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Immunotherapy in sarcoma

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The introduction of immunotherapy with checkpoint inhibitors into clinical practice has radically changed the treatment and prognosis of patients with cancer. This treatment is also extensively studied in patients diagnosed with advanced sarcomas, where the number of effective therapies is limited. The following review presents the latest reports on the use of immunotherapy in the treatment of patients with sarcomas.

Key words: sarcoma, soft tissue, bone, immunotherapy, anti-PD-1

Sarcomas are rare malignant tumors comprising about 1% of all adult cancers. Sarcomas can be found both in the soft tissues (STS) and bones (BS). Moreover, they affect all age groups, with a median age for STS patients of about 50-year-old, but much younger for bone tumors such as osteosarcoma or Ewing sarcoma. The cornerstone of therapy of locally advanced sarcomas is surgery, in most cases used with adjuvant radiotherapy and chemotherapy. However, metastatic recurrence is often found and concerns even 50% of sarcoma cases, depending on the subtype and initial tumor stage. As there are more than 60 subtypes of sarcoma, with different prognosis, risk of recurrence and sensitivity to systemic therapy, heterogeneity within this group of tumors and its rarity make it extremely difficult to develop a successful clinical trial for this group of patients. Furthermore, research undertaken over recent years has proven this thesis with several negative phase three trials for new therapies in sarcomas [1, 2].

Immunotherapy is based on the idea that a patient's immune system can be stimulated or enhanced so as to attack malignant tumors. As an anecdote, it is worth recalling that one of the first successful examples of the use of immunotherapy in cancers was described more than 100 years ago in sarcoma patients. They were treated by Dr. William B. Coley, who injected streptococcal organisms into patients with inoperable cancer, with some success; this consequently resulted in him being

given the title of the "Father of Immunotherapy" [3]. From that time, much has changed, and in recent years we have witnessed a real revolution in the use of immunotherapy to treat malignant tumors. We owe this breakthrough mainly to the introduction into clinical practice of drugs from the checkpoint inhibitors group, which have shown improved rates of patient survival with melanoma, lung cancer, or kidney cancer, among others.

Knowledge about the immune profile of sarcomas is still limited. Several important studies on this topic have already been published, although their results can sometimes be confusing because of the heterogeneity of this group of tumors [4]. This review will present some of the latest immunotherapy achievements in sarcoma, focusing on trials with checkpoint inhibitors in less selected groups of patients and in specific subtypes, where it seems that this type of therapy is most successful.

Immune checkpoints in sarcomas

One of the first studies analyzed the clinical impact of intra-tumoral infiltration of PD1-positive lymphocytes and PD-L1 expression in tumor cells in 105 cases of STS. Intra-tumoral infiltration of PD1-positive lymphocytes and PD-L1 expression was seen in 65% and 58% of STS, respectively. Both PD1-positivity and PD-L1 expression were significantly associated

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with advanced clinicopathological parameters such as higher clinical stage, distant metastasis, higher histological grade, a low differentiation of tumor and tumor necrosis. Moreover, both PD1-positivity and PD-L1 positivity were independent prognostic indicators of overall survival (OS) and event-free survival (EFS) of STS by multivariate analysis. The combined pattern of PD1- and PD-L1-positivity was also an independent prognostic indicator for OS and EFS by multivariate analysis. The patients with a PD1+/PD-L1+ pattern had the shortest survival time [5]. A study from the Memorial Sloan Kettering Cancer Center evaluated PD-L1 expression by immunohistochemistry in 50 sarcoma specimens and quantified tumor-infiltrating lymphocytes (TIL). 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%. "Low-density" TILs was defined 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 tumors (9 of 14), had high-density TILs. Tumor, lymphocyte, and macrophage PD-L1 expression was 12%, 30% and 58%, respectively, with the highest frequency of PD-L1 positivity seen in gastrointestinal stromal tumors (4 of 14). There was no association between clinical features, overall survival, and PD-L1 expression in tumor or immune infiltrates [6].

In tumor tissues collected by biopsy or surgical resection, 56 osteosarcoma patients (17%) showed PD-L1 expression. PD-L1 expression was not associated with poor prognosis. PD-L1 immunorexpression was significantly associated with the infiltration of CD3+ T cells, CD4+ T cells, and CD8+ T cells [7]. In Ewing's sarcoma, CD8+ TILs were detected in 15% of samples from 370 patients, but this finding was not correlated with the histological subtypes, location of the tumor, or PD-1 and PD-L1 expression, and it did not impact progression-free survival or overall survival. PD-1 was expressed in 26% of tumors. Histological subtypes were not correlated with PD-L1 or PD-1 positivity. Metastatic tumors had higher expression of PD-L1 ($p < 0.0001$). Lesions with elevated proliferation index (Ki-67) were associated with higher PD-L1 expression ($p = 0.049$). In terms of prognosis, no significant association was found between PD-L1 expression and progression-free survival (PFS) or overall survival (OS). However lack of PD-1 expression in tumor cells was correlated with both poor PFS ($p = 0.02$) and poor OS ($p = 0.004$) [8]. In chondrosarcoma, PD-L1 expression was absent in conventional ($n = 119$), mesenchymal ($n = 19$) and clear cell ($n = 20$) chondrosarcomas. 41% (9 of the 22) of dedifferentiated chondrosarcomas displayed PD-L1 positivity. TILs were detectable and correlated with PD-L1 expression, being highly expressed in dedifferentiated chondrosarcomas.

PD-L1 expression was also correlated with positive HLA class I expression, but not with a patient's survival [9].

Overall, it seems that the expression and clinical associations were found to be subtype dependent. A study of 208 sarcoma patients, programmed cell death-1 (PD-1), programmed death ligand-1 (PD-L1) and CD8 were assessed in tumors. Primary untreated osteosarcoma ($n = 46$), Ewing sarcoma ($n = 32$), alveolar rhabdomyosarcoma ($n = 20$), embryonal rhabdomyosarcoma ($n = 77$), synovial sarcoma ($n = 22$) and desmoplastic small round cell tumors (DSRCT) ($n = 11$) were examined immunohistochemically. PD-L1 expression was predominantly detected in alveolar and embryonal rhabdomyosarcomas (15% and 16%, respectively). In the alveolar subtype, PD-L1 expression was associated with better OS, EFS and metastases-free survival. PD-1 expression on lymphocytes was predominantly seen in synovial sarcomas (18%). High levels of CD8+ lymphocytes were predominantly detected in osteosarcomas (35%) and associated with worse event-free survival in synovial sarcomas. Ewing sarcoma and DSRCTs showed PD-1 on tumor cells instead of on tumor-infiltrating lymphocytes [10].

Using transcriptomic analysis of the microenvironment cell population, measuring the expression of eight immune and two stromal cell populations, sarcomas were classified into five different sarcoma immune classes (SIC). Each SIC exhibited a different profile, from A (immune desert-cold tumors), which showed the lowest expression of gene signatures of immune cells and vasculature expression, to E (immune and tertiary lymphoid structures) with the highest expression of genes related to immune cells. In the middle, C (vascularized) was characterized by a high expression of endothelial related genes. SIC B and D have expressed mixed profiles between A and C or C and E. This grouping of sarcomas into these five classes based on different profile expressions of tumor microenvironment also had a prognostic impact. So, SIC A patients showed poorer overall survival than SIC D ($p = 0.048$) or SIC E ($p = 0.025$). Furthermore, this genomic immune signature had a predictive role in a prospective series treated with pembrolizumab. The overall response rate (ORR) was 50%, 25%, 22%, 0% and 0% for SIC E, D, C, B and A respectively. Patients harboring SIC E had significantly higher ORR with pembrolizumab ($p = 0.026$). Patients grouped as SIC E only represented 17.8% of cases. A more detailed analysis revealed a significant correlation of survival with B-cell lineage signature, whereas CD8+ signature did not significantly correlate with survival [11, 12].

Clinical trials

A large study of immunotherapy in sarcomas was published in 2017 (SARC028 Trial) [13]. In this two-cohort, single-arm, open-label, phase 2 study, 86 patients were enrolled with soft-tissue sarcoma or bone sarcoma. Patients with soft-tissue sarcoma had to be aged 18 years or older to enroll; patients with bone sarcoma could enroll if they were aged 12 years or older.

Patients had histological evidence of metastatic or surgically unresectable locally advanced sarcoma, and had received up to three previous systemic anticancer therapy lines, with at least one measurable lesion according to the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST). Included subtypes were leiomyosarcoma, poorly differentiated or dedifferentiated liposarcoma, undifferentiated pleomorphic sarcoma, synovial sarcoma, Ewing's sarcoma, osteosarcoma and dedifferentiated or mesenchymal chondrosarcoma. All patients were treated with 200 mg of intravenous pembrolizumab every three weeks. The primary endpoint was the investigator-assessed objective response. One-third of the patients previously received three lines of systemic therapy. The median follow-up was 17.8 months (IQR 12.3–19.3).

Seven (18%) out of the 40 patients with STS had an objective response, including four (40%) of the ten patients with undifferentiated pleomorphic sarcoma, two (20%) of the ten patients with liposarcoma, and one (10%) of the ten patients with synovial sarcoma. One (10%) patient with undifferentiated pleomorphic sarcoma – a woman aged 50 years with primarily pulmonary lesions whose response lasted for longer than 13 months – achieved a confirmed complete response. Responses in patients with soft-tissue sarcoma were generally durable, with a median duration of 33 weeks (IQR 23–49). No patients with leiomyosarcoma (n=10) had an objective response. In the bone sarcoma group, a confirmed partial response was observed in one (5%) of the 22 patients with osteosarcoma and one (20%) of the five patients with chondrosarcoma. No patient with Ewing's sarcoma had an objective response. 37 (93%) of the 40 evaluable patients with soft-tissue sarcoma had a progression event (i.e., progressed or died), and median progression-free survival (PFS) was 18 weeks (95% CI 8–21).

The 12-week PFS was 55% (95% CI 40–70), which was significantly higher than the threshold of 40% expected from an active regimen in patients with soft-tissue sarcoma ($p = 0.039$). The median PFS was 30 weeks (95% CI 8–68) for patients with undifferentiated pleomorphic sarcoma (seven [70%] of whom had a progression event), and 12-week PFS was 70% (42–98). In ten patients with liposarcoma (all of whom had a progression event), the median PFS was 25 weeks (95% CI 8–42), and the 12-week PFS was 60% (30–90). The median OS for patients with soft-tissue sarcoma was 49 weeks (95% CI 34–73); 25 patients died because of disease progression. The median OS for patients with undifferentiated pleomorphic sarcoma had not been reached at the time of this analysis; four patients had died. 38 (95%) of the 40 patients with bone sarcoma had a progression event; data for one (3%) patient has been censored. The median PFS was eight weeks (95% CI 7–9). 25 (63%) patients with bone sarcoma died because of disease progression; the median OS was 52 weeks (95% CI 40–72). The median OS was not reached in patients with chondrosarcoma. The median duration of response was 43 weeks.

The most frequent grade 3 or worse adverse events were anemia (six [14%]), a decreased lymphocyte count (five [12%]), prolonged activated partial thromboplastin time (four [10%]), and decreased platelet count (three [7%]) in the bone sarcoma group; anemia, decreased lymphocyte count and prolonged activated partial thromboplastin time was evident in the soft-tissue sarcoma group (three [7%] each). Nine (11%) patients (five [12%] in the bone sarcoma group and four [10%] in the soft-tissue sarcoma group) had treatment-emergent serious adverse events (SAEs), five of whom had immune-related SAEs, including two with adrenal insufficiency, two with pneumonitis and one with nephritis.

As the results of the treatment seemed to be best in the group of patients with undifferentiated pleomorphic sarcoma (UPS) and liposarcoma (LPS), the investigators decided to have an expansion cohort in these subtypes. The results were presented at the American Society of Clinical Oncology conference in 2019. 30 patients were additionally enrolled in each of the 2 expansion cohorts for a total of 40 UPS and 40 LPS patients. The primary endpoint was the investigator-assessed response by RECIST v1.1. Secondary endpoints were safety, PFS, the 12-week PFS rate and OS. An ORR of 25% was considered clinically meaningful, and <10% was considered to lack efficacy. The use of pembrolizumab was considered a success if 8 or more of the 40 enrolled patients had a partial response (PR) to therapy or better (1-sided $\alpha = 0.042$, 82% power). The ORR in the UPS cohort was 23% (9/40), with an additional 5/30 PRs observed in the expansion cohort. In the LPS cohort, the ORR was 10% (4/39 evaluable patients), with an additional 2/30 PR observed (total 4 PR). The median PFS for the UPS group was 3 months (95% CI 2–5) and 2 months (95% CI 2–4) for the LPS group. The 12-week PFS rate was 50% in UPS (95% CI 35–65) and 44% in LPS (95% CI 28–60). The UPS group had a median OS of 12 months (95% CI 7–34) and 13 months (95% CI 8–NR) for the LPS group [14].

Results of the translational research from the study were recently published. Pretreatment (available for 78 patients) and 8-week on-treatment (from 68 patients) tumor biopsies were stained for PD-L1 and multiplex immunofluorescence panels. The density of positive cells was quantified to determine associations with the anti-PD-1 response. It turned out that patients that responded to pembrolizumab were more likely to have higher densities of activated T cells (CD8 + CD3 + PD-1+) and an increased percentage of tumor-associated macrophages expressing PD-L1 pre-treatment compared with non-responders. Pre-treatment tumors from responders also exhibited higher densities of effector memory cytotoxic T cells and regulatory T cells than non-responders. Moreover, a higher density of cytotoxic tumor-infiltrating T cells at baseline correlated with better PFS [15].

Additionally, the immunotherapy combination was studied in sarcomas. An open-label, unblinded, non-comparative multi-center randomized phase II study enrolled 96 sarcoma

patients [16]. Patients received either nivolumab 3 mg/kg every two weeks or nivolumab 3mg/kg and ipilimumab 1mg/kg every three weeks for four doses followed by nivolumab (3 mg/kg) every two weeks thereafter. Patients with a central pathology confirmation of sarcoma were included. They had to be at least 18 years old to enroll and have evidence of metastatic or unresectable disease and good performance status. Patients had to have received at least one previous systemic therapy line. The primary endpoint was the confirmed objective response rate (ORR). Secondary endpoints included safety, the duration of the response, clinical benefit rate, PFS and OS.

Patients were heavily pre-treated, with 61% of patients receiving at least three prior chemotherapy lines. The most common enrolled sarcoma types across both arms included: bone nine (10.6%), LMS 29 (34.1%), LPS five (5.9%), spindle cell sarcoma 11 (12.9%), UPS 11 (12.9%) and other 10 (11.7%).

Among the 38 patients that received nivolumab monotherapy, the confirmed ORR was 5% [92% CI 1–15%]. Responses occurred in the following histological subtypes: alveolar soft part sarcoma (ASPS), non-uterine LMS and sarcoma NOS. For the 38 patients that received combination therapy, the confirmed ORR was 16%, (92% CI 7–29%). Responses occurred in UPS, LMS, myxofibrosarcoma and angiosarcoma. The median PFS was 1.7 months [n = 42, 95% CI 1.4–4.3 months] for monotherapy. The median OS was 10.7 months (n = 42, 95% CI 5.5–15.4). The 12-month OS rates were 40.4% (n = 12, 95% CI 27.2–59.9%). For combination arm, the median PFS was 4.1 months [n = 41, 95% CI 2.6–4.7] and the median OS was 14.3 months (n = 41, 95% CI 9.6–not estimable). The 12-month OS rate for combination therapy was 54.6% (n = 41, 95% CI 41–72.7%). In the monotherapy arm, the most common grade 3 or worse adverse events included anemia (four – 10%), decreased lymphocyte count (three – 7% each) and dehydration, increased lipase, pain, pleural effusion, respiratory failure, secondary benign neoplasm and urinary tract obstruction (two – 5% each.) In the combination arm, the most common grade 3 or worse adverse events included: anemia (seven – 17%), hypotension (four – 10%), pain, and urinary tract infection (three – 7%). Treatment-related serious adverse events on the monotherapy arm occurred in eight patients and included anemia, anorexia, dehydration, decreased platelet count, diarrhea, fever, increased creatinine, and pleural effusion (one – 2% each). On the combination arm, treatment-related serious adverse events occurred in 11 patients. Three patients – 7% patients had adrenal insufficiency, two patients – 5% had increased alanine aminotransferase, two patients – 5% with hyponatremia, one patient – 2% each experienced anemia, increased aspartate aminotransferase, fatigue, pain and pruritus.

In an attempt to improve the modest results of immunotherapy alone in the treatment of advanced sarcomas, efforts have also been made to combine this treatment with other drugs commonly used in this indication.

Anthracycline-based therapy is a standard first-line treatment for most patients with advanced and metastatic sarcomas. Although multiple trials have attempted to show improved outcomes in patients with soft-tissue sarcoma over doxorubicin monotherapy, each has fallen short of demonstrating improved outcomes. A nonrandomized clinical trial used a 2-stage phase 2 design and was performed to assess the efficacy and safety of doxorubicin and pembrolizumab in patients with advanced anthracycline-naïve sarcoma [17]. Patients were adults with good performance status and end-organ function. Patients with all sarcoma subtypes were allowed to enroll with the exception of those with osteosarcoma, Ewing sarcoma, and alveolar and embryonal rhabdomyosarcoma. Two dose levels of doxorubicin (45 and 75 mg/m²) were tested for safety combined with pembrolizumab. The patients' initial cycle was pembrolizumab (200 mg administered intravenously) alone. Cycles were 21 days. Starting with cycle 2, doxorubicin was given before pembrolizumab, on the same day, every 3 weeks, for up to 6 cycles. After cycle 7, pembrolizumab treatment continued for up to 2 years. The primary endpoint was ORR. Secondary endpoints were PFS and OS. Correlative studies included immunohistochemistry, gene expression and serum cytokines.

A total of 37 patients (22 men, 15 women) were treated. The median patient age was 58.4 (ranging from 25–80) years. The most common histologic subtype was leiomyosarcoma (11 patients). Doxorubicin plus pembrolizumab was well-tolerated without significant unexpected toxic effects. The ORR was 19%, and 59% of patients had stable disease. Two of the three patients with UPS and two of the four patients with dedifferentiated liposarcoma had durable response to therapy. Three patients with chondrosarcoma had tumor regression, including one conventional chondrosarcoma with a 26% decrease in size. Median PFS was 8.1 (95% CI 7.6–10.8) months. The PFS rates at 12 and 24 weeks were 81% (95% CI 64–90%) and 73% (95% CI 56–84%), respectively. At 12 months, the PFS was 27% (95% CI 14–42%). The median OS was 27.6 (95% CI 18.7–not reached) months at the time of this analysis. Immunohistochemistry was evaluable for 29 patients; 66% had PD-L1 expression scores of 0, reflecting a low level of PD-L1 expression. Expression of PD-L1 was not associated with PFS or OS. Tumor-infiltrating lymphocytes were present in 21% of evaluable tumors and associated with inferior PFS (log-rank p = 0.03). This was confirmed in a multivariate Cox regression analysis adjusted for age, sex and the number of prior therapies (p = 0.04). No dose-limiting toxic effects were observed. The most common toxic effects were nausea (n = 32) and fatigue (n = 21). No grade 5 toxic effects were seen; the only attributable grade 4 toxic effects were neutropenia (n = 6), leukopenia (n = 1) and febrile neutropenia (n = 1), all of which resolved. Two patients had grade 3 reductions in ejection fraction attributable to doxorubicin. Notable pembrolizumab-related toxic effects included grade 3 adrenal insufficiency (n = 1) and hypothyroidism (n = 7).

This result is impressive for patients with advanced sarcoma, but of course, this result must be confirmed in a phase III trial.

Another attempt is supported by evidence that tumor angiogenesis promotes immunosuppression. A phase Ib/II trial tested the double inhibition of angiogenesis (sunitinib) and PD-1/PD-L1 axis (nivolumab). This single-arm, phase Ib/II trial enrolled adult patients with selected subtypes of sarcoma [18]. Phase Ib established two dose levels: level 0 with sunitinib 37.5 mg daily from day 1, plus nivolumab 3 mg/kg intravenously on day 15, and then every 2 weeks; and level – 1 with sunitinib 37.5 mg for the first 14 days (induction) and then 25 mg per day plus nivolumab on the same schedule. The primary endpoint was to determine the recommended dose for phase II (phase I) and the 6-month progression-free survival rate, according to RECIST in Solid Tumors 1.1 (phase II). 68 patients were enrolled and treated with the experimental compounds: 16 in phase Ib and 52 in the STS cohort of phase II. The recommended dose of sunitinib for phase II was 37.5 mg as induction and then 25 mg combined with nivolumab. The 6-month PFS, according to central and local assessments, was 48% (95% CI 41–55) and 51% (95% CI 44–58), respectively. The median PFS for central and local assessments was 5.6 months (3.0–8.1) and 6 months (3.1–9), respectively. Remarkably, the proportion of patients alive at 12 and 18 months was 75% (95% CI 68–81) and 67% (95% CI 59–74), respectively, and the median OS was 24 months (95% CI NA).

The central radiological assessment according to RECIST reported 1 complete response in 46 evaluable patients (2%), 5 partial responses (11%), 33 stabilizations (72%) and 7 progressions (15%). A complete response was observed in one patient with angiosarcoma and partial response in patients diagnosed with ASPS (n = 2), angiosarcoma (n = 1), extraskeletal myxoid chondrosarcoma (n = 1) and synovial sarcoma (n = 1). Central assessment, according to Choi criteria, showed 25 patients with partial response (63%), 10 with stable disease (25%), and 5 with progressive disease (12%). According to RECIST, the response assessment showed a significant prognostic difference for PFS and OS; by contrast, the Choi assessment only had prognostic relevance for PFS. Adding the 12 evaluable STS cases of phase I to the 46 evaluable patients with STS in phase II, the RECIST Overall Response Rate (ORR) was 21% (12 out of 58). The 18-month OS proportion was 100%, 75%, and 44% for those with a response, stable disease, and progressive disease, according to RECIST, respectively (p = 0.01).

The most frequent treatment-related toxicities per subject in phase II were fatigue in 33 of the 52 patients (63.5%) and increased aspartate aminotransferase (AST) in 25 out of 52 patients (48%). The most common reported grade 3 or 4 side effects were transaminitis in 9 out of 52 patients (17.3%) and neutropenia in 6 out of 52 patients (11.5%).

Alveolar soft part sarcoma (ASPS) is an exceedingly rare STS subtype inherently resistant to cytotoxic chemotherapy. It usually affects adolescents and young adults and presents

early with widespread metastases that are ultimately fatal. The conserved translocation of the *ASPSCR1-TFE3* fusion gene in ASPS leads to aberrant transcription of downstream target genes, including HIF-1 α , which upregulates proangiogenic factors, including VEGF. Tyrosine-kinase inhibitors are the most active treatment to date for patients with ASPS, although most patients ultimately develop resistance and die due to the disease [19, 20]. This subtype is interesting because, compared to other sarcomas, it is characterized by its exceptional sensitivity to immunotherapy treatment. There are many case reports of patients diagnosed with advanced ASPS who have been successfully treated with checkpoint inhibitors, including the case of a patient treated in the clinic where the author works [21, 22]. The phase II trial with atezolizumab monotherapy, a monoclonal antibody directed against a ligand of a PD-L1, proved to be a success in this setting. The results were presented during the Connective Tissue Oncology Society Annual Conference in 2018. 22 patients with advanced, metastatic ASPS were enrolled in the trials; most of them had previously undergone other therapies. According to RECIST criteria, a partial response was confirmed in 9 patients, disease stabilization in 9 patients and disease progression in 1 patient. In the 3 other patients treated, it was too early to make any evaluations [23]. The summary of studies in ASPS with immunotherapy is shown in table I.

A single-arm, phase 2 study was conducted on the safety and efficacy of the antiangiogenic drug axitinib (VEGF inhibitor) plus pembrolizumab in patients with advanced sarcomas, including alveolar soft-part sarcoma [24]. Patients were eligible if they were aged 16 years or older and had histologically confirmed advanced or metastatic sarcomas, including alveolar soft-part sarcoma (ASPS – who constituted 36% of the whole group of 33 patients); an ECOG performance status of 0–1; and disease progression after previous treatment with at least one line of systemic therapy (unless no standard treatment existed or the patient declined therapy). The first five patients were enrolled in a lead-in cohort and were given axitinib 5 mg orally, twice daily, and pembrolizumab 200 mg intravenously for 30 min on day 8 and every 3 weeks for cycles of 6 weeks for up to 2 years. After that, patients received escalating doses of axitinib (2–10 mg) plus a flat dose of pembrolizumab according to the schedule above. The 3-month PFS for all patients was 65.6% (95% CI 46.6–79.3), and the median PFS was 4.7 months (95% CI 3–9.4). The 6-month PFS was 46.9% (95% CI 29.2–62.8) and the 12-month PFS was 27.5% (13.4–43.6). The median overall survival for all 33 patients was 18.7 months (95% CI 12–not reached) with a 1-year overall survival of 72% (95% CI 53–84.4). Of the 32 patients evaluable for objective response, none achieved a complete response. Eight (25%, 95% CI 12.1–43.8) achieved a partial response at any point during treatment, and nine (28%) achieved stable disease, so the proportion of patients who achieved a clinical benefit was 53% (n = 17; 95% CI 35–70.5). The median duration of response was 29 weeks (IQR 21.8–76.5), and the median time to achieve partial

Table I. The summary of clinical trials with immunotherapy in ASPS

Therapy	Patient number	Response rate (95% CI)	Median progression-free survival (PFS); months, 95% CI	Reference
OSCAR, nivolumab (ASPS only)	14	7.1% (0.2–33.9)	6.0 (3.7–9.3)	Kawai et al., CTOS 2020
Hindi i wsp. Anti-PD-1/anti-PD-L1 + antiangiogenic drugs (retrospective data)	21	47.6% (not reported)	10.9 (9.9–11.9)	Hindi et al., CTOS 2020
durvalumab/tremelimumab (ASPS cohort)	10	50% (not reported)	34.23 (1.84–not reached)	Somaiah et al., ASCO 2019
atezolizumab (anti-PD-L1)	31	32% (not reported)	not reported	Coyne et al., CTOS 2019
axitinib/pembrolizumab (ASPS kohort)	11	54.5% (24.6–81.9)	12.4 (2.7–22.3)	Wilky et al., Lancet Oncol 2019
geptanolimab (GB226, anti-PD-1)	37	37.8% (22.5–55.2)	6.9 (5.0–not reached)	Shi et al., Clin Cancer Res 2020
toripalimab (anti-PD1), ASPS kohort	12	25.0% (not reported)	11.1 (not reported)	Yang et al., Eur J Cancer 2020

response was 19.4 weeks (IQR 12.8–31.4). Most responses occurred in patients with ASPS, with six of the eleven evaluable patients with ASPS achieving a partial response (54.5%, 95% CI 24.6–81.9), and two (18%) of the eleven achieving stable disease, so the proportion of patients who achieved a clinical benefit was 72.7% ($n = 8$; 95% CI 32.3–92.7). The median time to partial response in patients with ASPS was 25.1 weeks (IQR 12.7–34.3). In addition, partial responses were observed in two patients, one with conventional type epithelioid sarcoma and one with soft tissue leiomyosarcoma, and minor responses (a decrease in the size of the target lesion of less than 30%) in three patients, one with soft tissue leiomyosarcoma, one with synovial sarcoma and one with high-grade undifferentiated pleomorphic sarcoma.

The toxicity profile of axitinib plus pembrolizumab therapy was consistent with the drugs' previous clinical trials as monotherapy. Treatment-related toxicity occurred in only two (40%) of the five patients in the safety lead-in cohort, and no application of the early stopping rule was needed throughout the study. Treatment-related grade 3 or 4 adverse events occurred in 13 (39%) of the 33 patients, and grade 3 or 4 autoimmune, toxic effects in five (15%) patients. The most common treatment-related adverse events of any grade included fatigue (26–79%), oral mucositis (23–70%), hypothyroidism or hyperthyroidism (21–64%), nausea or vomiting (22–67%), nasopharyngeal congestion (18–55%), and diarrhoea (19–58%). Serious treatment-related adverse events occurred in seven (21%) of the 33 patients, including autoimmune colitis, transaminitis, pneumothorax, hemoptysis, seizures and hypertriglyceridemia.

Conclusion

The rarity and heterogeneity within sarcoma groups have contributed to the slow development of effective new therapies; outcomes for patients with advanced stages of the

disease remain poor. The progress of immunotherapy, mainly with the development of checkpoint inhibitors, has been spectacular and revolutionized everyday oncology practice over the last few years. Naturally, this approach is also being studied in sarcomas, with some success, as has been shown in this review. It is worth emphasizing that immunotherapy in sarcomas is also studied in other aspects, such as vaccines or adoptive cell therapy. This approach makes particular sense in some of the STS subtypes, although so far, evidence of their effectiveness is limited [12]. That said, the author does not doubt that in the coming years there will be optimistic news on breakthrough therapies for patients with advanced sarcomas, as has happened, for example, with melanoma. The development of immunotherapy will also undoubtedly, in this case, contribute to this.

Conflict of interest: none declared

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References

1. Casali PG, Abecassis N, Aro HT, et al. ESMO Guidelines Committee and EURACAN, ESMO Guidelines Committee and EURACAN. Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018; 29(Suppl 4): iv51–iv67, doi: [10.1093/annonc/mdy096](https://doi.org/10.1093/annonc/mdy096), indexed in Pubmed: [29846498](https://pubmed.ncbi.nlm.nih.gov/29846498/).
2. Casali PG, Bielack S, Abecassis N, et al. ESMO Guidelines Committee, PaedCan and ERN EURACAN. Bone sarcomas: ESMO-PaedCan-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2018; 29(Suppl 4): iv79–iv95, doi: [10.1093/annonc/mdy310](https://doi.org/10.1093/annonc/mdy310), indexed in Pubmed: [30285218](https://pubmed.ncbi.nlm.nih.gov/30285218/).
3. McCarthy EF. The toxins of William B. Coley and the treatment of bone and soft-tissue sarcomas. *Iowa Orthop J.* 2006; 26: 154–158.

4. Lee A, Huang P, DeMatteo RP, et al. Immunotherapy for Soft Tissue Sarcoma: Tomorrow Is Only a Day Away. *Am Soc Clin Oncol Educ Book*. 2016; 35: 281–290, doi: [10.1200/EDBK_157439](https://doi.org/10.1200/EDBK_157439), indexed in Pubmed: [27249707](https://pubmed.ncbi.nlm.nih.gov/27249707/).
5. Kim JR, Moon YJ, Kwon KS, et al. Tumor infiltrating PD1-positive lymphocytes and the expression of PD-L1 predict poor prognosis of soft tissue sarcomas. *PLoS One*. 2013; 8(12): e82870, doi: [10.1371/journal.pone.0082870](https://doi.org/10.1371/journal.pone.0082870), indexed in Pubmed: [24349382](https://pubmed.ncbi.nlm.nih.gov/24349382/).
6. D'Angelo SP, Shoushtari AN, Agaram NP, et al. Prevalence of tumor-infiltrating lymphocytes and PD-L1 expression in the soft tissue sarcoma microenvironment. *Hum Pathol*. 2015; 46(3): 357–365, doi: [10.1016/j.humpath.2014.11.001](https://doi.org/10.1016/j.humpath.2014.11.001), indexed in Pubmed: [25540867](https://pubmed.ncbi.nlm.nih.gov/25540867/).
7. Koirala P, Roth ME, Gill J, et al. Immune infiltration and PD-L1 expression in the tumor microenvironment are prognostic in osteosarcoma. *Sci Rep*. 2016; 6: 30093, doi: [10.1038/srep30093](https://doi.org/10.1038/srep30093), indexed in Pubmed: [27456063](https://pubmed.ncbi.nlm.nih.gov/27456063/).
8. Machado I, López-Guerrero JA, Scotlandi K, et al. Immunohistochemical analysis and prognostic significance of PD-L1, PD-1, and CD8+ tumor-infiltrating lymphocytes in Ewing's sarcoma family of tumors (ESFT). *Virchows Arch*. 2018; 472(5): 815–824, doi: [10.1007/s00428-018-2316-2](https://doi.org/10.1007/s00428-018-2316-2), indexed in Pubmed: [29445891](https://pubmed.ncbi.nlm.nih.gov/29445891/).
9. Kostine M, Cleven AHG, de Miranda NF, et al. Analysis of PD-L1, T-cell infiltrate and HLA expression in chondrosarcoma indicates potential for response to immunotherapy specifically in the dedifferentiated subtype. *Mod Pathol*. 2016; 29(9): 1028–1037, doi: [10.1038/modpathol.2016.108](https://doi.org/10.1038/modpathol.2016.108), indexed in Pubmed: [27312065](https://pubmed.ncbi.nlm.nih.gov/27312065/).
10. van Erp AEM, Versleijen-Jonkers YMH, Hillebrandt-Roefen MHS, et al. Expression and clinical association of programmed cell death-1, programmed death-ligand-1 and CD8 lymphocytes in primary sarcomas is subtype dependent. *Oncotarget*. 2017; 8(41): 71371–71384, doi: [10.18632/oncotarget.19071](https://doi.org/10.18632/oncotarget.19071), indexed in Pubmed: [29050367](https://pubmed.ncbi.nlm.nih.gov/29050367/).
11. Petitprez F, de Reyniès A, Keung EZ, et al. B cells are associated with survival and immunotherapy response in sarcoma. *Nature*. 2020; 577(7791): 556–560, doi: [10.1038/s41586-019-1906-8](https://doi.org/10.1038/s41586-019-1906-8), indexed in Pubmed: [31942077](https://pubmed.ncbi.nlm.nih.gov/31942077/).
12. Martin-Broto J, Hindi N, Grignani G, et al. Facts and Hopes in Immunotherapy of Soft-Tissue Sarcomas. *Clin Cancer Res*. 2020; 26(22): 5801–5808, doi: [10.1158/1078-0432.CCR-19-3335](https://doi.org/10.1158/1078-0432.CCR-19-3335), indexed in Pubmed: [32601077](https://pubmed.ncbi.nlm.nih.gov/32601077/).
13. Tawbi HA, Burgess M, Bolejack V, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol*. 2017; 18(11): 1493–1501, doi: [10.1016/S1470-2045\(17\)30624-1](https://doi.org/10.1016/S1470-2045(17)30624-1), indexed in Pubmed: [28988646](https://pubmed.ncbi.nlm.nih.gov/28988646/).
14. Burgess M, Bolejack V, Schuetz S, et al. Clinical activity of pembrolizumab (P) in undifferentiated pleomorphic sarcoma (UPS) and dedifferentiated/pleomorphic liposarcoma (LPS): Final results of SARC028 expansion cohorts. *Journal of Clinical Oncology*. 2019; 37(15_suppl): 11015–11015, doi: [10.1200/jco.2019.37.15_suppl.11015](https://doi.org/10.1200/jco.2019.37.15_suppl.11015).
15. Keung EZ, Burgess M, Salazar R, et al. Correlative Analyses of the SARC028 Trial Reveal an Association Between Sarcoma-Associated Immune Infiltrate and Response to Pembrolizumab. *Clin Cancer Res*. 2020; 26(6): 1258–1266, doi: [10.1158/1078-0432.CCR-19-1824](https://doi.org/10.1158/1078-0432.CCR-19-1824), indexed in Pubmed: [31900276](https://pubmed.ncbi.nlm.nih.gov/31900276/).
16. 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(3): 416–426, doi: [10.1016/S1470-2045\(18\)30006-8](https://doi.org/10.1016/S1470-2045(18)30006-8), indexed in Pubmed: [29370992](https://pubmed.ncbi.nlm.nih.gov/29370992/).
17. Pollack SM, Redman MW, Baker KK, et al. Assessment of Doxorubicin and Pembrolizumab in Patients With Advanced Anthracycline-Naive Sarcoma: A Phase 1/2 Nonrandomized Clinical Trial. *JAMA Oncol*. 2020 [Epub ahead of print], doi: [10.1001/jamaoncol.2020.3689](https://doi.org/10.1001/jamaoncol.2020.3689), indexed in Pubmed: [32910151](https://pubmed.ncbi.nlm.nih.gov/32910151/).
18. Martin-Broto J, Hindi N, Grignani G, et al. Nivolumab and sunitinib combination in advanced soft tissue sarcomas: a multicenter, single-arm, phase Ib/II trial. *J Immunother Cancer*. 2020; 8(2), doi: [10.1136/jitc-2020-001561](https://doi.org/10.1136/jitc-2020-001561), indexed in Pubmed: [33203665](https://pubmed.ncbi.nlm.nih.gov/33203665/).
19. Lazar AJF, Das P, Tuvin D, et al. Angiogenesis-promoting gene patterns in alveolar soft part sarcoma. *Clin Cancer Res*. 2007; 13(24): 7314–7321, doi: [10.1158/1078-0432.CCR-07-0174](https://doi.org/10.1158/1078-0432.CCR-07-0174), indexed in Pubmed: [18094412](https://pubmed.ncbi.nlm.nih.gov/18094412/).
20. Kummar S, Allen D, Monks A, et al. Cediranib for metastatic alveolar soft part sarcoma. *J Clin Oncol*. 2013; 31(18): 2296–2302, doi: [10.1200/JCO.2012.47.4288](https://doi.org/10.1200/JCO.2012.47.4288), indexed in Pubmed: [23630200](https://pubmed.ncbi.nlm.nih.gov/23630200/).
21. Mariuk-Jarema A, Kosela-Paterczyk H, Rogala P, et al. A durable complete response to immunotherapy in a patient with metastatic alveolar soft part sarcoma. *Tumori*. 2020 [Epub ahead of print]: 300891620928133, doi: [10.1177/0300891620928133](https://doi.org/10.1177/0300891620928133), indexed in Pubmed: [32567515](https://pubmed.ncbi.nlm.nih.gov/32567515/).
22. Conry A, Peters M, Fried DB, et al. Complete Response to Dual Immunotherapy in a Young Adult with Metastatic Alveolar Soft Part Sarcoma Enabled by a Drug Recovery Program in a Community Practice. *J Adolesc Young Adult Oncol*. 2020; 9(3): 449–452, doi: [10.1089/jayao.2019.0113](https://doi.org/10.1089/jayao.2019.0113), indexed in Pubmed: [31855495](https://pubmed.ncbi.nlm.nih.gov/31855495/).
23. Coyne GO SE, Moore N, et al. Phase II study of atezolizumab in patients with alveolar soft part sarcoma. *Connective Tissue Oncology Society Annual Meeting*. Abstr 3042818. Rome, 14–17 Nov 2018.
24. Wilky BA, Trucco MM, Subhawong TyK, 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(6): 837–848, doi: [10.1016/S1470-2045\(19\)30153-6](https://doi.org/10.1016/S1470-2045(19)30153-6), indexed in Pubmed: [31078463](https://pubmed.ncbi.nlm.nih.gov/31078463/).