved a three-months progression-free rate at around 40% in nearly all types of STS (19). In a subsequent randomized phase III study of patients with STS who failed standard chemotherapy, pazopanib demonstrated a superior median progression-free survival (PFS) than placebo control (4.6 *vs.* 1.6 months). Several other VEGFR TKIs such as regorafenib and sorafenib have also showed efficacy in STSs in phase II studies (20,52).

Alveolar soft part sarcoma (ASPS) is a rare tumor accounting for less than 1% of STS and occurs primarily in young adults. It has an indolent clinical course, but is highly metastatic and frequently affects lungs, brain, and bones. In patients with advanced disease, the median survival is around 40 months and a 5-year survival rate of 20% (53,54). Standard cytotoxic chemotherapy regimens are typically ineffective (55). ASPS is associated with an unbalanced t (X,17) (p11;q25) translocation, generating a *ASPL-TFE3* chimeric transcription factor with resultant MET-related signal activation (56). Gene expression profiling of ASPS revealed upregulation of genes associated with angiogenesis as well (57). Several VEGFR TKIs have demonstrated their activities in ASPS (58,59). In a phase II study of 43 patients with metastatic, unresectable ASPS, cediranib, another VEGFR TKI, resulted in a 35% of overall response rate (ORR). The disease control rate (partial response plus stable disease at 24 weeks) was 84% (36 of 43 patients). Gene profiling study revealed downregulation of genes related to vasculogenesis after treatment (21). Anti-angiogenesis therapy has also been shown efficacy in other rare STSs, such as desmoid tumor (22,23), angiosarcoma (60) or solitary fibrous tumor/ hemangiopericytoma (24,61).

### *PDGFR-α monoclonal antibody*

Olaratumab is a fully human IgG1 antibody that selectively binds the PDGF α-receptor and blocks ligand-induced

 

**Table 1** The list of new therapeutic agents in soft tissue sarcoma with their respective therapeutic targets and preferentially-targeted histology

| Therapeutic target | Histology | Drug name | References |
|---|---|---|---|
| Molecular targeted agents | | | |
| VEGFR | Various STS histologies | Pazopanib | (19) |
| | Various STS histologies | Regorafenib | (20) |
| | Alveolar soft part sarcoma | Cediranib | (21) |
| | Desmoid tumor | Sorafenib, pazopanib | (22,23) |
| | Solitary fibrous tumor | Sunitinib | (24) |
| mTOR | PEComa | Sirolimus, everolimus | (18) |
| PDGFR-α | Various STS histology | Olaratumab | (25) |
| CSF-1R | Tenosynovial giant cell tumor | Pexidartinib | (26,27) |
| Exportin-1 (XPO-1) | Liposarcoma | Selinexor | (28) |
| CDK 4/6 | Liposarcoma | Palbociclib | (29) |
| MDM2 | Liposarcoma<br>TP53 wild type tumor | HDM201, DS3032-b | (30-32) |
| EZH2 | Epithelioid sarcoma | Tazemetostat | (33) |
| COL1A1/PDGF-β fusion protein | Dermatofibrosarcoma protuberans | Imatinib | (17) |
| NTRK fusion protein | NTRK-fusion gene-positive cancers, including infantile fibrosarcoma | Larotrectinib, entrectinib | (34-36) |
| ALK fusion protein | Inflammatory myofibroblastic tumor | Crizotinib | (16) |
| BRAF V600E | Clear cell sarcoma (with BRAF V600E mutation) | Vemurafenib | (37) |
| Immunotherapy | | | |
| Immune checkpoint inhibitors (PD-1/PD-L1/CTLA-4) | Various STS histologies (no specific biomarkers) | Pembrolizumab (PD-1), nivolumab (PD-1), ipilimumab (CTLA-4) | (38,39) |
| Tumor-associated antigen (NY-ESO-1) | Synovial sarcoma, myxoid liposarcoma | CMB305 [third generation lentiviral vaccine (LV305) with adjuvant TLR4 agonist (G305)] | (40,41) |
| | Synovial sarcoma | Adoptive T cell | (42,43) |

CDK, cyclin-dependent kinase; CSF-1R, colony stimulating factor-1 receptor; CTLA-4, cytotoxic T lymphocyte associated antigen-4; EZH2, enhancer of zeste homolog 2; MDM2, murine double minute-2; mTOR, mammalian target of rapamycin; NTRK, neurotrophic tyrosine kinase; receptorPD-1/PD-L1, programmed cell death-1 (ligand); PDGFR-α, platelet-derived growth factor receptor-alpha; PEComa, perivascular epithelioid cell tumor; STS, soft tissue sarcoma; VEGFR, vascular endothelial growth factor receptor.

activation. Its anti-tumor activity in combination with doxorubicin has been confirmed in preclinical cancer models. Also it is generally believed that it may exert activity in modifying microenvironment (62).

In a phase Ib/II trial for olaratumab, patients were randomly assigned to receive either olaratumab plus doxorubicin or doxorubicin alone. After completion of 8 cycles of doxorubicin, patients in the olaratumab plus doxorubicin group could receive olaratumab monotherapy until disease progression, and patients in the doxorubicin group were under observation and could select to receive olaratumab monotherapy after documented disease progression. In this study, although median PFS was improved by only 2.5 months [median PFS by investigators 6.6 *vs.* 4.1 months, hazard ratio (HR) 0.67, P=0.0615], overall survival (OS) was markedly extended by nearly 12 months with the combination (median OS 26.5 *vs.* 14.77 months, HR 0.46, P=0.003) (25). The OS survival

 

benefit were similar across subgroup analyses, including different histologies. Grade 3 or 4 neutropenia occurred more commonly in the combination arm but the rate of febrile neutropenia was similar between treatment arms (25). Although OS was the secondary endpoint in the study, the significant increase in OS led to the approval of the combination of doxorubicin and olaratumab in the treatment of advanced STS by both the US Food and Drug Administration (FDA) and European Medical Agency (EMA). A confirmatory randomized phase III trial of the combination of doxorubicin plus olaratumab versus single agent doxorubicin is underway. The recruitment has completed and the OS result is highly anticipated.

### *Colony stimulating factor-1 receptor (CSF-1R) inhibitors*

Tenosynovial giant-cell tumors (TGCTs), also known as pigmented villonodular synovitis, is a locally invasive tumors of the joint or tendon sheath and characterized by proliferation of synoviocytes with infiltration of inflammatory cells including histiocytes and hemosiderin-laden macrophages (63). Surgical resection is the main therapeutic modality. However, for those tumors with diffuse joint involvement, destructive surgery including amputation may be necessary (64). Most of TGCTs harbored a unique t (1;2) translocation generating a fusion gene that links the *CSF1* gene on chromosome 1p13 to the *COL6A3* gene on chromosome 2q35 (65,66). Inhibition of signaling between CSF1 and CSF1 receptor (CSF1R) thus targets the underlying cause of the disease. CSF1 pathway is also associated with tumor-associated macrophages, which is also currently tested either single or in combination with other immunotherapies in solid tumors (67).

Pexidartinib (PLX3397) is a potent, selective CSF1R inhibitor that traps the kinase in an autoinhibited conformation (26). In a single-arm phase 2 study, among 23 TGCT patients, 12 patients had a partial response and 7 patients had stable disease. Responses usually occurred within the first 4 months of treatment, and the median duration of response exceeded 8 months (26). The most common adverse event is liver toxicity but most are reversible after discontinuation of the drug. In the phase III randomized study of pexidartinib versus placebo in TCGT (ENLIVEN), pexidartinib was started at 1,000 mg per day in split dose and then decreased to 800 mg per day in split dose because of concerns of liver toxicity. Tumor volume response was also a secondary endpoint in addition to standard RECIST criteria to compensate the difficulty in measuring the commonly irregular TGCT. The ORR per RECIST and volumetric criteria of pexidartinib *vs.* placebo were 39% *vs.* 0% and 56% *vs.* 0%, respectively, suggesting that using a volume-based measurement more properly detected the efficacy of treatment in TGCT. Tumor response were similar when patients in the placebo arm were crossed to the pexidartinib arm after tumor progression (27). Eight patients discontinued pexidartinib because of hepatic adverse events, and 4 cases were serious nonfatal adverse events with increased bilirubin, one lasting around 7 months (27). Outside of the TGCT treatment program, liver toxicity is also observed. Although mostly are reversible, one patient did receive liver transplantation after the treatment of pexidartinib plus paclitaxel (27). Other agents such as imatinib with CSF1R inhibition activities also have been showed efficacy in treating TGCTs (68,69). Overall, CSF1R inhibition is a reasonable choice with evident efficacy in TGCT. Although not common and mostly reversible, liver toxicities should receive greater attention when prescribing CSF1R inhibitors.

### *Selective inhibitors of nuclear export (SINE)*

Exportin 1 (XPO1) is a critical mediator of nuclear export responsible for shuttling more than 200 known cargo proteins from the nucleus to the cytoplasm, including many tumor suppressor proteins (TSPs) (70). Selinexor, a novel SINE, could inhibit XPO1 by covalently and reversibly binding cysteine-528, an essential residue for XPO1 cargo binding. Inhibition of XPO1 results in nuclear accumulation of TSPs such as p53, pRb, p21, p27, and restores cell-cycle checkpoints and induces growth arrest and apoptosis in malignant cells (71).

XPO1 overexpression has been reported in several types of tumors and is correlated with poor prognosis (72-74). In the preclinical study, selinexor has demonstrated a universal response, both *in vitro* or *in vivo*, in a variety of sarcoma cell lines, including GISTs, LPS, LMS, ASPS and undifferentiated sarcoma (75). Unfortunately, in a phase Ib study, among 52 patients evaluable for response, none experienced an objective response, with only 17 (33%) experiencing stable disease (SD) for 4 months or longer. However, it is interesting to find that for the 15 dedifferentiated liposarcoma (DD LPS) patients, six (40%) of them showed a reduction in target lesion size from baseline and seven (47%) of them showing SD for 4 months or longer (28). A registration-targeted clinical trial of selinexor specifically focused on in LPS is currently being

 

investigated (ClinicalTrials.gov identifier: NCT 02606461).

### *Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors*

LPS are malignant mesenchymal tumors that are classified into three main biologic groups: well-differentiated (WD LPS) and dedifferentiated liposarcoma (DD LPS), myxoid/round-cell LPS, and pleiomorphic LPS (76). WDLPS/DDLPS are considered two sides of the spectrum of the same disease. The dedifferentiated component, which can be rapidly growing, aggressive, and metastatic, is considered to arise from the well-differentiated component, which can grow slowly (77). Both WDLPS and DDLPS are relatively resistant to chemotherapy, and few viable treatments exist for patients with locally advanced or metastatic disease (78).

The most common cytogenetic abnormalities found in WDLPS and DDLPS are supernumerary rings and giant chromosomes, which frequently contain amplifications in the long arm of chromosome 12 (12q13-q15) (79). Further studies revealed that this region contained oncogene cyclin-dependent kinase 4 (*CDK4*) and murine double minute-2 (*MDM2*) and found amplified in more than 90% of WDLPS/DDLPS (80). Gene profiling studies shown that CDK4 expression is 10 times higher in WDLPS/DDLPS than in normal fat tissue (81). In vitro study showed that inhibition of CDK4 expression with short hairpin RNA inhibits growth of WDLPS/DDLPS cells (82).

Palbociclib is a potent oral inhibitor of CDK4 and CDK6 that prevents downstream phosphorylation of the retinoblastoma protein (83). It has been demonstrated its efficacy in preclinical model of *CDK4*-amplified LPS cell lines and xenograft models (82). In a phase I study of palbociclib, two patients with Rb-positive WD or DDLPS achieved a long-term stable disease lasting several years (84). In a phase 2 study that enrolled 60 patients with advanced WD or DDLPS, treatment with palbociclib achieved a 57.2% PFS at 12 weeks, and the median PFS was 17.9 weeks. There was 1 complete response. This agent showed promising result in the treatment of WD/DDLPS (29). Other CDK4/6 inhibitors including ribociclib and abemaciclib are also under investigation for WD/DD LPS patients.

### *MDM2 inhibitors*

The tumor suppressor gene *TP53*, considered as "the guardian of the genome" is commonly mutated in around 50% of all cancer types. Another mechanism that could dysregulate p53 protein function is increasing the degradation of p53 through ubiquitination. MDM2 is responsible for p53 ubiquitination and is found to be overexpressed in certain types of cancer including sarcoma (20%) (85). Besides WD and DD LPS, other sarcoma subtypes that are associated with *MDM2* amplification include intimal sarcoma and parosteal osteosarcoma (86,87); however, other rare histologies such as rhabdomyosarcoma have also been reported to have *MDM2* amplification occasionally (88). Single agent mdm2 inhibitors have shown some signals of activity in wild-type p53 sarcoma patients, but mostly are WD or DD LPS with stable disease (30,31). In addition, because MDM2 and CDK4 are commonly co-amplified in WD/DD LPS, a combination of mdm2 inhibitor HDM201 and CDK4/6 inhibitor ribociclib was also tested in this population that showed a 4% response rate and 49% stable disease rate (32). However, because stabilizing p53 through mdm2 inhibition causes cell apoptosis, the common class effect toxicity for mdm2 inhibitors is bone marrow toxicities. Grade 3 or 4 neutropenia or even prolonged thrombocytopenia has been experienced by 30% or higher of patients (30-32). Multiple different drugs dosage schedules are currently explored to find the best schedule. For mdm2 inhibitors, although some efficacy potential is noted in STS with *MDM2* amplification or a wild type *TP53*, reaching a balance between the efficacy and toxicities will be critical to the drug development process of mdm2 inhibitors.

### *Epigenetic modifying drugs*

Histone deacetylase inhibitors, although promising in preclinical studies of sarcoma, did not show activity in unselected sarcoma patients (89). However, newer generation drugs that target the chromatin modifying machinery enhancer of zeste homolog 2 (EZH2) have shown promising results. EZH2 is a major catalytic unit in the polycomb repressive complex 2 (PRC2) that is commonly aberrantly expressed in tumors (90). Another chromatin modifying complex in the cell, the SWI/SNF, acts as a suppressor of EZH2. When a key component of SWI/SNF complex, SMARCB1 (SWI/SNF related matrix-associated actin-dependent regulator of chromatin subfamily B member 1, or more commonly INI-1) lost its function, tumor cells are more likely to shift the balance toward EZH2 reprogramming, which more favors progression (91). INI-1 is commonly lost in epithelioid sarcoma, synovial sarcoma, epithelioid malignant peripheral nerve sheath tumor, myoepithelial tumor, and extraskeletal myxoid

 

chondrosarcoma (92,93). It is noteworthy that functional loss of INI-1 is observed in more than 90% of epithelioid sarcoma patients (94). An EZH2 small molecular inhibitor, tazemetostat, is currently being tested in a multiple arms two-step phase II study including rhabdoid tumors, synovial sarcoma, INI-1 loss malignancy, epithelioid sarcoma and poorly-differentiated chordoma. Confirmed response were seen in epithelioid sarcoma, with the ORR 13% among 31 patients and a median PFS of 5.7 months (33). However, in the synovial sarcoma cohort, no responders were noted (95). The adverse events were generally well tolerated. The efficacy signal of epithelioid sarcoma warranted an expansion of the ES patient for further testing (ClinicalTrials.gov identifier: NCT02601950).

### *Fusion-gene targets*

Specific fusions are pathognomonic and driver for many STS histologies and have been main targets of therapeutic potential. The success of crizotinib in *ALK* translocation positive IMT (16) and imatinib in *COL1A1-PDGFB* positive DFSP (17) certainly speaks that it is worthwhile to develop drugs specific for fusion-genes.

The tropomyosin receptor kinase (TRK) plays significant role in neuronal growth and differentiation but the fusion of the coding gene *NTRK* with a non-related gene have been found in infrequently in various adult and pediatric solid tumors with transformative capability (96). Most often, the 5'-end of the *NTRK*-1, -2 or -3 gene that includes the kinase domain of TRK protein is fused in-frame with the 3'-end of another gene, causing an oncogenic fusion protein (96). Although rarely found, certain STS subtypes such as infantile fibrosarcoma and uterine sarcoma may have higher chances of harboring *NTRK*-specific fusion genes (34,97). The first report of the efficacy of TRK kinase inhibitor was reported in a sarcoma patient with *LMNA-TRKA* fusion oncoprotein (35). The tumors responded exceptionally well to the single agent larotrectinib, a pan-TRK inhibitor. In further phase I/II study of larotrectinib, an ORR of 78% and a complete response (CR) rate of 13% were observed among adult and pediatric patients who harbored *NTRK* fusions, including 10 of the 11 patients with sarcoma (34). Another pan-TRK, ROS, and ALK inhibitor, entrectinib, also demonstrated promising clinical activity in patients harboring *NTRK* fusion gene, including patients with brain metastases (36). This result further highlights the need to screen multiple possible molecular targets in STS patients in a tissue agnostic fashion in order to find the best way to treatment the tumor.

### *Precision oncology and STS treatment*

The uprising of inexpensive and efficient massively parallel next generation sequencing (NGS) has changed the clinical practice of oncology (98). Patients can now obtain the genetic alterations landscape for mutations, indels, amplifications and translocations of hundreds of actionable targets in one test (99). Institutional studies have shown that NGS testing may increase the chance of finding a molecular-based treatment in rare cancers such as sarcoma. In a retrospective analysis from the Memorial Sloan Kettering Cancer Center, 5,635 sarcoma patients worldwide were screened for a NGS panel that included 405 cancer-related genes and 265 genes rearranged in RNA. By using an in-house bioinformatics pipeline OncoKB (100), they found that 16% and 7% of the patients had treatment-linked alterations known to respond to FDA approved or study drug (101). Another sarcoma-specific NGS database analysis showed that of 584 sarcoma patients, at least one targetable genetic alteration was noted in 41% of patients (102).

Despite the promising initial findings, some caveats exist. First, many of the "actionable" alterations selected into the NGS panels are based on preclinical or sound biological speculation but not by evidence of clinical efficacy. For instance, the common actionable mutations detected in STS included *TP53*, *ATRX*, *MDM2*, *CDK4*, and *RB* (103). Except that *MDM2* and *CDK4* have specific inhibitors, the loss of function of tumor suppressor genes such as *TP53*, *ATRX* and *RB* are much more difficult to find a target to treat. Even with MDM2 and CDK4/6 inhibitors, the clinical trial results of these drugs in STS are not exuberant (as mentioned in previous section). Secondly, it is still uncertain if actionable alterations are equal among different cancer types. For instance, melanoma with *BRAF V600E* mutations responded exceptionally well to BRAF inhibitor vemurafenib (104). Based the concept that BRAF mutation may be the driver oncogene in all cancer types, a basket clinical trial for nonmelanoma patients was initiated. In this study, lung cancer, Erdheim-Chester disease/Langerhans'-cell histiocytosis, and clear cell sarcoma patients with *BRAF V600E* mutation responded well to vemurafenib (37). However, colorectal cancer patients responded poorly (37). The discrepant responses to driver mutations in different cancer types also brought skeptical viewpoints toward the actual benefit of NGS testing in daily clinical setting (105).

 

To provide a framework for precision oncology in across all cancer types, both the National Cancer Institution (NCI) and American Society of Clinical Oncology (ASCO) have initiated precision oncology clinical trials: the NCI-Molecular Analysis for Therapy Choice (MATCH) and ASCO Targeted Agent and Profiling Utilization Registry (TAPUR) (106). Both clinical trials have been well accepted by both the medical community and the patients, hence with a higher than expected recruitment rate, especially for rare and uncommon cancers like sarcoma. In NCI-MATCH, about 60% of the enrolled patients are cancers other than colon, rectal, breast, non-small cell lung, and prostate, much exceeding the previous expected rate of 25% (107). Enrolled patients will be allocated to specific molecular treatment groups by their genomic sequencing results and to monitor the tumor response (108). Pre-set rule-based criteria will be used to determine the efficacy of these molecularly-matched agents. The results of these precision oncology clinical trials are highly anticipated and may bring more genetically or molecularly-tailored precision medicine into the treatment paradigm of advanced STS patients.

### *Immunotherapy in STS*

The immune system plays a significant role in control tumorigenesis (44). One of the mechanisms that the cancer cells utilize to evade the immune system is to exploit the immunosuppressive molecules that are physiologically substantial to avoid autoimmune and uncontrolled immune responses—the immune checkpoint signaling pathways that include cytotoxic T-lymphocyte associated protein-4 (CTLA-4) and the programmed cell death receptor-1 (PD-1) and its ligand, PD-L1 (109). The success of immune checkpoint inhibitor (ICI) monoclonal antibodies such as pembrolizumab (anti-PD-1), nivolumab (anti-PD-1), atezolizumab (anti-PD-L1), avelumab (anti-PD-L1), durvalumab (anti-PD-L1), and ipilimumab (anti-CTLA-4) in melanoma, lung cancer, renal cell carcinoma and other malignancies have resulted in a paradigm shift in the cancer therapy field (109).

Both soft tissue and bone sarcoma have evidence suggesting that the immune system is involved in sarcomagenesis. Dr. Coley first noted immune-induced tumor response in sarcoma patients after erysipelas infection more than 130 years ago (110). Many sarcoma subtypes such as LMS, angiosarcoma, and Kaposi's sarcoma are more common among patients who are immunosuppressive such as allograft transplantation receivers and HIV-infected patients (111,112). Furthermore, the amount and type of tumor infiltrating lymphocytes (TILs) have also been documented to correlate with prognosis in both STS and bone sarcomas (113,114). Tumor associated antigens (TAAs), which may lead to tumor antigen expression and priming of the immune system, are also common in STS (discussed in the next section). Taken together, these evidences support that immune system is substantial in STS and provide the rationale to investigate immunotherapy in advanced STS.

### *Immune checkpoint inhibitors (ICI) in sarcoma*

SARC028 is one of the largest prospective clinical trial to date to test the efficacy of single agent ICI in bone and STS (38). In SARC 028, 40 STS patients [10 LMS, 10 LPS, 10 synovial sarcoma (SS), and 10 undifferentiated pleomorphic sarcoma (UPS)] were treated with single agent pembrolizumab 200mg every 3 weeks. All patients have received at least one-line of prior therapy. The results showed an overall objective response rate (ORR) of 18% in 40 STS patients and a median duration of response of 33 weeks (38). However, ORR among histologies varied. The histology that had the highest ORR was UPS, with 4 out of 10 (40%) patients having tumor response; LMS had the lowest ORR with 0 out of 10 (0%) of patients responded. Two patients with DDLPS and 1 patient of SS also had tumor response (38). The patient numbers are too small to reach final conclusion and expansion studies of pembrolizumab in DD LPS and UPS is ongoing. Interestingly, another study using nivolumab (3 mg/kg every 2 weeks) in uterine LMS also saw 0 responders out of 12 patients (115). The study was closed prematurely with the lack of efficacy. Although it is too early to specify that certain histologies of STS are unlikely to response to ICI, different histologies are likely to have different immune evasion mechanisms. For instance, studies have suggested that loss of PTEN protein in LMS may be associated with ICI treatment resistance (116).

The combination of nivolumab and ipilimumab have the advantage to eliminate two inhibitory signals on T cells and potentially improve the response rate in solid tumors (109). In melanoma and renal cell carcinoma, the combination of nivolumab and ipilimumab have shown to improve response rate and disease control over either single agent nivolumab or ipilimumab (in melanoma) (117) or single agent sunitinib (in intermediate or poor-risk renal cell carcinoma patients) (118). But the toxicities because of immune-

 

related adverse events were higher in the combination arm as well, with more than 40% of patients had grade 3 or higher toxicities (117,118). The combination of nivolumab and ipilimumab was also tested in the Sarcoma Alliance Study A091401. The study was designed as a two-arm study to either single agent nivolumab or the combination of nivolumab plus ipilimumab. Patients who progressed on the nivolumab arm could choose to cross-over to the combination of nivolumab and ipilimumab (39). The ORR for single agent nivolumab and the combination was 5% (2 of 38) and 16% (6 of 38). Median PFS and OS for nivolumab and nivolumab plus ipilimumab combination was 1.7 and 10.7, 4.1 and 14.3 months, respectively. A lower dose of ipilimumab (1 mg/kg as compared to 3 mg/kg in other studies) led to a lower than expected grade 3 or higher treatment related adverse events (14%) in the combination arm (39). In the Alliance study, they also observed that STS subtypes such as LMS, angiosarcoma, myxofibrosarcoma, and ASPS responded to ICI treatment. However, not all combination of immunotherapies showed positive results. Metronomic cyclophosphamide is a low-dose daily administrative regimen that could decrease the number of regulatory T cells (Tregs) in the peripheral blood and could antagonize the immunosuppressive microenvironment (119). In a study to evaluate the combination of metronomic cyclophosphamide plus pembrolizumab, out of 50 evaluable patients, only one solitary fibrous tumor patients responded to the combination and the 6-month PFS rate for LMS (n=15) and UPS (n=16) were both 0% (120). This result further signifies that a better understanding of the predictive factors that is associated with response to immunotherapy is warranted.

### *Modulation of the tumor microenvironment to improve response to immunotherapy*

The tumor microenvironment plays an important role in determining the response to immunotherapy (121) and STS are generally "cold tumors" with less T cell infiltration (122). Angiogenesis molecules are also involved in dendritic cell maturation and T cell trafficking and are generally immunosuppressive in tumor immune system (123). In two studies, the administration of anti-VEGF antibody before atezolizumab or ipilimumab showed increased T cell infiltration in the tumor microenvironment (124,125). In a phase Ib study, axitinib (an VEGFR 1, 2 and, 3 inhibitor) plus pembrolizumab combination in renal cell carcinoma yielded an 73% (38 out of 52) ORR (126). Axitinib and pembrolizumab combination was also tested in STS patients. In 30 evaluable patients that included ASPS, UPS, LMS, and other histologies, the overall ORR was 21.9%. Interestingly, ASPS histology have the highest ORR at 45% (127). Other studies also have suggested that ASPS may be more susceptible to ICI because of a genomic mismatch repair deficiency mutation signature (128), which is associated with a higher response to ICI in other cancer types (129). It is now widely accepted that molecular targeted agents not only affect the cancer cell but also can influence or reshape the contexture of the tumor immune microenvironment (123). Clinical trials that integrate biomarker study to fully understand the modulation of the immune microenvironment in the combination of anti-angiogenic molecules or other targeted agents with immunotherapy are highly anticipated.

### *Expression of PD-L1 as predictive biomarkers of response to ICI*

Expression of PD-L1 on tumor cells may be a reflection of immune evasion through the PD-1/PD-L1 axis and more likely to be associated with increased T cell infiltration (121). In many solid tumors, increased expression of PD-L1 on tumor cells are correlated with ICI treatment benefit (109). The expression of PD-L1 on sarcoma tumor cells varies with histology but UPS generally have the highest PD-L1 expression (122,130). In SARC 028, although only 2 patients (5%) had positive PD-L1 expression on tumor cells, both of these patients are UPS and were responsive to pembrolizumab (38). Interestingly, high PD-L1 expression on the immune cells (including both lymphocytes and macrophages) of STS have been found in many studies (120,122,130). Recent biomarkers studies have also suggested that a combined analyses of PD-L1 on both tumor cells and immune cells may be more predictive of the benefit to ICI than tumor cells alone (131,132). Further studies to delineate the role of PD-L1 on both tumor cells and immune cells in STS and correlation with ICI treatment benefit is further warranted.

### *Targeting tumor-associated antigens (TAA)*

Tumor possess antigens that are not commonly observed or low quantity in normal cells. Generally, TAA are categorized in 3 types: antigens that are uniquely only expressed on tumor cells (e.g., neoantigens), antigens

 

that have much higher quantity as compared with normal cells (e.g., epidermal growth factor receptor), or antigens that are only expressed on tumor cells and normal body parts that are immune-neglect [e.g., cancer-testis antigen (CTA)] (133). CTA has been an attractive target for immunotherapy because of the lack of human leukocyte antigen (HLA)-class I molecule on male germ cells, limiting T cell responses that may come along after antigen stimulation (134).

NY-ESO-1 is a TAA that has been found to be expressed in testicular and ovarian fetal germ cells and placenta. As in STS, the common histologies with NY-ESO-1 expression are synovial sarcoma (SS) and myxoid round cell liposarcoma (MCL LPS). In a series of 25 MCL LPS patients, NY-ESO-1 was found to be homogeneously expressed in 70% of patients and both the myxoid and round cell component tend to stain positive for NY-ESO-1 (135). Around 50–80% of SS are positive for NY-ESO-1. Similar to the findings of MRC LPS, either monophasic or biphasic (both the epithelial and spindle cell components) staining equally positive for NY-ESO-1 (136,137). Other sarcomas that has a lower percentage of NY-ESO-1 expression included myxofibrosarcoma (35%) and conventional chondrosarcoma (28%) (136). Overall, because of the high and homogenous expression in certain types of STS and the limited expression in normal tissue, NY-ESO-1 has been an attractive target for immunotherapy in STS.

Recent advancement in targeting NY-ESO-1 generally focuses on two methods to harness the immune system to target NY-ESO-1 positive STS: (I) using a lentiviral vector with NY-ESO-1 peptide to stimulate the immune system; (II) using adoptive T cells with T cell-receptor (TCR) targeting NY-ESO-1.

### *Viral cancer vaccine to active the immune system toward NY-ESO-1*

Dendritic cells (DC) play an important role in priming and activating the T cells against cancer cells. Through the antigen-presentation machinery in the cytoplasm, the DC could efficiently load the exogenous peptide into the MHC-complex to generate T cell responses (138). Viral vaccines with DC tropism have shown some anti-tumor efficacy either through *ex vivo* stimulation or direct tumor injection (139). LV305 is a vaccine with a third generation lentiviral vector that utilizes a modified Sindbis virus coat with tropism toward dendritic cells. LV305 loaded with the NY-ESO-1 peptide injected subcutaneously have been shown to be safe (140). In a phase I trial testing LV305 in NY-ESO-1+ tumors, a patient with SS had a PR (80% regression) with evidence of increased tumor-specific T cell clones (40). Furthermore, a primed-boost regimen (CMB305) was developed to enhance the immune response. CMB305 is composed of LV305 and an adjuvant G305 that contains a full-length NY-ESO-1 protein and a toll-like receptor 4 agonist (140). CMB305 regimen schedule is to start with the LV305 priming vaccines on Days 0, 21, 49, and 77 while the adjuvant G305 starts on D35 every 4 weeks for 3 doses then every 8 weeks for up to one year. In the phase I trial that included 25 advanced sarcoma patients (80% with homogeneous NY-ESO-1 expression), 1-year survival rate higher than 85% was observed in SS and MRC LPS patients. Immunity against NY-ESO-1 was induced in at least 60% of SS or myxoid round cell LPS patients (41). A randomized phase III study investigating the role of CMB305 in advanced SS positive for NY-ESO-1 in the maintenance setting after first-line chemotherapy is currently undergoing (ClinicalTrials.gov Identifier: NCT03520959).

### *NY-ESO-1-specific adoptive T cells*

The first generation of adoptive T cell therapy involves the extraction of TILs and re-infused into the patients after *ex vivo* stimulation (141). Albeit promising activity, the difficulty in obtaining of TILs makes this method less attractive. The second generation of adoptive T cells involves a transfection of retroviral vector with a genetically modified T-cell receptor that could recognize NY-ESO-1. In the initial study, Dr. Rosenberg and colleagues at the NCI tested the adoptive TCR in SS and melanoma patients (42). Patients need to receive pre-conditioning lympho-depletion chemotherapy regimens such as fludarabine and cyclophosphamide and interleukin-2 injections along with engineered T cells to boost the proliferation. In the first 6 patients with SS, all with HLA-A*0201 haplotype and high expression of NY-ESO-1, four had objective response lasting 5–18 months. Toxicities were generally considered from the lympho-depleting chemotherapy or interleukin-2 and not from the injected adoptive T cells (42). Because of the promising activity, an expansion cohort including 12 SS patients was initiated. Among these patients, 5 received addition NY-ESO-1 peptide vaccine to boost the anti-tumor immunity (43). With 7 patients in the expansion cohort having objective

 

response, the overall response rate of NY-ESO-1 TCR in SS was 61%, with response lasting from 3 to 47+ months. However, re-treatment with NY-ESO-1 TCR in recurrent patient only showed short or no response. The 3- and 5-year OS was 38% and 14%; and 4-year PFS was at 11%. Interestingly, the addition of NY-ESO-1 vaccination was not correlated with an increased response rate but the number of infused T cells and NY-ESO-1-reactive T cells are more likely predictors of response (43).

There are still some limitations of the adoptive T cell therapy in SS or other sarcoma with strong expression of NY-ESO-1. The strong preconditioning chemotherapy regimen and interleukin-2 injection excludes patients that are more fragile from receiving T-cell infusion. Studies that are testing different but lower intensity of chemotherapy before NY-ESO-1 TCR infusion are being investigated. Secondly, currently NY-ESO-1 TCR are generated with the specificity to HLA-A2 haplotype. Although HLA-A2 may be the most common haplotype in Western Countries (27% of US Caucasians), other ethnicities will have a different HLA-A landscape pattern that may limit the application of the NY-ESO-1 TCR (142). Further understanding the NY-ESO-1 presentation to different haplotypes of HLA may improve the scalability and applicability to a wider population or ethnicity of STS patients with NY-ESO-1 expression.

## Summary

Two trends are pushing the frontiers in the treatment of oncology patients: molecular target agents that more closely matched to the genomic alterations or biological mechanisms of the cancer and reactivation or modulation of the immune system to fight cancer. STS treatments have not lagged too much behind in both of these two categories. In molecular targeted agents, many anti-angiogenic factors have shown activity in STS and PDGFRA monoclonal antibody in combination with doxorubicin have also improved the survival of advanced STS patients. Other STS-specific genomic or molecular target inhibitors such as CSF-1R, SINE, MDM2, CDK4, and EZH2 are also showing promising future. How to match the current wave of precision oncology with sound and solid clinical trial evidence is also a key to finding the optimal treatments of each STS patient.

In immunotherapy treatments, single agent ICI may have activity in certain histologies but definitely is not the answer for most advanced STS patients. Combinations of either two ICI inhibitors or other molecular targeted agents that can modulate the tumor microenvironment is under intense investigation. Other immunotherapy methods such as viral vaccines or adoptive T cells are front-runners that target the CTA NY-ESO-1. Immune system is like the yin and yang, always in process of balancing the enhancing and suppressive factors of the immune system. A deeper understanding of the immune contexture to understand the resistance in immunotherapy plays another key role to extending the envelope of the frontier in the treatment of advanced STS.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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