Immunotherapies in sarcoma: Updates and future perspectives

Marwan Ghosn, Elie El Rassy, Hampig Raphael Kourie

Marwan Ghosn, Elie El Rassy, Hampig Raphael Kourie, Department of Oncology, Hotel Dieu de France University Hospital, Faculty of Medicine, Saint Joseph University, Beirut 2038 3054, Lebanon

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Correspondence to: Elie El Rassy, MD, Department of Oncology, Hotel Dieu de France University Hospital, Faculty of Medicine, Saint Joseph University, Monot St, Beirut, PO Box 166830, Beirut 2038 3054, Lebanon. elie.rassy@hotmail.com
Telephone: +961-1-615300
Fax: +961-1-615300

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Abstract

Sarcomas are malignant tumors that are characterized by a wide diversity of subtypes with various cytogenetic profiles. Despite major treatment breakthroughs, standard treatment modalities combining chemotherapy, radiotherapy, and surgery failed to improve overall survival. Therefore, high expectations are foreseen with immunotherapy upon its maturation and better understanding of its mechanism of action. This paper presents a targeted review of the published data and ongoing clinical trials in immunotherapies of sarcomas, mainly adoptive cell therapies, cancer vaccines and immune checkpoint inhibitors.

Key words: Adoptive cell therapy; Cancer vaccines; Immunotherapy; Immune checkpoint inhibitors; Sarcoma

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Core tip: This paper is a review that outlines the most recent updates on the immunotherapy treatment of sarcomas. After a brief review of the concept of immunotherapies and the different treatment modalities, we discuss the available data, the limitations and future perspectives of each treatment option.

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INTRODUCTION

Sarcomas are malignant tumors that derive from embryonic mesodermic tissues including fat, muscles, bones, nerves and blood vessels[1]. Epidemiologic studies report its predominance in the pediatric populations and its rare occurrence in adults[2]. Sarcomas are
characterized by a wide diversity of subtypes with various cytogenetic profiles conferring treatment resistances. These findings combined with an advanced stage at diagnosis substantially increase the years of life lost[3]. The standard treatment modalities combining chemotherapy, radiotherapy, and surgery have failed to improve overall survival (OS)[4]. Despite the major breakthroughs in the treatment armamentarium, the recent data reports a relative 5-year survival rate limited to 66% for bone and soft tissue sarcomas, 53.9% for osteosarcomas, 75.2% for chondrosarcomas, and 50.6% for Ewing's sarcomas[5].

Interestingly, Coley described in 1891 a complete regression of sarcomas secondary to severe episodes of erysipelas but failed to regenerate these results in other patients[6]. The Food and Drug Administration thereafter banned the use of toxin therapy without a new drug-approval process. Fortunately, Coley's paper has encouraged scientists to analyze the role of the immune system in carcinogenesis[7].

After more than a century since Coley’s research efforts that marked the history of immunotherapy, we present a review on this elegant treatment modality in the management of sarcomas including adoptive cell therapies (ACT), monoclonal antibodies, vaccines, and immune checkpoint inhibitors (ICI).

**APPROVED THERAPIES IN SARCOMAS FROM CHEMOTHERAPY TO TARGETED THERAPIES**

Specialized centers in the management of sarcomas have demonstrated a better OS and low recurrence rate[8]. Yet, all patients are managed uniformly according to their prognosis dictated by the stage of the disease, which is determined by the grade, depth and size of the tumor[9]. For patients with localized disease, a complete resection with wide 2-3 cm margins followed by adjuvant radiation therapy is the mainstay treatment for a curative approach. However, survival is not only determined by local control since most patients die from systemic disease. The choice of the chemotherapy regimen depends on the tumor chemosensitivity which varies with the tumor subtype and grade, the patient’s performance status, and the timing of metastatic disease[10]. Unfortunately, the benefits of adjuvant chemotherapy are limited to rhabdomyosarcomas, osteosarcomas and Ewing’s sarcomas. Moreover, Trabectidine is showing promising results encountered in the adjuvant and neoadjuvant settings of patients with myxoid liposarcomas[11]. The role of adjuvant and neoadjuvant chemotherapy in the management of soft tissue sarcomas is yet to be clearly established. The actual recommendations by NCCN and ESMO are to address this issue on a case by case basis according to the patient’s performance status, comorbid factors, disease location, tumor size, and histologic subtype. In case of advanced and recurrent sarcomas, induction regimens include Cyclophosphamide and Ifosfamide, Vincristine, Doxorubicin, Dactinomycin, and Etoposide[12]. For patients with unresectable or metastatic disease, the management plan is limited to a palliative approach with Trabectedin or Ifosfamide and Doxorubicin based chemotherapy[13,14].

The rationale of using targeted therapies in sarcomas goes back to 1984 when sarcomagenesis was correlated to recurrent translocations[15]. Genetic profiling thus defined two groups of sarcomas. The first group is characterized by a simple karyotype associated with specific tumor genetic alterations that include chromosomal translocations, oncogenetic mutations, and recurrent gene amplifications. The second group is characterized by a complex karyotype associated with nonspecific and nonrecurring genetic alterations[16]. Subsequent to these advances, Pazopanib, a multitargeted tyrosine kinase inhibitor against VEGFR1-3, PDGFRA-B, and KIT was approved for pretreated metastatic nonlipomatous sarcomas based on the phase III PALETTE study[17]. Clinical and preclinical mechanistic studies are being conducted to validate a possible therapeutic role of the various targeted therapies available. Among these novel targeted therapies, we report the trials of Cediranib and Sunitinib in alveolar soft part sarcoma, Tivantinib and Cabozantinib in clear cell sarcoma, Imatinib in dermatofibrosarcoma protuberans, Cabozantinib in endometrial stromal tumors, and Everolimus in perivascular epithelioid cell tumor[18].

**ADVANCES IN IMMUNO-ONCOLOGY**

In fact, the previous cancer treatment approaches addressed distinctive and complementary hallmarks of carcinogenesis that included sustained proliferative signaling, evasion of growth suppressors, resistance of cell death, enabling of replicative immortality, induction of angiogenesis and activation of invasions and metastasis[19]. The well-known conventional cytotoxic drugs and targeted therapies have reached a plateau in effect that required a re-assessment of the six hallmarks of carcinogenesis.

Recent conceptual progress has added two new hallmarks, namely reprogramming of energy metabolism and signaling interactions of the tumor microenvironment[20].

The later resides in the concept of the cancer-immunity cycle and is actually a turning point in the history of cancer therapy[21]. This cycle is the result of a counterbalance between immune-stimulatory and inhibitory factors. It occurs physiologically and starts with the release of cancer cell antigens and ends with the apoptosis of cancer cells via the activated effectors of the immune system[22]. Subsequently, cancer immunoeediting may proceed with any of the three following phases[23]. The elimination phase describes an activation of the innate and adaptive immune effectors in response to cytokine secretion. The equilibrium phase occurs in the setting of a balance between tumor immune destruction and proliferation. The immunologic phase takes place when the tumor cells are capable of evading the immune system[24].

Recent advances recommend addressing only one step of the immune cycle to avoid potential unwanted
activation of autoimmunity mechanism and normal cells damage. Therefore, immunotherapy aims at initiating or maintaining the cancer-immunity cycle by acting on its rate limiting step. Consequently, ICI often address the immunostar function of the tumor microenvironment[24]. The PD-1/PD-L1 axis is a potential therapeutic target in view of the confirmed expression of PD-L1 in various sarcomas[25]. Inhibition of this axis enables the immune system to quickly adapt to cancer resistances thus allowing durable responses with ICI[26].

**IMMUNOTHERAPEUTIC MODALITIES EVALUATED IN SARCOMAS**

Sarcomas mainly occur either secondary to the activation of oncogenes via translocations and inversions, or secondary to the natural expression of germ cell peptides[27,28]. The issuing peptides generate an immune cascade directed against the aberrant cells[29]. Consequently, multiple rationales to immunotherapy including ACT, therapeutic vaccines, and ICI have been assessed in the treatment of sarcomas (Table 1).

**Adoptive cell therapy in sarcomas**

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 the tumor cells. Those T-cells may be harvested from tumor infiltrating lymphocytes (TIL) and re-transfused into the same patient after ensuring their expansion. Lymphocyte T-cells may also be harvested from peripheral blood, and those that recognize tumor antigens are selectively expanded. Alternatively, lymphocyte T-cells may be genetically engineered either by modifying a T-cell receptor for cancer antigen (transgenic TCR) or by adding a chimeric antigen receptor (CAR) that recognizes a specific cancer antigen[30,31]. Apart from T-cells, NK ACT has also been proven efficacious with several advantages over the classical T-cell ACT in the absence of MHC/HLA restriction, namely their NKG2D-dependent cytotoxicity against autologous tumor cells[30,31].

To our knowledge, the use of TIL has never been reported in the treatment of sarcomas whilst the use of NK ACT has been limited to case reports[33]. On the other hand, tumor antigens such as GD2 (93% of sarcomas) and NY-ESO-1 (80% to 100% of different subtype of sarcomas) were found to represent interesting targets for adoptive cells therapies. Moreover, other cancer tests antigens such as LAGE, MAGE-A3 and PRAME were frequently expressed in sarcomas and would be potential immunotherapeutic targets. In this setting, a phase I study evaluated the ability of adoptively transferred autologous T-cells transduced with a T-cell receptor (TCR) directed against NY-ESO-1 to mediate tumor regression in patients with metastatic synovial cell sarcoma expressing NY-ESO-1. The results showed an objective clinical response in 4 out of 6 patients[31].

Two ongoing trials are evaluating genetically engineered NY-ESO-1 T-cells for children and adults in metastatic synovial sarcoma (NCT01343043). Another phase I trial is testing the role of CAR T-cell therapy targeting the GD2 protein in children and young adults with sarcomas and rhabdomyosarcomas (NCT00743496).

**Therapeutic vaccines in sarcomas**

The therapeutic effects of cancer vaccines rely on the activation of dendritic cells upon the presence of an immunogenic predetermined antigen. However, most of the initial studies of vaccines in sarcomas did not determine specific antigens and used inefficaciously the entirety of the tumor cells[34,35]. Later studies used SYT-SSX, a fusion derived peptide present in 90% of synovial sarcoma, and also failed to demonstrate an objective response[36-38]. Takahashi *et al*[39] personalized the peptide vaccination patients with refractory sarcoma and administered multiple tumor antigens chosen according to preexisting peptide-specific IgG titers. The median OS was 9.6 mo with disease stabilization occurring in 30% of patients but no objective responses were seen. Another vaccination modality used *in situ* vaccination through combining preoperative gamma radiation (50 Gy) with intratumoral dendritic cells injection. The studied population was limited to high risk, localized, and resected extremity soft tissue sarcoma and resulted in 71% progression free survival at one year[40].

Major efforts in this field are being conducted namely in children with Ewing sarcomas. Recent data demonstrated a 75% OS at one year with FANG immunotherapy in adolescent patients with Ewing’s sarcoma. The treatment was well tolerated with a favorable OS[41]. 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 demethylating agent and a cancer vaccine composed of dendritic cells pulsed with overlapping peptides of NY-ESO-1, MAGE-A1, and MAGE-A3 (NCT01241162). Another dendritic cell vaccine is also being assessed in combination with Gemcitabine in a phase I trial for adults and children with soft tissue and bone sarcomas (NCT01803152).

**Immune checkpoint inhibitors in sarcomas**

The concept of ICI relies on deactivating the suppressed activity of the immune system. ICI remove the brakes (PD-1 and CTLA4) thus enhancing the immune function of already sensitized T-cells. Effectively, PD-1 and CTLA4 inhibitors are showing interesting results with acceptable response rates in different cancers, including those considered for a long time as non-immunogenic[42]. Unlike CTLA4 inhibitors, the response to PD1 and PDL-1 inhibitors has been correlated with the expression of PD-1 and PDL-1 on tumor cells and to the mutational load of the tumors[43]. Moreover, PD-1 and PDL-1 expression seems to vary between sarcoma subtypes, a finding that may direct immunotherapy management in patients with sarcomas[43].
Unfortunately, the efficacy of ICI in sarcomas has been evaluated in only one study so far. It is a phase II study that administered Ipilimumab (3 mg/kg intravenously every 3 wk for 3 cycles), a CTLA-4 inhibitor, to six patients with synovial sarcoma. The median OS was 8.75 mo ranging between 0.8 and 19.7 mo. The study was closed prematurely when none of the patients had an objective tumor response. All patients expressed NY-ESO-1 but its titers did not change after treatment administration. PD-1 and PDL-1 inhibitors present a different mechanism of action compared to anti-CTLA4 agents and consequently may present better response rates. Many ongoing phase I trials are assessing the role of anti-PD1 agents in sarcomas as single agent or in combination with Ipilimumab and Dasatinib (NCT0 1643278).

**PERSPECTIVE**

The proof of the immunotherapy concept in sarcomas has been undoubtedly validated with the benefits encountered upon the use of liposomal muramyl-tripeptide-phosphatidylethanolamine, an immunoinactivator agent derived from BCG. However, its role remains controversial in view of the discordant results between the preliminary data and final results in both the adjuvant and metastatic setting. Even though the actual trend is moving towards immunotherapy as an essential tool in the treatment of cancer, the recent ASCO 2016 meeting was unfortunately disappointing in this regard. Five studies have been presented, of which one trial of chemotherapy (Busulphan and Melphalan), three trials of tyrosine kinase inhibitors, monotherapy (Anlotinib and Regorafenib) or in combination with chemotherapy (Gemcitabine plus Pazopanib), and one study reporting the evident detrimental impact of disease progression and altered quality of life on the long-term care and survival of patients with sarcomas. The ongoing trials including the promising results of immunotherapies are awaited. The available results reported a failure of Pembrolizumab in multiple soft tissue sarcomas (NCT02301039) and Nivolumab in metastatic uterine leiomyosarcoma (NCT02428192) despite the promising findings encountered with Nivolumab in retrospective experiences. In fact, the biological preclinical rationale is not fully elucidated in view of the absence of any correlation between PD-L1 expression and OS. Thus, the actual state of knowledge does not predict the patient profile that might benefit from immunotherapy.

**CONCLUSION**

The cornerstone treatment for sarcomas consists of complete surgical resection, chemotherapy, and radiotherapy. Unfortunately, these treatment options fall short from achieving an optimal clinical outcome. Immunotherapy is therefore expected to further improve the survival of patients with sarcomas. Until recently, the field of immunotherapy has not yet matured enough to present robust effects. The better understanding of oncoimmunotherapy principles is essential to adjust the design of clinical trials and the selection of inclusion criteria. The published data shows that ACT is yet to be more elucidated and evaluated, vaccine therapy requires tailoring and personalization, and ICI, preferably PD-1 and PDL-1 inhibitors, necessitate better patient selection. Such results

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**Table 1 Summary of the phase I/II trials of immunotherapies in sarcoma**

| Treatment modality | Ref. | Agent | Phase/Patients | Indication | RR | Survival |
|-------------------|------|-------|----------------|------------|----|----------|
| Adoptive cell therapy | Robbins et al[31], 2011 | Adoptively transferred autologous T cells transduced with a T-cell receptor directed against NY-ESO-1 | 1 /6 | Metastatic synovial cell sarcoma expressing NY-ESO-1 | RR: 4/6 | N/A |
| Vaccines | Malvi et al[32], 2002 | GM-CSF treated tumor cells | 1 /16 | Melanoma and sarcomas | RR: 1/16 | N/A |
| | Dillman et al[33], 2004 | Autologous tumor cell line-derived vaccines | 1 /23 | Recurrent or metastatic sarcoma | No objective response assessed | 10 patients lived more than 1 year | N/A |
| Kawaguchi et al[34], 2005 | Vaccination By SYT-SSX junction peptide | 1 /6 | Disseminated synovial sarcoma | RR: 0/6 | N/A |
| Kawaguchi et al[35], 2012 | SYT-SSX breakpoint peptide vaccines | 1 /21 | Metastatic synovial sarcoma | SD: 6/21 | Median OS: 9.6 mo | One-year PFS: 70.6% |
| Takahashi et al[36], 2013 | Personalized peptide vaccination | 1 /20 | Refractory bone and soft tissue sarcoma | SD in all patients | Median OS: 70.6% |
| Finkelstein et al[37], 2012 | Combination of external beam radiotherapy with intratumoral injection of dendritic cells | 1 /17 | Nesoadjuvant treatment in high-risk soft tissue sarcoma | RR: 9/17 | N/A |
| Ghisoli et al[38], 2015 | FANG autologous immunotherapy | 1 /12 | Advanced and metastatic Ewing's sarcoma | RR: 1/12 | One-year OS: 75% |
| Checkpoint inhibitors | Makki et al[39], 2013 | Ipilimumab | 1 /6 | Advanced synovial sarcoma | RR: 0/6 (closed prematurely) | Median OS: 8.75 mo |

GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; N/A: Not available; OS: Overall survival; PFS: Progression free survival; RR: Response rate.
would allow more understanding of the antitumor immunity mechanisms and improvement of the treatment arsenal against sarcomas.

REFERENCES

1. Burningham Z, Hashibe M, Spector L, Schiffman JD. The epidemiology of sarcoma. Clin Sarcoma Res 2012; 2: 14 [PMID: 23036164 DOI: 10.1186/2045-3329-2-14]

2. Star Database: Incidence - SEER 9 Regs Research Data, Nov 2012; Rimbaut C, Buffe D, Zucker JM, Mazabraud A.

3. 2014; Molecular biology of soft-tissue sarcomas.

4. Stat Database: Incidence - SEER 9 Regs Research Data, Nov 15 2013

5. Against sarcomas.

6. Molecular mechanisms and improvement of the treatment arsenal would allow more understanding of the antitumor immunity mechanisms and improvement of the treatment arsenal against sarcomas.

7. Ray-Coquard I, Modlin RL, Coley WB, Damron TA, National Cancer Institute.

8. DOI: 10.1200/JCO.2004.05.210

9. Taamma A, Jimeno J, Martin C, Salhi Y, Cvitkovic E, Misset JL.

10. Intensive chemotherapy with doxorubicin and ifosfamide in patients J Clin Oncol 2003; 21: 317-321 [PMID: 9626808]

11. Mccarter MD, Jaques DP, Brennan MF. Randomized clinical trials in soft tissue sarcoma. Surg Oncol Clin N Am 2002; 11: 11-22 [PMID: 11928795]

12. Kobl EA, Kushner BH, Gorlick R, Laverdiere C, Healey JH, La Quaglia MP, Huvos AG, Qin J, Vu HT, Wexler L, Wolden S, Meyers PA. Long-term event-free survival after intensive chemotherapy for Ewing's family of tumors in children and young adults. J Clin Oncol 2003; 21: 3423-3430 [PMID: 12972518 DOI: 10.1200/JCO.2003.10.033]

13. Patel SR, Vadhvan-Raj S, Burgess MA, Plager C, Papadopolous N, Jenkins J, Benjamin RS. Results of two consecutive trials of dose-intensive chemotherapy with doxorubicin and ifosfamide in patients with sarcomas. J Clin Oncol 1998; 26: 317-321 [PMID: 9626808]

14. Yavine A, Rofirio M, Blay JY, Brain E, Alexandre J, Kahatt C, Taamna A, Jimeno J, Martin C, Salhi Y, Cvitkovic E, Misset JL. Phase II study of eteinsinacid-734 in advanced pretreated soft tissue sarcoma patients. J Clin Oncol 2004; 22: 890-899 [PMID: 14990645 DOI: 10.1200/JCO.2004.05.210]

15. Aurias A, Rimbaut C, Buffe D, Zucker JM, Mazabraud A. Translocation involving chromosome 22 in Ewing's sarcoma. A cytogenetic study of four fresh tumors. Cancer Genet Cytofgenet 1984; 12: 21-25 [PMID: 6713357]

16. Coindre JM. [Molecular biology of soft-tissue sarcomas]. Bull Cancer 2010; 97: 1373-1345 [PMID: 21084242 DOI: 10.1684/bdc.2010.1213]

17. Coens C, van der Graaf WT, Blay JY, Chawla SP, Judson I, Sanfilippo R, Manson SC, Hodge RA, Marreaud S, Prins JB, Lugowska I, Litiere S, Bottomley A. Health-related quality-of-life results from PALETTE: A randomized, double-blind, phase 3 trial of pazopanib versus placebo in patients with soft tissue sarcoma whose disease has progressed during or after prior chemotherapy-a European Organization for research and treatment of cancer soft tissue and bone sarcoma group global network study (EORTC 62072). Cancer 2015; 121: 2933-2941 [PMID: 26033286 DOI: 10.1002/cncr.29426]

18. Linch M, Miah AB, Thway K, Judson IR, Benson C. Systemic treatment of soft-tissue sarcoma-gold standard and novel therapies. Nat Rev Clin Oncol 2014; 11: 187-202 [PMID: 24642677 DOI: 10.1038/nrcan.2014.26]

19. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100: 57-70 [PMID: 10647931]

20. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011; 144: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

21. Chen DS, Millman I. Oncology meets immunology: the cancer-immunity cycle. Immunity 2013; 39: 1-10 [PMID: 23890059 DOI: 10.1016/j.immuni.2013.07.012]

22. Motz GT, Cokouks G. Deciphering and reversing tumor immune suppression. Immunity 2013; 39: 61-73 [PMID: 23890064 DOI: 10.1016/j.immuni.2013.07.005]

23. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoeediting: integrating immunobiology and roles in cancer suppression and promotion. Science 2011; 331: 1565-1570 [PMID: 21436444 DOI: 10.1126/science.1203486]

24. Predina J, Erusalov E, Judy B, Kapoor V, Cheng G, Wang LC, Sun J, Moon EK, Friedlinger ZG, Albeda S, Singhal S. Changes in the local tumor microenvironment in recurrent cancers may explain the failure of vaccines after surgery. Proc Natl Acad Sci USA 2011; 108: E415-E424 [PMID: 23271806 DOI: 10.1073/pnas.1118501108]

25. Kim C, Kim JK, Jung H, Chon HI, Han JW, Shin KH, Hu H, Kim KS, Choi YD, Kim S, Lee YH, Suh JS, Ahn JB, Chung HC, Noh SH, Rha SY, Kim SH, Kim HS. Prognostic implications of PD-L1 expression in patients with soft tissue sarcoma. BMC Cancer 2016; 16: 434 [PMID: 27393385 DOI: 10.1186/s12885-016-2451-6]

26. Russier DM, O'Neill L, Nieves LM, McAfee MS, Holechek SA, Collins AW, Dickman P, Jacobsen J, Hingerori P, Blattmann JN. Enhanced T-cell immunity to osteosarcoma through antibody blockade of PD-1/PD-L1 interactions. J Immunother 2015; 38: 96-106 [PMID: 25715499 DOI: 10.1007/s10875-015-00065]

27. Worley BS, van den Broeke LT, Goletz TJ, Pendleton CD, Daschbach EM, Thomas KE, Marincola FM, Helman LJ, Berzofsky JA. Antigenicity of fusion proteins from sarcoma-associated chromosomal translocations. Cancer Res 2001; 61: 6808-6873 [PMID: 11559563]

28. Tseng WW, Somaiah N, Engelman EG. Potential for immunotherapy in soft tissue sarcoma. Hum Vaccin Immunother 2014; 10: 3117-3124 [PMID: 25625925 DOI: 10.4161/21645515.2014.93003]

29. Makri RG. Immunity against soft-tissue sarcomas. Curr Oncol Rep 2003; 5: 282-287 [PMID: 12781069]

30. Yee C. The use of endogenous T cells for adoptive transfer. Immunol Rev 2014; 257: 250-263 [PMID: 24329802 DOI: 10.1111/imr.12134]

31. Robbins PF, Morgan RA, Feldman SA, Yang JC, Sherry RM, Dudley ME, Wunderlich JR, Nahvi AV, Helman LJ, Mackall CL, Kammluma US, Hughes MS, Ruffolo NF, Raffeld M, Lee CC, Levy CL, Li YF, El-Garallah M, Schwartz SL, Laurencot C, Wei BL, Thomas EK, Marincola FM, Helman LJ, Berzofsky JA. Antigenicity of fusion proteins from sarcoma-associated chromosomal translocations. Cancer Res 2001; 61: 6808-6873 [PMID: 11559563]

32. Sangiolo D, Mesiano G, Giannattasio L, Leuci V, Dotoridiani M, Giraudo I, Cammarata C, Dell'Aglio C, D'Ambrosio L, Piscanne A, Sarotto I, Miano S, Ferrero I, Carnevale-Schiante F, Pignochino
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Y, Sassi F, Bertotti A, Paciello W, Fagioli F, Aglietta M, Grignani G. Cytokine-induced killer cells eradicate bone and soft-tissue sarcomas. Cancer Res 2014; 74: 119-129 [PMID: 24356422 DOI: 10.1158/0008-5472.CAN-13-1559]

Rattavelu K, Subramani B, Puliia CR, Krishnan K, Sugasdan RD, Rao MS, Veerakumarasivam A, Deng X, Hiroshi T. Autologous immune enhancement therapy against an advanced epithelialoid sarcoma: A case report. Oncol Lett 2013; 5: 1457-1460 [PMID: 23761810 DOI: 10.3892/ol.2013.1247]

Mahvi DM, Shi FS, Yang NS, Weber S, Hank J, Albertini M, Schiller J, Schahle H, Larson M, Pharo L, Gan J, Heisey D, Warner T, Sondel PM. Immunization by particle-mediated transfer of the granulocyte-macrophage colony-stimulating factor gene into autologous tumor cells in melanoma or sarcoma patients: report of a phase IIB study. Hum Gene Ther 2002; 13: 1711-1721 [PMID: 12396624 DOI: 10.1089/9/104303402760293556]

Dillman R, Barth N, Selvan S, Beutel L, de Leon C, DePriest C, Peterson C, Nayak S. Phase I/II trial of autologous tumor cell line-derived vaccines for recurrent or metastatic sarcomas. Cancer Biother Radiopharm 2004; 19: 581-588 [PMID: 15650450 DOI: 10.1089/cbr.2004.19.581]

Kawaguchi S, Wada T, Ida K, Sato Y, Nagoya S, Tsukahara T, Kimura S, Sahara H, Ikeda H, Shimozawa K, Asanuma H, Torigoe T, Hiraga H, Ishii T, Tazekazi SI, Sato N, Yamashita T. Phase I vaccination trial of SYT-SSX junction peptide in patients with disseminated synovial sarcoma. J Transl Med 2005; 3: 1 [PMID: 15647119 DOI: 10.1186/1479-5876-3-1]

Sato Y, Nabeta Y, Tsukahara T, Hirohashi Y, Syunrui R, Maeda A, Sahara H, Ikeda H, Torigoe T, Ichimiya S, Wada T, Yamashita T, Hiraga H, Kawai A, Ishii T, Araki N, Myoi A, Matsumoto S, Umeda T, Ishii S, Kawaguchi S, Sato N. Detection and induction of CTLs specific for SYT-SSX-derived peptides in HLA-A24(+) patients with synovial sarcoma. J Immunol 2002; 169: 1611-1618 [PMID: 12139991]

Kawaguchi S, Tsukahara T, Ida K, Kimura S, Murase M, Kano M, Emori M, Nagoya S, Kaya M, Torigoe T, Ueda E, Takahashi A, Ishii T, Tazekazi SI, Toguchiha J, Tsuchiya H, Osumi T, Sugita T, Sugihara H, Ieguchi M, Iba K, Hamada K, Kikizaki H, Mori T, Yasuda T, Tanizawa T, Ogose A, Yabe H, Yamashita T, Sato N, Wada T. SYT-SSX breakpoint peptide vaccines in patients with synovial sarcoma: a study from the Japanese Musculoskeletal Oncology Group. Cancer Sci 2012; 103: 1625-1630 [PMID: 22726592 DOI: 10.1111/j.1349-7006.2012.02570.x]

Takahashi Y, Ishibashi Y, Hiraoka K, Matsueda S, Kawano K, Kawahara A, Kage M, Ohshima K, Yamanaka R, Shihoju S, Shirouzu K, Itoh K, Sasada T. Phase II study of personalized peptide vaccination for refractory bone and soft tissue sarcoma patients. Cancer Sci 2013; 104: 1285-1294 [PMID: 23829867 DOI: 10.1111/cas.12226]

Finkelsstein SE, Iclozan C, Bui MM, Cotter MJ, Ramakrishnan R, Ahmed J, Noyes DR, Cheong D, Gonzalez RJ, Heysk RA, Berman C, Lenox BC, Janssen W, Zager JS, Sondak VK, Letson GD, Antonia SJ, Gabrilovich DI. Combination of external beam radiotherapy (EBRT) with intratumoral injection of dendritic cells as neo-adjuvant treatment of high-risk soft tissue sarcoma patients. Int J Radiat Oncol Biol Phys 2012; 82: 924-932 [PMID: 21398051 DOI: 10.1016/j.ijrobp.2010.12.068]

Ghisolii M, Barve M, Schneider R, Menzel R, Lenarsky C, Wallraven G, Pappen BO, LaNoue J, Kumar P, Nemunaitis D, Roth A, Nemunaitis J, Whiting S, Senzer N, Fletcher EA, Nemunaitis J. Pilot Trial of FANG Immunotherapy in Ewing’s Sarcoma. Mol Ther 2015; 23: 1103-1109 [PMID: 25917459 DOI: 10.1038/mt.2015.43]

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, Powelley DR, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardoll DM, Chen L, Sharifman WH, Anders RA, Taube JM, McMüller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012; 366: 2443-2454 [PMID: 22658127 DOI: 10.1056/NEJMoa120690]

Kim JR, Moon YJ, Kwon KS, Bae JS, Wagle S, Kim KM, Park HS, Lee H, Moon WS, Chang MJ, Kang MJ, Jung KY. Tumor infiltrating PD1-positive lymphocytes and the expression of PD-L1 predict poor prognosis of soft tissue sarcomas. Cancer Res 2013; 73: 12439382 DOI: 10.1371/journal.pone.0082870

Maki RG, Jungbluth AA, Gnir S, Schwartz G, D’Adamo DR, Keohan ML, Wagner M, Scheu K, Chiu R, Ritter E, Kachell J, Lowy I, Old LJ, Ritter G. A Pilot Study of Anti-CTLA4 Antibody Ipilimumab in Patients with Synovial Sarcoma. Sarcoma 2013; 2013: 168145 [PMID: 23554566 DOI: 10.1155/2013/168145]

Paoluzzi I, Ghesani MV, Caravio A, Rakiewicz A, Rosen G. Anti-PD1 therapy with nivolumab in sarcoma. J Clin Oncol 2013; 31: suppl: abstr 11047 [accessed 2016 Sep 3]. Available from: URL: http://meetinglibrary.asco.org/content/166876-176

D’Angelo SP, Shoushtari AN, Agaram NP, Kuk D, Qin LX, Carvajal RD, Dickson MA, Gounder M, Keohan ML, Schwartz GK, Tap WD. Prevalence of tumor-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment. Hum Pathol 2015; 46: 357-365 [PMID: 25540867 DOI: 10.1016/j.humpath.2014.11.001]

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