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A Pilot Study of Pembrolizumab Combined With Stereotactic Ablative Radiotherapy for Patients With Advanced or Metastatic Sarcoma

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Abstract

Objectives: Immunotherapy with immune checkpoint inhibitors has shown only limited success in the management of metastatic soft tissue sarcoma. Overall response rates (ORR) with single agent pembrolizumab were 18% and median PFS was 18 weeks on the clinical trial SARC028. One strategy to improve the responses to immunotherapy is with stereotactic body radiation therapy (SBRT), which can enhance the antitumor CD8 T cell response through the release of tumor-specific antigens, potentially priming a more diverse class of T cell receptors.

Methods: This is a phase 0, pilot prospective study taking place at a single center with 2 arms. In Arm A, patients are treated with pembrolizumab 400 mg IV infusion on day 1 of a 42-day cycle. Stereotactic body radiation therapy (SBRT) is delivered in 1-5 fractions starting on C1D15-28 and given every other day. In Arm B, patients who have started an immune checkpoint inhibitor within 60 days are treated with SBRT in addition to the current therapy.

Results: In this study we outline testing the feasibility of adding SBRT to pembrolizumab.

Conclusion: The ultimate goal of combination therapy is improved overall response, including tumors not treated with SBRT. This trial can be found registered online: NCT05488366.

Keywords

immunotherapy, pembrolizumab, radiation, sarcoma, stereotactic body radiation therapy

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Introduction

Metastatic disease is common among patients with soft tissue sarcomas. The standard of care for synchronous or metachronous metastatic undifferentiated pleomorphic sarcoma (UPS) or undifferentiated sarcoma is anthracycline-based chemotherapy. Overall response rates with single agent doxorubicin are approximately 14-19% and median progression-free survival (PFS) estimates are 20-23 weeks.[1,2] Perhaps due to the modest response rates with single-agent

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doxorubicin, the population-based METASARC study found that there was no dominant first-line strategy.[3] In METASARC, 51% (810 out of 1575) of patients' first-line therapy was off-label.

As for immunotherapy, following initial interest with mifamurtide for osteosarcoma, clinical trials utilizing a single immune modulating agent have shown limited success.[4-7] In the SARC028 study of pembrolizumab, there was an 18% response rate and median PFS of 18 weeks for the 40 patients with soft tissue sarcoma.[5]

One strategy to improve responses to immunotherapy is with multiple agents, and studies of combination or dual immune-modulating therapy for sarcoma have generally shown greater promise.[8,9] For some cancers, stereotactic body radiation therapy (SBRT) has been shown to improve the immune response when combined with immunotherapy.[10] While there has been success with non-small-cell lung cancer (NSCLC) and urothelial carcinoma, such systemic responses have not been seen with head and neck cancers, melanoma, or renal cell carcinoma.[11-17] Furthermore, sarcomas are generally less immunogenic, with low response rates to single-agent immunotherapy and low PD-L1 expression.[4-7] Herein we outline a pilot study designed to test the feasibility of treating patients with metastatic sarcoma with the immune checkpoint inhibitor (ICI) pembrolizumab and SBRT as second-line or greater therapy.

The goal of such combination therapy is improved overall response, including tumors not treated with SBRT. SBRT can also result in systemic responses outside of the irradiated site due to what is thought to be an underlying immunologic mechanism.[18] The tumor-specific antigens that are released following radiation can potentially prime a more diverse class of T cell receptors.[19] Consequently, the antitumor CD8 T cell response can be enhanced. Thus, there is a potential for radiation to activate local immune cells, which, in combination with checkpoint inhibitor therapy, may synergistically improve distant control.

Study Design

This is a phase 0, pilot prospective study with 2 arms taking place at a single academic hospital in the US, with recruitment and referral from any of the specialists treating sarcoma or the multidisciplinary tumor board (Figure 1). In Arm A, patients will be treated with pembrolizumab 400 mg IV infusion on day 1 of a 42-day cycle. Stereotactic body radiation therapy (SBRT) will be delivered in 1-5 fractions starting on C1D15-28 and given every other day (Table 1). For central lung tumors, SBRT is allowed to be up to 10 fractions, which is given every day. In Arm B, patients who have started an immune checkpoint inhibitor within 60 days are treated with SBRT in addition to the current therapy.

Screening will occur within 45 days of starting protocol therapy. A signed and dated written informed consent form will be obtained from the patient at screening. Treatment will be administered on an outpatient basis. Pembrolizumab delivery will be based on institutional standards and those from the FDA. SBRT will be delivered on an outpatient basis using institutional standards. This study has been approved by the Institutional Review Board (IRB #978), with current protocol version 3 (6/8/23). All protocol or consent amendments must be reviewed and approved by the IRB. The reporting of this study conforms to SPIRIT guidelines.[20]

Inclusion Criteria

Patients must be at least 18 years old, ECOG 0-2, life expectancy of at least 3 months, and have histologically or cytologically confirmed soft-tissue sarcoma. The disease must be initially advanced, progressive, recurrent, or metastatic, and not amenable to curative intent surgery. There must be at least 2 measurable lesions, at least 1 site which is amenable to treatment with radiation therapy.

Adequate organ and marrow function for pembrolizumab administration includes evaluation of leukocytes, neutrophils, platelets, hemoglobin, AST, ALT, total bilirubin, creatinine, thyroid stimulating hormone.

Arm A. Acceptable histology includes undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma, myxofibrosarcoma, or undifferentiated sarcoma (unclassified histology), or any histology with a tumor mutational burden ≥10 mut/Mb.

Arm B. Patients must have started a checkpoint inhibitor immunotherapy within 60 days.

Interventions

Arm A. Pembrolizumab 400 mg IV infusion on day 1 of a 42-day cycle. SBRT is given C1D15-28.

Arm B. Patients continue with their checkpoint inhibitor therapy and SBRT is given C1D1-14.

Assessment by CT or MRI will be done every 8 weeks, and clinic visits every 3 months until 12 months. Patients may discontinue study treatment for disease progression, death, or unacceptable adverse events (including dose delay >12 weeks). Research personnel will ensure adherence to all infusions, radiation sessions, and laboratory testing. Concomitant chemotherapy, biological therapy, immunotherapy, or radiation therapy outside the protocol are prohibited.

The irradiated target will be one non-CNS lesion deemed by the treating oncologist to be symptomatic or most likely to become symptomatic; there is no size restriction. The selected lesion may have received prior radiation so long as 6 months from completion of the prior radiation have passed and re-irradiation dose constraints are met. This lesion may have been previously treated with radiation if the cumulative spinal cord dose will remain below a Biologically Effective Dose $(BED)_{\alpha/\beta\ 2Gy}$ of 112 Gy (single fraction equivalent 14 Gy). BED will be calculated using the

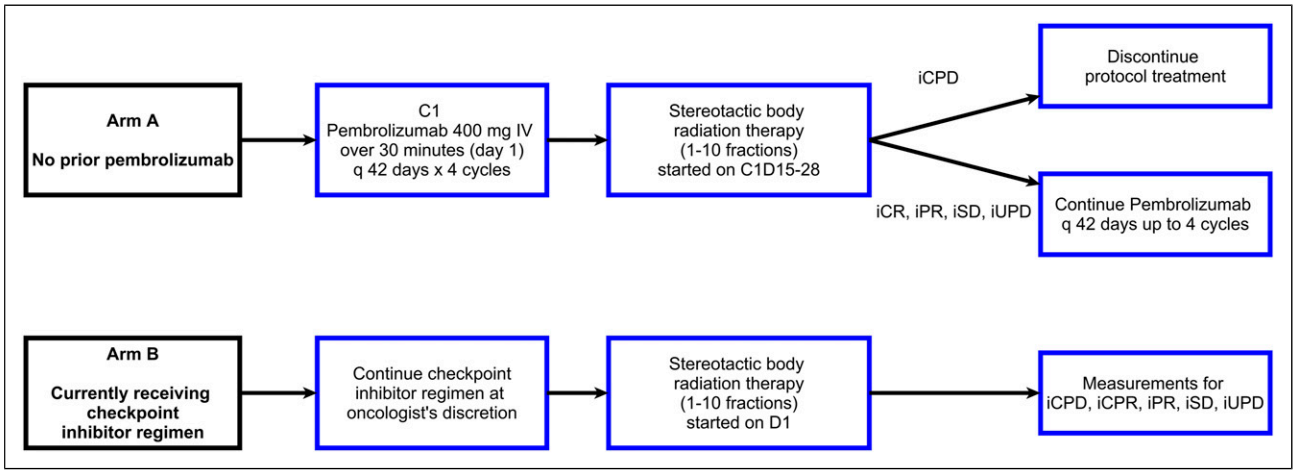

Figure 1. Schema. Immune-based responses are used for disease assessment (designated by prefix "i"). iCR = complete response. iPR = partial response. iSD = stable disease. iUPD = unconfirmed progression. iCPD = confirmed progression.

Table 1. Radiation Regimens.

Total Dose (Gy)	Total Fractions	Location
20-24	1	Bone or spine
28-34	1	Peripheral lung
45-54	3	Liver
50-60	5-10	Central lung[a]
40-50	5	Soft tissue or not otherwise specified
30	5	Any site[b]
18	3	Any site[b]

[a]Central lung tumors are those within 2 cm from the proximal bronchial tree (PBT), or with a planning target volume (PTV) that is overlapping mediastinal or pericardial pleura. The PBT is defined as the carina, right and left upper lobe bronchi, bronchus intermedius, right middle lobe bronchus, lingular bronchus, and left and right lower lobe bronchi.
[b]These doses may be used for any site in the setting of 3D conformal planning technique or if normal tissue constraints cannot be met.

linear-quadratic formula: $d * f * (1 + [d/(\alpha/\beta)])$, where d is the dose per fraction, f is the total number of fractions, and α/β is the property of irradiated tissue measured in Gray.

Primary Objective and Endpoint

The primary endpoint is feasibility, which will be defined by the ability to complete one cycle of immune checkpoint inhibitor and SBRT. The immunotherapy regimen will be pembrolizumab (Arm A) or any recently administered immune checkpoint inhibitor (Arm B). Feasibility will be met if 6 patients (across Arms A and B combined) complete the combined therapy. If patients withdraw for any reason prior to completion of SBRT, up to 6 replacements will be allowed.

Secondary and Exploratory Objectives and Endpoints

1. To measure the overall response rate (ORR) at non-irradiated sites. SARC028 established an 11% objective response rate with pembrolizumab alone across sarcoma subtypes.[5] The distant effect from radiation therapy is the potential added clinical benefit to immunotherapy. Thus, the standard for measuring the objective response rate (ORR) excludes the irradiated site.[10-12,14] RECIST v1.1 and iRECIST modified to exclude the irradiated target will be used for response and progression evaluation.[21,22]
2. To determine the local failure rate at the irradiated site. In general, SBRT alone results in a high local control rate.[23] However, sarcomas are radioresistant tumors, and the primary role of radiation is adjuvant.[24,25] With lung tumors, local failure rates can be 3-fold higher than for other more radiosensitive tumors.[26] Higher doses of SBRT are required for adequate local control with sarcomas.[27] In addition, it is well-established that immunotherapy acts as a potent radiosensitizer.[28] Thus, the current study will create preliminary local failure data, which should be useful in the setting of a radioresistant tumor histology when combined with a radiosensitizing agent.

3. To determine the duration of response, progression-free survival, and overall survival.
4. To describe the adverse events associated with SBRT when combined with pembrolizumab.
5. To describe the health-related quality of life, toxicity, and treatment satisfaction associated with combined SBRT and pembrolizumab. Health-related quality of life and patient-reported toxicity will be measured by the summary scores from the Functional Assessment of Cancer Therapy-Immune Checkpoint Modulator (FACT-ICM), which includes the FACT-General (FACT-G). Patient-reported treatment satisfaction will be measured by the summary score of the Functional Assessment of Chronic Illness Therapy-Treatment Satisfaction-General (FACIT-TS-G).
6. Exploratory outcomes include major pathologic response (as at least 90% necrosis or non-viable tumor) for any tumors that are resected following treatment. This study will also generate preliminary data to examine whether PD-L1 expression (<1% vs ≥1% staining) or TMB status (<10 mut/Mb vs ≥ 10 mut/Mb) are associated with clinical outcomes.

Data Management

Data collected in this study will be entered into Advarra Electronic Data Capture Platform (Advarra, Columbia, MD). Adverse events, serious adverse events, deviations, and unanticipated problems be entered into the OnCore clinical trial management system (Advarra, Columbia, MD). The Principal Investigator will have access to the final dataset.

Statistical Analysis

The primary objective is feasibility, determined by completion of at least 1 cycle of pembrolizumab and completion of the course of SBRT. This phase zero study is primarily data and hypothesis generating. The primary objective will have been met if 6 subjects complete at least 1 cycle of pembrolizumab and a complete course of SBRT while the study is open (anticipated for 24 months). Up to 12 patients will be enrolled (allowing for up to 6 replacements). Should 5 or fewer complete 1 cycle of pembrolizumab and a complete course of SBRT, the study will be considered to have not met the primary objective.

Safety and efficacy evaluable populations are those that have received at least 1 cycle of pembrolizumab and an SBRT course (Arm A) or an SBRT course (Arm B). The secondary objective of this study is to establish the overall response rate (ORR) at the non-irradiated sites. Assuming a doubling in response rates based on a pooled analysis of studies testing SBRT combined with pembrolizumab in non-small-cell lung cancer, there is an expected ORR of 22%.[5,10] The one-sided 80% upper-limit Clopper-Pearson confidence interval is estimated to be 36.2%.

Data Monitoring, Auditing, and Dissemination

Quality assurance activities will be conducted as per the institutional Data and Safety Monitoring Board in order to ensure patient safety and data integrity oversight. Auditing will be done by an internal Quality Assurance Officer. Results will be disseminated to the public through publication at time of study completion, including with full protocol.

Discussion

In pursuit of improved efficacy of immune checkpoint inhibitor therapy, novel methods for immune stimulation are needed. In this study we outline testing the feasibility of adding SBRT to pembrolizumab. The goal of such combination therapy is improved overall response, including tumors not treated with SBRT.

In soft tissue sarcoma, the greatest challenge with ICI therapy has been lackluster success with single immune modulating agents.[5-7] In the SARC028 study of pembrolizumab, there was a reported 18% response rate and median PFS of 18 weeks for the 40 patients with soft tissue sarcoma, and a 5% response rate for those with a bone sarcoma.[5] Evidence is growing that histologic subtype is a major predictor for ICI response, with 4 of 10 patients with UPS and 2 of 9 with dedifferentiated liposarcoma having an objective response on SARC028. In a study of RNA and T cell receptor sequencing, it was found that UPS is the most highly mutated subtype and UPS T cells are the most oligoclonal.[29] Other clinical data points to limited responses to ICI for leiomyosarcoma or synovial sarcoma.[6,7] Based on these experiences, the current study is limited to UPS, dedifferentiated liposarcoma, or a sarcoma with high TMB.

For sarcoma, combination strategies have shown some success compared to single-agent ICI.[8,9] One example is with the combination of pembrolizumab and talimogene laherparepvec (T-VEC), an oncolytic modified herpes simplex virus that causes the release of tumor antigens, which resulted in a 35% response rate among 20 patients.[9] Similar to how T-VEC can produce a tumor response distant to the site of injection, external beam radiation therapy (RT) can result in systemic responses outside of the irradiated site.[18] Producing a favorable distant effect is uncommon with radiation alone, in-part because tumor cells upregulate checkpoint protein expression that limits the immune response, and because the tumor infiltrating lymphocytes that are associated with improved oncologic outcomes are radiosensitive. However, radiation can result in the release of tumor-specific antigens through immunogenic cell death, which in turn can potentially prime a more diverse class of T cell receptors.[19] Consequently, the antitumor CD8 T cell response can be enhanced. Thus, there is a potential for radiation to activate local immune cells, which, in combination with checkpoint inhibitor therapy, may synergistically improve distant control.

There are comparable studies of ICI combined with SBRT across other disease sites, with mixed results dependent on histology.[11-17] In one analysis of the 148 patients from two studies for NSCLC it was found that response rates at the non-irradiated tumors were doubled with SBRT (19.7% compared to 41.7% with SBRT [$P = .0039$]).[10] The benefit to SBRT was most notable for tumors with <1% PD-L1 expression, which raises the tantalizing hypothesis that this approach may be of particular benefit with sarcomas, since the majority of sarcomas have low PD-L1 expression.[5,11,30]

In sarcoma, the abscopal effect has been observed in cases, but has been less rigorously tested. For example, in a case report of a patient with UPS, the combination of nivolumab with palliative radiation (30 Gy in 10 fractions) at day 11 with a distant response for 13 months.[31] Additionally, a case-series of patients with metastatic soft tissue sarcoma found that the one patient who had an abscopal response had a UPS with low PD-L1 expression treated with pembrolizumab and SBRT (24 Gy in 3 fractions) at week 5.[32] Other ongoing studies are investigating the combination of ICI with RT prior to surgery for resectable disease (NCT05774275, NCT03338959, NCT06128863, NCT03116529, NCT03307616, NCT03463408, NCT03092323) or with SBRT to all sites of disease (NCT03548428, NCT06074692, NCT06114225). There are also studies of radiation combined with ICI open to multiple disease groups (NCT04616248, NCT02992912). However, none are focused on soft tissue sarcoma or the subtypes that have seen greater response with ICI.

The optimal SBRT timing and dose remain unknown. Preclinical data have suggested a benefit to the initiation of immunotherapy prior to radiation.[33] Clinical studies have supported these data - one retrospective analysis of 758 patients treated with an ICI combined with radiation found that the median OS was longest for those who started immunotherapy at least one month prior to RT.[34] As for radiation dose, it has been demonstrated that radiation can result in accumulation of cytosolic DNA starting at around 4 Gy.[35] Double stranded DNA breaks from radiation lead to cytosolic activation of cGAS, accumulation of cGAMP, activation of STING, and secretion of interferon-$\boldsymbol{\beta}$.[36] The DNA exonuclease Trex1 can inhibit the STING pathway by degrading cytosolic DNA, and is induced with doses greater than 10-15 Gy, with a drop in cytosolic DNA noted at 12-18 Gy.[35] Other work has indicated a role for even lower doses of RT to improve CD8 T cell infiltration in the tumor microenvironment through macrophage differentiation pathways.[37,38] However, clinical results have been variable, even with doses of 8-10 Gy x 3 that have been suggested by preclinical work.[11,13-17] Some have argued that higher doses that are typically associated with local control should be employed.[39,40] Indeed, the abscopal response has been observed with higher-dose regimens and associated with an increase in peripheral CD8 T cells.[12,41] In the current study, a variety of SBRT doses are allowed with the goal of higher biologically effective dose that would typically be associated with improved local control. However, lower dose regimens of 6 Gy x 3-5 are also allowed, in particular when tissue constraints cannot be met, as these doses are thought to be sufficient for immune stimulation.[35]

The safety of pembrolizumab and SBRT are well-established when delivered separately.[42-47] The goal of the current study is evaluating the combination approach, with growing data similarly showing rare grade ≥3 toxicity events.[48]

Limitations of the current study include that it is a single-instution, pilot study with a feasibility endpoint, and ultimately will be hypothesis generating to guide larger trials. The underlying principle of this trial is aimed at the abscopal effect, but this may not be observed with a small sample size. The questions highlighted above may also preclude observation of the abscopal effect, including that the optimal immune-checkpoint inhibitor regimen to be combined with RT is unknown, and that the optimal SBRT dose, timing, and fractionation are not known.

Conclusion

In conclusion, metastatic soft tissue sarcoma is an aggressive disease, and the majority of patients progress within months of starting conventional chemotherapy. This study tests the feasibility of adding SBRT to pembrolizumab, with an ultimate goal of improving the response and durability of treatment. This trial can be found registered online: NCT05488366.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Statement

Ethical Approval

This study has been approved by the University of California, Irvine Institutional Review Board (IRB #978 UCI 21-03). Written consent from all subjects is obtained.

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