CURRENT ONCOLOGY
A Canadian Cancer Research Journal

REVIEW ARTICLE

Immunotherapy in soft-tissue sarcoma

O. Ayodele MBBS and A.R. Abdul Razak MB MRCPI

ABSTRACT

Soft-tissue sarcoma (STS) is a rare mesenchymal malignancy that accounts for less than 1% of all adult tumours. Despite the successful advancement of localized therapies such as surgery and radiotherapy, these tumours can, for many, recur—often with metastatic disease. In the advanced setting, the role of systemic therapies is modest and is associated with poor survival. With the discovery of immunotherapies in other tumour types such as melanoma and lung cancer, interest has been renewed in exploring immunotherapy in STS. The biology of some STSs makes them ripe for immunotherapy intervention; for example, some STSs might have chromosomal translocations resulting in pathognomonic fusion products that have been shown to express cancer/testis antigens. Here, we present a targeted review of the published data and ongoing clinical trials for immunotherapies in patients with sarcoma, which comprise immune checkpoint inhibitors, adoptive cell therapies, and cancer vaccines.

Key Words Adoptive cell therapy, cancer vaccines, immunotherapy, checkpoint inhibitors, soft-tissue sarcoma, alveolar soft-part sarcoma, undifferentiated pleomorphic sarcoma

Curr Oncol. 2020 February;27(S1):17-23 www.current-oncology.com

INTRODUCTION

Soft-tissue sarcoma (STS) represents a heterogeneous group of malignancies, encompassing more than 60 distinct diagnoses. Despite that variety, STS is rare, accounting for less than 1% of all adult cancers. Since the 1990s, improved surgery, delivered in specialist centres, together with preoperative or postoperative radiotherapy or chemoradiotherapy, has led to improved outcomes in patients with localized disease. However, despite the success of initial treatments, disease recurs in approximately 50% of patients, often with distant failure. In the metastatic setting, cytotoxic chemotherapies are commonly used, but with modest effects on overall survival, which currently hovers at approximately 12–18 months[1].

Breakthroughs in STS treatments have been slow. One of the most successful examples of systemic therapy in STS has been the use of imatinib mesylate in gastrointestinal stromal tumours. Those tumours contain an activating *KIT* mutation in approximately 80% of cases[2–4]. Imatinib mesylate inhibits both KIT and platelet-derived growth factor receptor α, resulting in partial responses or stable disease for more than 85% of patients treated for advanced disease and dramatically improving the overall survival landscape in that disease[5,6]. Despite that initial success, the mainstay of treatment in STS has not generally progressed—the landscape is still found wanting for the "imatinib" in other STS diagnoses.

The immuno-oncology field has seen a revival in therapies for solid tumours, with U.S. Food and Drug Administration approvals in melanoma, prostate cancer, renal cell carcinoma, and non-small-cell lung cancer, among others. The most successful of those strategies involve immune checkpoint inhibitors (ICIs). Historically, sarcoma is no stranger to immunotherapy as a treatment strategy. That approach has been considered since, more than century ago, immune-induced tumour regression occurred after infection in sarcoma patients. Given the lack of highly effective therapies in STS, coupled with immunotherapy successes in other tumour types and a deepening understanding of STS biology, interest has been renewed for immunotherapy in sarcomas. Here, we detail evidence for the various immunotherapy strategies in STS, with a focus on ICIs, vaccine trials, and adoptive cell therapies.

METHODS

A literature search in Ovid MEDLINE and PubMed used the search terms "sarcoma," "soft tissue sarcoma," "immunotherapy," "vaccines," "immune T-cells," "checkpoint blockade," "anti–CTLA-4 antibody," "anti–PD-1 antibody," and "anti–PD-L1 antibody." A search of ClinicalTrials.gov for relevant clinical trials involving immunotherapy and sarcomas also used the foregoing keywords. Additionally, relevant abstracts from recent major meetings (American

Correspondence to: Albiruni R. Abdul Razak, Toronto Sarcoma Program, 600 University Avenue, Room 12-23, Toronto, Ontario M8Z 1H3.
E-mail: albiruni.razak@uhn.ca **DOI:** https://doi.org/10.3747/co.27.5407

Society of Clinical Oncology, European Society for Medical Oncology) were also reviewed.

REVIEW

Mechanisms of Action

The immune system plays a critical role in the surveillance, prevention, and development of cancer. Evasion of the immune system has been established as a hallmark of cancer[7]. It is therefore highly attractive to manipulate the immune system in such a way as to induce an antitumour response.

Components of the immunologic milieu include cytokines; tumour-infiltrating lymphocytes (TILs) and associated macrophages; expression of ICIs such as CTLA-4, PD-1, and PD-L1; and expression of major histocompatibility complex antigen. Other pathways or molecules of interest include the tumour necrosis factor receptor superfamily agonists, including OX40, CD27, CD137 (4-1BB), and CD357. All of those components might be important not only for prognostication, but also as potential therapeutic targets in STS[8].

The human adaptive immune response requires two activation signals. For example, activation of CD8+ cytotoxic T lymphocytes requires signalling through the T cell receptor and a costimulatory molecule. Initial immunotherapy strategies sought to stimulate the immune system through the use of signalling molecules such as interleukin 2, which can activate cytotoxic T cells, or interferon alfa[9,10]. In addition to costimulatory molecules, multiple co-inhibitory molecules exist, such as CTLA-4 or the interaction of PD-1 with PD-L1 or PD-L2.

Current immunotherapy trials are using monoclonal antibodies to target those molecules or interactions, essentially "taking the brakes off" the immune system. However, if no underlying immune response is active, simply taking the brakes off will be insufficient. In tumours that do not trigger a sufficient immune response, the immune system has to be "reprogrammed" with adoptive T cell strategies or cancer vaccines to trigger an antitumour immune response.

Immunotherapy Modalities

ICIs

"Hot" or "inflamed" tumours are those that are immunogenic (associated with high numbers of TILs and tumour-associated macrophages), but that are actively modulating the immune response to survive—for example, by expressing immune checkpoint ligands that suppress the antitumour immune response. Hot tumours are those most likely to benefit from immunomodulatory therapies such as ICIs.

Knowledge about immunoprofiling in STS is limited. D'Angelo *et al.*[11] conducted an immunohistochemistry survey of 50 samples from patients with STS. Those authors evaluated the presence of TILs, tumour-associated macrophages, and PD-1 or PD-L1. Immunohistochemical staining for CD3, CD4 (helper T cells), CD8 (cytotoxic T cells), FOXP3 (regulatory T cells), and PD-1 and PD-L1 expression, and multiplex immunohistochemistry for CD3/PD-1, CD3/CD8, and CD3/CD4/FOXP3 were performed. Lymphocyte infiltration was observed in 98% of cases, and macrophage infiltration, in 90%. Defining "low-density" TILs as below 5% and "high-density" as above 5%, they noted that 27 patients (54%), mainly those with leiomyosarcoma (LMS, 3 of 4), synovial sarcoma (4 of 5), and chondrosarcoma (1 of 1), had low-density TILs; another 22 patients (44%), mainly those with gastrointestinal stromal tumour (9 of 14), had high-density TILs. Tumour, lymphocyte, and macrophage PD-L1 expression was 12%, 30%, and 58% respectively, with the highest frequency of PD-L1 positivity seen in gastrointestinal stromal tumours (4 of 14). In that small study, no clear correlation was evident between biomarker expression and clinical outcomes.

Movva *et al.*[12] also assessed PD-L1 expression by immunohistochemistry in 221 sarcomas and found that 57% expressed PD-L1 and that 54.8% were PD-1–positive. Significantly high of PD-L1 expression was seen in 19 of 60 LMS cases (32%), 12 of 16 chondrosarcoma cases (75%), 23 of 30 liposarcoma (LPS) cases (77%), and 7 of 10 undifferentiated pleomorphic sarcoma (UPS) cases (70%).

Smaller studies focusing on specific subtypes revealed broadly similar results. A study of 35 cases of well-differentiated and dedifferentiated LPS found TILs in all samples by flow cytometry, with a greater prevalence of CD4+ (80%) than CD8+ (20%) T cells[13]. Of CD8 T cells, 65% expressed PD-1. The authors also found mature dendritic cells in close proximity to CD4+ T cells, suggesting intratumoural antigen presentation. Similar findings have also been demonstrated in non-STS populations. Feng *et al.*[14] examined 78 chordomas by immunohistochemistry and found that, in 75%, TILs were present. Although PD-L1 expression was seen in 95% of samples, 43% were classified as "PD-L1 high" because of moderate or strong staining intensities. The presence of the TILs correlated with PD-L1 expression, but no clear correlation with survival was observed. In osteosarcoma, Fritzsching *et al.*[15] surveyed 135 samples for CD8+ and FOXP3+ T cell presence by immunohistochemistry, finding that CD8+ and FOXP3+ T cells were both present in 95% of the samples and that a high CD8:FOXP3 ratio correlated with improved survival.

It is clear that, in sarcomas, the immune microenvironment is highly variable; however, the strong immune presence in some subtypes offers a promise for immunotherapy in many of those malignancies, leading to the clinical interrogation of ICIs in sarcoma patients.

Tawbi *et al.*[16] presented the first results from SARC028, a nonrandomized multi-cohort phase II study of the PD-1 inhibitor pembrolizumab in 42 soft-tissue tumours (LMS, dedifferentiated LPS, UPS, and synovial sarcoma; 40 evaluable patients). The study also included multiple cohorts for bone sarcomas (osteosarcoma, Ewing sarcoma, chondrosarcoma). At a median follow-up of 17.8 months in the STS cohorts, 7 of 40 patients (18%) experienced an objective response, including 1 patient with a complete response. By subtype of STS, the breakdown included 4 of 10 patients with UPS (40%, 1 complete response), 2 of 10 patients with liposarcoma (20%), and 1 of 10 patients with synovial sarcoma (10%). No responses were seen in the LMS cohort. In the study, 2 patients (5%) with positive PD-L1 expression on tumour cells also experienced a radiologic response to pembrolizumab. An update on the longer-term outcomes

for the UPS and LPS cohorts in SARC028, presented at the 2019 American Society of Clinical Oncology annual meeting, showed that the UPS cohort achieved its primary endpoint [overall response rate (ORR): 23%]; however, the activity of pembrolizumab was not confirmed in the LPS cohort (ORR: 10%)[17]. Meanwhile, the lack of response to PD-1/-L1 inhibition in LMS was further demonstrated in another study. Ben-Ami *et al.*[18] reported a single-arm study of nivolumab in uterine LMS. In 12 treated patients, no responses occurred, and the study closed early because of lack of efficacy.

Unfortunately, the efficacy of monotherapy with CTLA-4 inhibitors in sarcoma has been evaluated in only one study so far. In that study, ipilimumab was administered to 6 patients with synovial sarcoma at a dose of 3 mg/kg every 21 days. Median overall survival was 8.75 months (range: 0.8–19.7 months). The study was closed prematurely when none of the patients experienced an objective tumour response. All patients expressed the cancer/testis antigen New York esophageal squamous cell carcinoma 1 (NY-ESO-1), but their titres did not change after treatment[19].

Compared with anti–CTLA-4 agents, inhibitors of PD-1 and PD-L1 have a different mechanism of action and consequently might result in better response rates[20]. The encouraging results seen in UPS and LPS have led to the use of multi-agent regimens for further immunotherapy interrogation in STS. In an open-label, unblinded, noncomparative, multicentre phase II study, patients with STS were randomized to nivolumab monotherapy or to nivolumab–ipilimumab, followed by maintenance nivolumab[21]. Of the 76 patients evaluable at time of reporting, 38 had received single-agent nivolumab, achieving a response rate of 5% (UPS and sarcoma not otherwise specified). The remaining patients had received combination therapy, with a response rate of 16%. Interestingly, responses were seen not only in UPS, but also in LMS, myxofibrosarcoma, and angiosarcoma. As expected, more toxicities were observed in the combination arm. The authors concluded that nivolumab monotherapy is inactive and warrants no further interrogation in STS. In Canada, combination immunotherapy studies are ongoing. One such study is IND.226, a multi-cohort basket study of rare cancers, including UPS and osteosarcoma. That study is being conducted by the IND group at the Canadian Cancer Trials Group (see NCT02879162 at https://ClinicalTrials.gov/).

Therapy combining an anti–vascular endothelial growth factor agent and immunotherapy is also of interest, because recent findings have demonstrated a connection between angiogenesis and innate and adaptive immunity. In animal models, the vascular endothelial growth factor pathway has been shown to inhibit T cell development, to promote suppressive immune cell populations such as T regulatory cells and myeloid-derived suppressor cells, and to impair the maturation of dendritic cells, thus preventing tumour antigen presentation and induction of a T cell response. Normalizing the tumour vasculature with antiangiogenic drugs can help to traffic tumour-specific T cells into the tumour bed.

Wilky *et al.*[22] carried out a phase II trial of axitinib–pembrolizumab in patients with advanced alveolar soft-part sarcoma (ASPS) and other STS subtypes that enrolled 33 patients. At a median follow-up of 14.7 months, the 6-month progression-free survival (PFS) was 47% (95% confidence interval: 29.2% to 62.8%), and the 12-month PFS was 28%. Best ORR was 25%, demonstrated in 8 patients. Of those 8 patients, 6 had ASPS; an ORR of 50.4% was demonstrated in the 11 evaluable patients with ASPS. A separate paper by Lewin *et al.*[23] also described the responses seen in ASPS patients. In that paper, mismatch repair deficiency signatures were cited as a putative reason for the high response rates seen in patients with ASPS treated with ICIs. In Canada, a basket study using a similar strategy (axitinib–pembrolizumab) has recently started randomizing LMS patients, among others, to durvalumab with or without cediranib or olaparib (see NCT03851614 at https://ClinicalTrials.gov/).

Other strategies in the pursuit of improved outcomes with ICIs in STS involve combinations with chemotherapy. The use of certain chemotherapies, such as metronomic chemotherapy, has immunomodulatory properties. Additionally, metronomic chemotherapy with cyclophosphamide has been shown to have a synergistic effect on immune stimulation when combined with immunotherapies that include PD-1 antibodies. In one study, 50 evaluable patients with STS underwent treatment with metronomic cyclophosphamide and pembrolizumab. Only 1 response was seen—in a patient with a solitary fibrous tumour. None of the patients with LMS or UPS demonstrated a response or durable disease control[24]. A study of doxorubicin combined with pembrolizumab in patients with STS, presented at the 2019 American Society of Clinical Oncology annual meeting (see NCT02888665 at https://ClinicalTrials.gov/), failed to meet its primary response rate of 29%; however, compared with doxorubicin alone, the combination therapy was associated with a significantly longer median PFS (8.1 months vs. 4.1 months, $p < 0.001$)[25].

Currently, several ongoing phase I/II trials are assessing the role of anti–PD-1 agents in sarcoma, often in combination therapy with either other immunomodulatory agents, chemotherapy, or radiation. Given the promising but somewhat modest results with the use of ICIs in STS (bar the effect seen in patients with ASPS), a significant amount of work has to be done to show utility for those agents in sarcoma. Tables I and II summarize select trials that are, respectively, complete or ongoing.

Adoptive Cell Therapy in Sarcoma

Adoptive cell therapy is a new therapeutic strategy based on the modulation, manipulation, and selection of autologous T cells *in vitro* to overcome the tolerance of the immune system to tumour cells. The T cells can be harvested from TILs and reinfused into the donor patient after population expansion is ensured. Lymphocyte T cells can also be harvested from peripheral blood, with those that recognize tumour antigens being selectively expanded. Alternatively, lymphocyte T cells can be genetically engineered either by modifying a T cell receptor for a cancer antigen ("transgenic T cell receptor") or by adding a chimeric antigen receptor that recognizes a specific cancer antigen[27,33–35]. To our knowledge, the use of TILs has never been investigated in sarcoma-specific cohorts, and the use of activated natural killer cells has been limited to case reports[35].

On the other hand, tumour antigens such as GD2 (93% of sarcomas) and NY-ESO-1 (80%–100% of various sarcoma

TABLE I Selected completed immunotherapy studies in soft-tissue sarcoma (STS)

Reference	Agent	Phase	Pts (*n*)	Indication	Response rate	Survival
Checkpoint inhibitors						
Maki *et al.,* 2013[19]	Ipilimumab	I	6	Advanced SyS	0 of 6	mOS: 8.75 months
Tawbi *et al.,* 2017[16]	Pembrolizumab	II		Selected STSs and bone sarcomas	18% in STS, 40% in UPS, 20% in LPS, 10% in SyS	mPFS: 18 weeks; OS: 49 weeks
D'Angelo *et al.,* 2018[21]	Nivolumab with or without ipilimumab	II	96	Metastatic STS	Nivolumab: 5%; Ipilimumab–nivolumab: 16%	mPFS: 4.1 months; OS: 14.3 months
Toulmonde *et al.,* 2018[26]	Pembrolizumab, cyclophosphamide	II	57	Advanced STS	Solitary fibrous tumour in 1 patient	NA
Wilky *et al.,* 2019[22]	Axitinib, pembrolizumab	II		ASPS and other STSs	25%, all STS patients; 50.4%, ASPS patients	3-Month PFS: 66%; in ASPS patients: 73%
Adoptive cell therapy						
Robbins *et al.,* 2011[27]	Adoptively transferred autologous T cells transduced with a T cell receptor directed against NY-ESO-1	I	6	Metastatic SyS expressing NY-ESO-1	4 of 6	NA
Vaccines						
Mahvi *et al.,* 2002[28]	Tumour cells treated with granulocyte macrophage colony–stimulating factor	I	16	Melanoma and sarcoma	1 of 16	NA
Dillman *et al.,* 2004[29]	Autologous tumour cell-line-derived vaccines	I/II	23	Recurrent or metastatic sarcoma	No objective response	10 Patients lived more than 1 year
Kawaguchi *et al.,* 2005[30]	Vaccination with SYT–SSX junction peptide	I	6	Metastatic SyS	0 of 6	NA
Finkelstein *et al.,* 2012[31]	Radiotherapy with intratumoural injection of dendritic cells	I/II	17	Neoadjuvant treatment in high-risk STS	9 of 17	1-Year PFS: 70.6%
Kawaguchi *et al.,* 2012[32]	SYT–SSX breakpoint peptide vaccines	I/II	21	Metastatic SyS	1 of 21 (stable disease: 6 of 21)	NA

Pts = patients; SyS = synovial sarcoma; mOS = median overall survival; UPS = undifferentiated pleomorphic sarcoma; LPS = liposarcoma; mPFS = median progression-free survival; OS = overall survival; NA = not applicable; ASPS = alveolar soft-part sarcoma; PFS = progression-free survival.

subtypes) have been found to represent interesting targets for adoptive cell therapies. Tumour-associated antigens are antigens that are not routinely observed or that are present in low levels in normal cells. Examples of tumour-associated antigens include those that are expressed only on tumour cells and on normal cells in body parts that are immune-neglected—for example, cancer/testis antigen. Cancer/testis antigen is an attractive target for immune targeting because of the lack of human leukocyte antigen class I molecules on male germ cells, limiting the T cell response that results after antigen presentation. The cancer/testis antigen NY-ESO-1 has been found to be highly expressed in approximately 70%–80% cases of synovial and myxoid round-cell liposarcomas. It is also highly expressed, but in lesser proportion, in myxofibrosarcoma. Because of the high expression of NY-ESO-1 in selected STS subtypes, targeting that molecule is rational and interesting. Other cancer/testis antigens of interest in STS include LAG, MAGE-A3, and PRAME, which are frequently expressed in some STS subtypes and could be potential immunotherapeutic targets.

In this setting, a phase I study involving patients with melanoma and synovial sarcoma evaluated the efficacy of adoptively transferred autologous T cells transduced with a T cell receptor directed against NY-ESO-1. An objective clinical response was attained in 4 of 6 patients with synovial sarcoma[27]. Subsequently, an expansion cohort including 12 patients with synovial sarcoma was initiated, and 7 patients attained an objective response lasting between 3 and at least 47 months. Two ongoing trials are evaluating genetically engineered NY-ESO-1 T cells for children and adults with metastatic synovial sarcoma (see NCT01343043 at https://ClinicalTrials.gov/).

Another phase I trial is testing the role of chimeric antigen receptor T cell therapy targeting the GD2 protein in children and young adults with sarcoma and rhabdomyosarcoma (NCT00743496).

TABLE II Selected ongoing immunotherapy studies in soft-tissue sarcoma (STS)

ClinicalTrials.gov ID	Details
NCT03463408	*Study title:* Immunotherapy + radiation in resectable soft tissue sarcoma *Phase:* I *Status:* Recruiting *Location:* U.S.A. *Interventions:* Ipilimumab, nivolumab, and radiation
NCT03116529	*Study title:* Neoadjuvant durvalumab and tremelimumab plus radiation for high risk soft-tissue sarcoma (NEXIS) *Phase:* I/II *Status:* Recruiting *Location:* U.S.A. *Interventions:* Durvalumab, tremelimumab, and radiation
NCT02815995	*Study title:* Multi-arm study to test the efficacy of immunotherapeutic agents in multiple sarcoma subtypes *Phase:* II *Status:* Active, not recruiting *Location:* U.S.A. *Interventions:* Durvalumab and tremelimumab
NCT03138161	*Study title:* SAINT: trabectedin, ipilimumab and nivolumab as first line treatment for advanced soft tissue sarcoma *Phase:* I/II *Status:* Recruiting *Location:* U.S.A. *Interventions:* Trabectedin, ipilimumab, and nivolumab
NCT02609984	*Study title:* Trial of CMB305 and atezolizumab in patients with sarcoma (IMDZ-C232) *Phase:* II *Status:* Active, not recruiting *Location:* U.S.A. *Interventions:* Atezolizumab and CMB305
NCT03851614	*Study title:* Basket combination study of inhibitors of DNA damage response, angiogenesis and programmed death ligand 1 in patients with advanced solid tumors (DAPPER) *Phase:* II *Status:* Recruiting *Location:* Canada *Interventions:* Durvalumab and olaparib–cediranib
NCT02879162	*Study title:* Durvalumab and tremelimumab in patients with advanced rare tumours *Phase:* II *Status:* Recruiting *Location:* Canada *Interventions:* Durvalumab and tremelimumab
NCT03141684	*Study title:* Atezolizumab in treating patients with newly diagnosed and metastatic alveolar soft part sarcoma that cannot be removed by surgery *Phase:* II *Status:* Recruiting *Location:* U.S.A. *Interventions:* Atezolizumab
NCT03450122	*Study title:* Modified T cells, chemotherapy, and aldesleukin with or without LV305 and CMB305 in treating participants with advanced or recurrent sarcoma *Phase:* I *Status:* Active, not recruiting *Location:* U.S.A. *Interventions:* Modified T cells; LV305 or CMB305
NCT00902044	*Study title:* HER2 chimeric antigen receptor expressing T cells in advanced sarcoma *Phase:* I *Status:* Recruiting *Location:* U.S.A. *Interventions:* Autologous HER2-specific T cells; fludarabine, cyclophosphamide
NCT02423863	*Study title:* *In situ,* autologous therapeutic vaccination against solid cancers with intratumoral Hiltonol (poly-ICLC) *Phase:* II *Status:* Recruiting *Location:* U.S.A. *Interventions:* Hiltonol

Therapeutic Vaccines in Sarcoma

The therapeutic effects of cancer vaccines rely on the activation of dendritic cells in the presence of a predetermined immunogenic antigen. However, most of the initial studies of vaccines in sarcoma did not determine specific antigens and inefficaciously used the entirety of tumour cells[28,29]. Later studies used SYT–SSX, a fusion-derived peptide present in 90% of synovial sarcomas, but also failed to demonstrate an objective response[30,32,36].

Takahashi *et al.*[37] personalized the peptide vaccination for patients with refractory sarcoma and administered multiple tumour antigens chosen according to pre-existing peptide-specific immunoglobulin G titres. Median overall survival was 9.6 months, with disease stabilization

occurring in 30% of patients; however, no objective responses were seen. Another vaccination trial used *in situ* vaccination by combining preoperative gamma radiation (50 Gy) with an intratumoural dendritic cell injection. The study population was limited to individuals with high-risk, localized, and resected extremity STS; it resulted in 71% PFS at 1 year[31].

A seemingly interesting phase I trial designed for the treatment of pediatric patients with relapsed high-risk Ewing sarcoma, osteogenic sarcoma, rhabdomyosarcoma, synovial sarcoma, and neuroblastoma is using a combination of decitabine as a demethylating agent and a cancer vaccine composed of dendritic cells pulsed with overlapping peptides of NY-ESO-1, MAGE-A1, and MAGE-A3 (see NCT01241162 at https://ClinicalTrials.gov/). Another dendritic cell vaccine is also being assessed in combination with gemcitabine in a phase I trial for adults and children with STS or bone sarcoma (NCT01803152).

A study of 25 patients with sarcomas treated with irradiated tumour cells and interferon or granulocyte macrophage colony–stimulating factor was associated with a difference in survival of 8.2 months (patients who did not have a positive immune response) compared with 16.6 months (patients who had a positive immune response), although no clinical responses were attained[31,38]. Those studies support the development of a tumour-specific immune response, resulting in sustained clinical benefit in some patients, despite no radiographic improvement.

Future Perspectives

Centralizing the treatment of STS in Canada would continuously help the understanding of sarcoma, thereby improving outcomes. From a research perspective, such an endeavour is partly served by the Canadian Cancer Trials Group, which provides access to important studies in STS.

The Canadian Sarcoma Research and Clinical Collaboration is a group of health care providers across Canada who have jointly formed a team to facilitate maintenance of an interdisciplinary clinical and scientific database with the overarching aim of solidifying a pan-Canadian collaboration in clinical and translation research in sarcoma. The vision of the Canadian Sarcoma Research and Clinical Collaboration is to improve outcomes for patients with sarcoma. The Collaboration's mission is to develop a comprehensive national bioinformatics network that will capture high-quality data linked to a biorepository for quantity and quality research to help achieve the vision. The Collaboration is currently supported by philanthropic funding through the Princess Margaret Cancer Foundation.

France is a pacesetter in sarcoma, having a robust and successful model for biobanking. The IARC (International Agency for Research on Cancer) BioBank is one of the largest, most varied, and richest international collections of samples in the world. The BioBank is publicly funded, with approximately 60% of its budget being provided by IARC participating states. (The remainder comes from research grants.) The IARC BioBank contains 5.1 million biologic samples from 562,000 individuals. Most of the samples are bodily fluids (plasma, serum, and urine); extracted DNA samples are also preserved. This model perhaps warrants emulation in Canada, given the importance of "big data" in this rare tumour.

SUMMARY

The field of immunotherapy is rapidly expanding. Some of the most promising strategies involve deregulating the immune system through immune checkpoint blockade, and reprogramming the immune system using adoptive cell transfer with re-infusion of *ex vivo* expanded TILs or genetically engineered T lymphocytes[26].

The diverse and rare biology that underlies STS has historically contributed to the often painstakingly slow and inefficient development of effective new therapies. Outcomes for patients with STS remain poor. However, a growing understanding of the molecular pathology of some STS subtypes has yielded important therapeutic breakthroughs. The dramatic and increasingly far-reaching impacts that modern immunotherapeutic techniques have had on oncology present a tremendous opportunity in sarcoma treatment. Centralization of sarcoma research in Canada, beyond what currently exists, would further contribute to progress in sarcoma treatment.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: ARAR has a consulting role for Lilly, Merck, and Boehringer Ingelheim, and has received research funding from CASI Pharmaceuticals, Boehringer Ingelheim, Lilly, Novartis, Deciphera Pharmaceuticals, Karyopharm Therapeutics, Pfizer, Roche/Genentech, Boston Biomedical, Bristol–Myers Squibb, MedImmune, Amgen, GlaxoSmithKline, Blueprint Medicines, Merck, AbbVie, and Adaptimmune. OA has no conflicts of interested to declare.

AUTHOR AFFILIATIONS

*Toronto Sarcoma Program, Princess Margaret Cancer Centre and Mount Sinai Hospital, Toronto, ON.

REFERENCES

1. Karavasilis V, Seddon BM, Ashley S, Al-Muderis O, Fisher C, Judson I. Significant clinical benefit of first-line palliative chemotherapy in advanced soft-tissue sarcoma: retrospective analysis and identification of prognostic factors in 488 patients. *Cancer* 2008;112:1585–91.
2. Ducimetiere F, Lurkin A, Ranchere-Vince D, *et al.* Incidence of sarcoma histotypes and molecular subtypes in a prospective epidemiological study with central pathology review and molecular testing. *PLoS One* 2011;6:e20294.
3. Hirota S, Isozaki K, Moriyama Y, *et al.* Gain-of-function mutations of *c-KIT* in human gastrointestinal stromal tumours. *Science* 1998;279:577–80.
4. Heinrich MC, Corless CL, Duensing A, *et al. PDGFRA* activating mutations in gastrointestinal stromal tumours. *Science* 2003;299:708–10.
5. Verweij J, Casali PG, Zalcberg J, *et al.* Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* 2004;364:1127–34.
6. Blanke CD, Rankin C, Demetri GD, *et al.* Phase III randomized, Intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumours expressing the KIT receptor tyrosine kinase: S0033. *J Clin Oncol* 2008;26:626–32.
7. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–74.

8. Bhardwaj N. Harnessing the immune system to treat cancer. *J Clin Invest* 2007;117:1130–6.
9. Dagher R, Long LM, Read EJ, *et al.* Pilot trial of tumour-specific peptide vaccination and continuous infusion interleukin-2 in patients with recurrent Ewing sarcoma and alveolar rhabdomyosarcoma: an inter-institute NIH study. *Med Pediatr Oncol* 2002;38:158–64.
10. Bielack SS, Smeland S, Whelan JS, *et al.* on behalf of the EURAMOS-1 investigators. Methotrexate, doxorubicin, and cisplatin (MAP) plus maintenance pegylated interferon alfa-2b versus MAP alone in patients with resectable high-grade osteosarcoma and good histologic response to preoperative map: first results of the EURAMOS-1 Good Response randomized controlled trial. *J Clin Oncol* 2015;33:2279–87.
11. D'Angelo SP, Shoushtari AN, Agaram NP, *et al.* Prevalence of tumour-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment. *Hum Pathol* 2015;46:357–65.
12. Movva S, Wen W, Chen W, *et al.* Multi-platform profiling of over 2000 sarcomas: identification of biomarkers and novel therapeutic targets. *Oncotarget* 2015;6:12234–47.
13. Tseng WW, Malu S, Zhang M, *et al.* Analysis of the intratumoural adaptive immune response in well differentiated and dedifferentiated retroperitoneal liposarcoma. *Sarcoma* 2015;2015:547460.
14. Feng Y, Shen J, Gao Y, *et al.* Expression of programmed cell death ligand 1 (PD-L1) and prevalence of tumour-infiltrating lymphocytes (TILs) in chordoma. *Oncotarget* 2015;6:11139–49.
15. Fritzsching B, Fellenberg J, Moskovszky L, *et al.* $CD8^+/FOXP3^+$–ratio in osteosarcoma microenvironment separates survivors from non-survivors: a multicenter validated retrospective study. *Oncoimmunology* 2015;4:e990800.
16. Tawbi HA, Burgess MA, 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;18:1493–501.
17. Burgess MA, Bolejack V, Schuetze S, *et al.* Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated/pleomorphic liposarcoma (LPS): final results of SARC028 expansion cohorts [abstract 11015]. *J Clin Oncol* 2019;39:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.11015; cited 12 September 2019]
18. Ben-Ami E, Barysauskas CM, Solomon S, *et al.* Immunotherapy with single agent nivolumab for advanced leiomyosarcoma of the uterus: results of a phase 2 study. *Cancer* 2017;123:3285–90.
19. Maki RG, Jungbluth AA, Gnjatic S, *et al.* A pilot study of anti-CTLA4 antibody ipilimumab in patients with synovial sarcoma. *Sarcoma* 2013;2013:168145.
20. Kim JR, Moon YJ, Kwon KS, *et al.* Tumour infiltrating PD1-positive lymphocytes and the expression of PD-L1 predict poor prognosis of soft tissue sarcomas. *PLoS One* 2013;8:e82870.
21. D'Angelo SP, Mahoney MR, Van Tine BA, *et al.* Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. *Lancet Oncol* 2018;19:416–46.
22. 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;20:837–48.
23. Lewin J, Davidson S, Anderson ND, *et al.* Response to immune checkpoint inhibition in two patients with alveolar soft-part sarcoma. *Cancer Immunol Res* 2018;6:1001–7.
24. Rosenberg SA. Cell transfer immunotherapy for metastatic solid cancer: what clinicians need to know. *Nat Rev Clin Oncol* 2011;8:577–85.
25. Pollack S, Redman MW, Wagner M, *et al.* A phase I/II study of pembrolizumab (Pem) and doxorubicin (Dox) in treating patients with metastatic/unresectable sarcoma [abstract 11009]. *J Clin Oncol* 2019;37:. [Available online at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.11009; cited 12 September 2019]
26. Toulmonde M, Penel N, Adam J, *et al.* Use of PD-1 targeting, macrophage infiltration, and IDO pathway activation in sarcomas: a phase 2 clinical trial. *JAMA Oncol* 2018;4:93–7.
27. Robbins PF, Morgan RA, Feldman SA, *et al.* Tumour regression in patients with metastatic synovial cell sarcoma and melanoma using genetically engineered lymphocytes reactive with NY-ESO-1. *J Clin Oncol* 2011;29:917–24.
28. Mahvi DM, Shi FS, Yang NS, *et al.* Immunization by particle-mediated transfer of the granulocyte macrophage colony–stimulating factor gene into autologous tumour cells in melanoma or sarcoma patients: report of a phase I/IB study. *Hum Gene Ther* 2002;13:1711–21.
29. Dillman R, Barth N, Selvan S, *et al.* Phase I/II trial of autologous tumour cell line derived vaccines for recurrent or metastatic sarcomas. *Cancer Biother Radiopharm* 2004;19:581–8.
30. Kawaguchi S, Wada T, Ida K, *et al.* Phase I vaccination trial of SYT–SSX junction peptide in patients with disseminated synovial sarcoma. *J Transl Med* 2005;3:1.
31. Finkelstein SE, Iclozan C, Bui MM, *et al.* Combination of external beam radiotherapy (EBRT) with intratumoural injection of dendritic cells as neo-adjuvant treatment of high-risk soft tissue sarcoma patients. *Int J Radiat Oncol Biol Phys* 2012;82:924–32.
32. Kawaguchi S, Tsukahara T, Ida K, *et al.* SYTSSX breakpoint peptide vaccines in patients with synovial sarcoma: a study from the Japanese Musculoskeletal Oncology Group. *Cancer Sci* 2012;103:1625–30.
33. Yee C. The use of endogenous T cells for adoptive transfer. *Immunol Rev* 2014;257:250–63.
34. Sangiolo D, Mesiano G, Gammaitoni L, *et al.* Cytokine-induced killer cells eradicate bone and soft-tissue sarcomas. *Cancer Res* 2014;74:119–29.
35. Ratnavelu K, Subramani B, Pullai CR, *et al.* Autologous immune enhancement therapy against an advanced epithelioid sarcoma: a case report. *Oncol Lett* 2013;5:1457–60.
36. Sato Y, Nabeta Y, Tsukahara T, *et al.* Detection and induction of CTLs specific for SYT–SSX—derived peptides in HLA-$A24^+$ patients with synovial sarcoma. *J Immunol* 2002;169:1611–18.
37. Takahashi R, Ishibashi Y, Hiraoka K, *et al.* Phase II study of personalized peptide vaccination for refractory bone and soft tissue sarcoma patients. *Cancer Sci* 2013;104:1285–94.
38. Dillman RO, Wiemann M, Nayak SK, DeLeon C, Hood K, DePriest C. Interferon-gamma or granulocyte–macrophage colony stimulating factor administered as adjuvants with a vaccine of irradiated autologous tumour cells from short-term cell line cultures: a randomized phase 2 trial of the Cancer Biotherapy Research Group. *J Immunother* 2003;26:367–73.