

**ORIGINAL ARTICLE**

# PD-1 blockade using pembrolizumab in adolescent and young adult patients with advanced bone and soft tissue sarcoma

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**Abstract**

**Background:** Sarcomas represent 10%–15% of cancers in adolescent and young adult (AYA) patients, and survival for those with metastatic disease or relapse is poor. Immunotherapy with checkpoint inhibition has improved outcomes in multiple tumor types, but data in advanced sarcomas, particularly within the AYA population, are limited.

**Aim:** We aim to evaluate response and toxicity for AYA patients with sarcoma treated with pembrolizumab.

**Methods and results:** We retrospectively reviewed AYA patients with advanced bone and soft tissue sarcoma who received self-funded pembrolizumab between May 2015 and January 2019. Eighteen patients were identified. One patient with Ewing sarcoma had a sustained complete response to therapy. Two patients with alveolar soft part sarcoma received a clinical benefit from pembrolizumab: one had a radiological partial response with an excellent clinical response and one patient achieved stable disease. Four patients died of disease prior to first scheduled assessment and thus were not evaluable. The remaining eleven patients had progressive disease.

**Conclusion:** The role of immunotherapy in AYA sarcoma warrants further investigation. Biomarkers of response need to be further evaluated in order to guide patient selection.

**KEYWORDS**

adolescent, bone neoplasms, immunotherapy, sarcoma, young adult

## 1 | BACKGROUND

Sarcomas are mesenchymal tumors, which although rare in adults, comprise 10%–15% of tumors in the adolescent and young adult (AYA) population (aged 15–39 years as defined by the United States National Cancer Institute).<sup>1</sup>

Although many who present with localized disease are long-term survivors, those with recurrent metastatic sarcoma have poor outcomes, with 5-year overall survival of 7% in metastatic Ewing sarcoma and 19%–30% in advanced osteosarcoma.<sup>1</sup>

PD-1/PD-L1 inhibition has shown durable benefit in melanoma, non-small cell lung cancer (NSCLC), and other malignancies. However, data on immunotherapy in sarcoma are limited.<sup>2</sup>

Biomarkers associated with response to immunotherapy include tumor PD-L1 status, the presence of tumor infiltrating lymphocytes, tumor mutational burden (TMB), and mismatch repair deficiency/microsatellite instability.<sup>2,3</sup>

PD-L1 expression has been evaluated in a variety of sarcomas, with 57% of Ewing sarcomas, 47% of osteosarcomas, 50% of embryonal rhabdomyosarcomas, and 86% of alveolar rhabdomyosarcomas expressing PD-L1 (>5% tumor cells showing PD-L1 membranous staining).<sup>4</sup>

At diagnosis, most pediatric and AYA cancers have a low mutational burden; however, relapsed samples have higher mutation burdens.<sup>5</sup> Osteosarcomas are genetically complex, and thus are attractive targets for immunotherapy. Translocation-associated sarcomas such as Ewing sarcomas have low mutational burdens.<sup>2</sup>

In Australia, immunotherapy funded under the Pharmaceutical Benefit Scheme is restricted to patients with Hodgkin lymphoma, melanoma, NSCLC, renal cell carcinoma, urothelial cancer, Merkel cell carcinoma, or head and neck squamous cell carcinoma. Patients treated outside these indications must self-fund treatment, at significant expense.

This study describes the outcomes and toxicity of immunotherapy in a cohort of AYA patients with advanced sarcoma.

## 2 | METHODS

AYA patients with sarcoma who received self-funded pembrolizumab at Chris O'Brien Lifecare or Children's Hospital Westmead between May 2015 and January 2019 were identified. Pembrolizumab 2 mg/kg was administered intravenously every three weeks. Immune related adverse events (irAE) were graded according to the National Cancer Institute CTCAE, version 4.0. Response was assessed according to RECIST 1.1. First response evaluation was scheduled after cycle three or four.

Immunohistochemical staining of PD-L1 was performed using BenchMark ULTRA automated staining platform (Roche, Australia). Heat-mediated antigen retrieval (100°C) was used at pH 9 for 64 minutes. The primary antibody (PD-L1, Clone: SP263) was incubated for 16 minutes at 36°C. OptiView DAB IHC Detection was used with the standard Ventana protocol. PD-L1 status was scored by the percentage of tumor cells with membranous staining by two pathologists, and discordant results were reviewed together. PD-L1 analysis

was performed on primary diagnostic tumor samples where available, and from relapsed tumors where primary sites were unavailable.

TMB (mutations/Mb) was estimated by dividing the number of observed single nucleotide variants (synonymous and non-synonymous) and indels by the size of the targeted capture panel. Mutations with an allele frequency <5% were excluded to eliminate noise. Potential germline variants (mutations with a frequency  $>1 \times 10^{-6}$ ) were filtered out according to published databases of known germline polymorphisms, including Exac,<sup>6</sup> gnomAD v2.0.2,<sup>7</sup> and the Medical Genome Reference Bank.<sup>8</sup> To eliminate bias due to capture panel enrichment for cancer driver mutations, mutations with a count > 1 in COSMIC<sup>9</sup> (<https://cancer.sanger.ac.uk>) and truncation mutations of tumor suppressor genes were excluded.

The primary endpoint was objective response rate (ORR). The secondary endpoints were safety and exploratory descriptive biomarker analysis. Data were summarized using descriptive statistics. All research adhered to the Declaration of Helsinki.

## 3 | RESULTS

Eighteen patients were identified. Patient characteristics are included in Table 1. Sixteen patients had died by last follow-up.

**TABLE 1** Patient and disease characteristics

Patient characteristics	Self-funded pembrolizumab (n = 18)
Median age (range)—years	24 (14–35)
Male sex—no. (%)	9 (50%)
<i>ECOG Performance status—no. (%)</i>	
0–1	8 (44%)
2	7 (39%)
3–4	3 (17%)
<i>Malignancy type—no. (%)</i>	
Osteosarcoma	4 (22%)
Ewing sarcoma	6 (33%)
Synovial sarcoma	3 (17%)
Alveolar Soft Part Sarcoma	3 (17%)
Embryonal Rhabdomyosarcoma	1 (6%)
Clear cell sarcoma	1 (6%)
<i>Prior lines of treatment—no. (%)</i>	
1	0
2–4	16
>4	2
<i>Cycles of pembrolizumab administered—no.</i>	
1–2	4
3–4	11
5–6	0
7–9	2
>9	1

**TABLE 2** Response to treatment

Tumor response—best overall response at any assessment	Self-funded pembrolizumab
Evaluable—no. (%)	14
CR	1 (7%)
PR	1 (7%)
SD	1 (7%)
PD	11 (79%)
Not evaluable—no. (%)	4

The median number of pembrolizumab doses was three (1-50), with one patient still receiving treatment at last follow-up. One patient had a complete response (CR) to pembrolizumab, one patient had a partial response (PR) but significant clinical improvement and one patient achieved stable disease (SD), with an ORR of 11% (Table 2). Individual results are presented in Table 3.

### 3.1 | Patient achieving CR

A 25-year-old male with metastatic Ewing sarcoma (lung and bone metastases) had received eight prior lines of therapy and had an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0. His primary site was the C5 vertebra and at the time of pembrolizumab initiation he had widespread bone (including vertebral) and lung metastases. As previously reported, he achieved CR on PET after nine cycles.<sup>10</sup> He developed grade 2 hypothyroidism, grade 1 fever, and grade 1 acneiform rash. Due to complete disease response and significant costs of self-funding therapy, treatment was stopped after nine cycles and he remains in remission after 48 months of follow-up. Tissue was not available for PD-L1 staining or TMB.

### 3.2 | Patient achieving PR

A 24-year-old female with metastatic alveolar soft part sarcoma (ASPS) (soft tissue, lung and bone metastases) had received two prior lines of therapy and had an ECOG PS of 2-3. Her primary site was the iliopsoas muscle and ASPS was confirmed by the presence of t(X;17)(p11.2;q25) translocation. She achieved PR on initial CT and further responses on subsequent imaging. She had significant clinical benefit with an improvement in symptoms and ECOG PS improved to 1. She had grade 1 fever. She has received 50 cycles of treatment to date. Although she has been offered a break in treatment, she remained adamant that she wished to continue treatment beyond two years. PD-L1 was positive in 90% of tumor cells and TMB was 6.8 mutations/Mb (normal 2.3-13.5 mutations/Mb).

### 3.3 | Patient achieving SD

A 29-year-old male with metastatic ASPS (soft tissue, lung, and bone metastases) had received two prior lines of therapy and had an ECOG

PS of 0. His primary site was the thigh and ASPS was confirmed by the presence of t(X;17)(p11.2;q25) translocation. He achieved SD on his initial CT. He had no irAEs. Treatment was stopped after nine cycles as measurements had increased by 10% from baseline. While not meeting RECIST 1.1 criteria for progressive disease (PD), it was felt that maximal benefit was reached. Since stopping therapy, he had progression of bone metastases, requiring operative management, further systemic therapy and subsequently died. PD-L1 was negative, with 0% of tumor cells positive and TMB was 5.8 mutations/Mb.

### 3.4 | Non-responders to pembrolizumab

Eleven out of 14 patients (79%) who were evaluable for response experienced PD, and nine received subsequent lines of treatment. No patients experienced pseudo-progression prior to response. Of the nine patients with tissue available for PD-L1 assessment, seven were negative for PD-L1 (0% staining) and two were PD-L1 positive in 1%-2% of tumor cells on IHC (Table 3).

### 3.5 | Not evaluable

Four patients died prior to radiological evaluation. One died four days after receiving his first dose of pembrolizumab. This patient was PD-L1 positive in 5%-10% of tumor cells on IHC. One received two doses of pembrolizumab and then deteriorated functionally. One developed cauda equina syndrome following the first cycle. He received two further cycles but continued to deteriorate. This patient was PD-L1 positive in 1%-2% of tumor cells on IHC. One experienced a flare of bone pain and spinal cord compression two days after starting pembrolizumab. After dexamethasone, he proceeded to the second cycle. This was complicated by grade three pneumonitis requiring a brief ICU admission for stabilization but did not require respiratory support. He did not receive further treatment prior to death. This patient was negative for PD-L1 (0% PD-L1 staining).

### 3.6 | Adverse events

IrAE of any grade occurred in four (22%) patients. One had grade 2 hypothyroidism, two had grade 1 fever, and one had grade 3 pneumonitis, as described above. One additional patient had grade 2 hepatic transaminitis requiring steroids but went on to safely receive further pembrolizumab.

## 4 | DISCUSSION

In our cohort, three (21%) of the evaluable patients who received pembrolizumab achieved a clinically meaningful response and pembrolizumab was well tolerated. Although responses to immunotherapy have been reported in ASPS, this cohort included the only


**TABLE 3** Individual patient results

Patient number	Sarcoma type	Age	Sex	ECOG PS	Prior lines of treatment	Cycles of pembrolizumab administered	irAEs	Tumor response	PD-L1 positive tumor cells	Tumor Mutational Burden (normal 2.3-13.5 Mut/Mb)
1	Osteosarcoma	16	F	0-1	2	4	Nil	PD	0%	NA
2	Osteosarcoma	24	M	4	2	4	Nil	PD	0%	NA
3	Osteosarcoma	35	F	2	5	6	Nil	PD	1-2%	NA
4	Osteosarcoma	18	M	1	2	3	Nil	PD	0%	2.6 Mut/Mb
5	Ewing sarcoma	24	M	0	8	9	G1 fever, G2 hypothyroidism	CR	NA	NA
6	Ewing sarcoma	24	M	0	4	4	Nil	PD	NA	NA
7	Ewing sarcoma	14	F	2	4	2	Nil	NE	NA	NA
8	Ewing sarcoma	20	M	2	2	3	Nil	PD	0%	NA
9	Ewing sarcoma	19	M	2	2	2	Nil	NE	1-2%	NA
10	Ewing sarcoma	18	M	4	3	2	G3 pneumonitis	NE	0%	2.6 Mut/Mb
11	Synovial sarcoma	30	F	0-1	3	3	Nil	PD	0%	NA
12	Synovial sarcoma	24	F	1	3	3	Nil	PD	0%	NA
13	Synovial sarcoma	35	F	1	2	3	G2 hepatic transaminitis	PD	0%	NA
14	Alveolar soft part sarcoma	29	M	0	2	9	Nil	SD	90%	5.8 Mut/Mb
15	Alveolar soft part sarcoma	24	F	2	2	50	G1 fever	PR	0%	6.8 Mut/Mb
16	Alveolar soft part sarcoma	27	F	2	2	4	Nil	PD	1-2%	NA
17	Embryonal rhabdomyosarcoma	20	M	3	3	1	Nil	NE	5-10%	NA
18	Clear cell sarcoma	15	F	2	3	3	Nil	PD	NA	NA

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; irAEs, immune related adverse events; F, female; PD, progressive disease; M, male; G, grade; CR, complete response; NE, not evaluable; SD, stable disease; PR, partial response; NA, not available; Mut/Mb, mutations/Mb.

reported response in Ewing sarcoma.<sup>10,11</sup> As previously reported, this patient had a more indolent course than is often seen in relapsed Ewing sarcoma, and had had multiple sites irradiated previously. This may potentially have resulted in a more immunogenic state, resulting in the sustained complete response that was seen.<sup>10</sup>

Other small series have reported on immunotherapy in AYA sarcomas. Six patients with advanced synovial sarcoma treated with ipilimumab showed no responses.<sup>12</sup> In a study of 16 sarcoma patients treated with sunitinib and nivolumab, six patients achieved PR (2/4 clear cell sarcoma, 1/3 angiosarcoma, 1/1 dedifferentiated chondrosarcoma, 1/2 synovial sarcoma, and 1/3 ASPS).<sup>13</sup> A report of ipilimumab and nivolumab in one patient with metastatic ASPS showed PR.<sup>11</sup>

The SARC028 trial of pembrolizumab in advanced sarcoma identified responses in some AYA sarcomas (PR in 1/10 synovial sarcoma, 1/5 chondrosarcoma, 1/22 osteosarcoma). Additional patients had SD. Responses were durable.<sup>14</sup>

A retrospective review of nivolumab in metastatic sarcoma (median age 58 [24-78]) found 3/24 patients had PR (one dedifferentiated chondrosarcoma (nivolumab alone), one osteosarcoma, and one proximal epithelioid sarcoma (both on concomitant pazopanib)).<sup>15</sup> A trial of nivolumab with or without ipilimumab for metastatic sarcoma (Alliance A091401) included AYA patients. One patient with ASPS had PR (nivolumab alone). Two patients with undifferentiated pleomorphic sarcoma and one with angiosarcoma achieved PR (nivolumab with ipilimumab).<sup>16</sup>

There are data to suggest that PD-L1 expression can be upregulated by prior or concomitant treatments. A study of 46 patients with stage II-III soft tissue sarcoma treated with pre-operative radiotherapy examined the expression of PD-L1 pre- and post-radiotherapy. Although no patients demonstrated PD-L1 tumor expression pre-radiotherapy, five patients (11%) demonstrated PD-L1 tumor expression following radiotherapy.<sup>17</sup> A study of 86 patients with NSCLC treated with neoadjuvant platinum chemotherapy demonstrated that the overall proportion of patients with positive tumor PD-L1 expression increased significantly after treatment with chemotherapy (45/86 [52%] before chemotherapy and 65/86 [75%] after chemotherapy). Of note, 26 patients were negative for tumor PD-L1 expression before chemotherapy and became positive after chemotherapy.<sup>18</sup> PD-1 blockade alone may not be effective in unselected groups of patients; however, further research in AYA sarcoma could consider combination treatments, either combination systemic therapy or combined with local treatment modalities.

Cytotoxic chemotherapy in patients with poor performance status is associated with shorter survival and worse quality of life in some cancers.<sup>19</sup> The original KEYNOTE trials were restricted to patients with ECOG PS 0-1. There are conflicting data on immunotherapy in patients with poor performance status. Wong et al<sup>20</sup> examined the records of patients with metastatic melanoma who received anti-PD1 therapy, including those with poor PS. Although toxicity did not differ significantly between those with ECOG PS 0-1 and those with ECOG PS 2-3, the overall response rate and overall survival in the ECOG PS 2-3 group were low (12% and 6.43 months respectively).<sup>20</sup> A 2018 meta-analysis of patient PS and immunotherapy suggested that there

was no difference in overall survival between those with ECOG PS 0 and those with ECOG PS 1-2.<sup>21</sup> However, a meta-analysis of PS as a prognostic factor in patients with advanced NSCLC treated with immunotherapy found that an ECOG PS of 2 or worse resulted in worse overall survival, progression free survival, and overall response rates.<sup>22</sup> Of patients who had a response to pembrolizumab in our cohort, two had an ECOG PS of 0 and one had an ECOG PS of 2-3. None of the patients with an ECOG PS of 3-4 responded to pembrolizumab.

Performance status is an independent prognostic factor for patients with advanced sarcoma. A study of 3002 patients with advanced soft tissue sarcoma found that ECOG PS  $\geq$  2 was the most powerful prognostic factor associated with early death (ie, death by 90 days) among patients receiving first-line systemic therapy.<sup>23</sup> It is widely accepted that patients treated with immunotherapy can have delayed but deep and durable responses. Alternatively, patients may experience pseudo-progression, where new lesions are identified or lesions increase in size, but this is not sustained on subsequent imaging.<sup>24</sup> Unfortunately, for those patients who deteriorate clinically in the meantime, including those with a poor performance status prior to starting treatment, subsequent treatment and disease assessment may be limited.

Young people with cancer have unique health needs that affect their quality of life, long-term health, and engagement in society, education, and employment. They are also under-represented in clinical trials, and this has been associated with a corresponding lack of improvement in survival rates.<sup>25</sup> These patients are young, with few co-morbidities, with a large potential societal burden of years-of-life lost. In our experience, we have shown that some AYA patients with sarcoma can have durable responses to pembrolizumab. Unfortunately, we are unable to predict which patients are likely to respond.

There are limitations with PD-L1 as a biomarker for response. There is no consensus on PD-L1 positivity, with definitions varying between 1% and 50%. Even patients with negative PD-L1 have shown benefits, albeit at lower frequencies. PD-L1 can be expressed in tumor and inflammatory cells, and the importance of either is unclear. There are technical limitations with PD-L1 assays and PD-L1 gene expression is dynamic in space and time.<sup>3</sup> Given the small numbers in our series and incomplete PD-L1 and TMB data, we were unable to determine if response was associated with PD-L1 expression and TMB. Given our reports of significant, albeit uncommon, responses to immunotherapy in our population, further investigation of biomarkers of response are required.

Limitations of this study are the retrospective data collection and single arm design. This also limits the assessment of hyper-progression. This study has used RECIST 1.1 criteria for progression rather than iRECIST.<sup>24</sup> At the time that many of these patients were enrolled (in 2015 and 2016), iRECIST was not widely utilized. Further, as patients were self-funding their treatment, at significant personal cost, cost was a barrier to continuing treatment beyond the initial scan showing unconfirmed progression. Given the rare nature of these tumors, and limited conventional treatment options, randomized, controlled studies may be prohibitive in this population. Due to the low



patient numbers, and heterogeneity of the tumors included, the biomarker analysis was descriptive only.

## 5 | CONCLUSION

We have reported that a subset of AYA patients with sarcoma have durable responses to immunotherapy with pembrolizumab. The efficacy of immunotherapy in AYA sarcoma warrants further investigation and biomarkers of response need to be further evaluated in order to guide patient selection.

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### CONFLICT OF INTEREST

The authors declare no competing interests.

### AUTHORS' CONTRIBUTIONS

All authors were responsible for final approval of the manuscript and are accountable for all aspects of the work. *Collection of data*, T.S., V.B., F.B., R.K., and P.P.L.; *Data analysis*, T.S., V.B., F.B., R.K., and P.P.L.; *Writing - Original Draft*, T.S., V.B., F.B., R.K., and P.P.L.; *Protocol Development*, T.S., V.B., A.M., and A.L.; *Provision*, M.T., D.T., G.M., M.S., and V.B.

### ETHICAL STATEMENT

Ethics committee approval was obtained for publication of this retrospective data: Sydney Local Health District Ethics Review Committee (RPA zone) - X16-0420/LH17.002 and Sydney Local health District Ethics Review Committee (CRGH) - CH2018-045/LH18.018. The requirement for consent was waived.

### DATA AVAILABILITY STATEMENT

The dataset supporting the conclusions of this article is included within the article.

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