

Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors

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A B S T R A C T

Purpose

Stereotactic body radiotherapy (SBRT) may stimulate innate and adaptive immunity to augment immunotherapy response. Multisite SBRT is an emerging paradigm for treating metastatic disease. Anti-PD-1–treatment outcomes may be improved with lower disease burden. In this context, we conducted a phase I study to evaluate the safety of pembrolizumab with multisite SBRT in patients with metastatic solid tumors.

Patients and Methods

Patients progressing on standard treatment received SBRT to two to four metastases. Not all metastases were targeted, and metastases > 65 mL were partially irradiated. SBRT dosing varied by site and ranged from 30 to 50 Gy in three to five fractions with predefined dose de-escalation if excess dose-limiting toxicities were observed. Pembrolizumab was initiated within 7 days after completion of SBRT. Pre- and post-SBRT biopsy specimens were analyzed in a subset of patients to quantify interferon- γ –induced gene expression.

Results

A total of 79 patients were enrolled; three patients did not receive any treatment and three patients only received SBRT. Patients included in the analysis were treated with SBRT and at least one cycle of pembrolizumab. Most (94.5%) of patients received SBRT to two metastases. Median follow-up for toxicity was 5.5 months (interquartile range, 3.3 to 8.1 months). Six patients experienced dose-limiting toxicities with no radiation dose reductions. In the 68 patients with imaging follow-up, the overall objective response rate was 13.2%. Median overall survival was 9.6 months (95% CI, 6.5 months to undetermined) and median progression-free survival was 3.1 months (95% CI, 2.9 to 3.4 months). Expression of interferon- γ –associated genes from post-SBRT tumor biopsy specimens significantly correlated with nonirradiated tumor response.

Conclusion

Multisite SBRT followed by pembrolizumab was well tolerated with acceptable toxicity. Additional studies exploring the clinical benefit and predictive biomarkers of combined multisite SBRT and PD-1–directed immunotherapy are warranted.

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INTRODUCTION

Immunotherapy has changed treatment paradigms in oncology, particularly with the addition of PD-1 inhibition to the armamentarium. However, despite the optimism surrounding treatment with immune-checkpoint blockade, most patients do not respond.¹ Predictive biomarkers, such as programmed death-ligand 1 (PD-L1) expression,

tumor-infiltrating lymphocytes, and interferon (IFN)- γ –induced gene expression are under investigation.²⁻⁴

An approach to expand the benefit of PD-1 immunotherapy may involve combinations with treatments that induce IFN-associated T-cell inflammation, such as ionizing radiation. Modeling of high-dose ablative radiation in murine systems suggests activation of innate immune signaling pathways, potentially leading to adaptive immune

ASSOCIATED CONTENT



Appendix
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responses within tumors in the radiation field as well as in distant tumors.^{3,4} Mechanisms facilitating the augmentation of immunotherapy by radiation include increased tumor antigen release, activation of innate immune pathways, increased T-cell infiltration, augmented antigen presentation, and modulation of immunosuppressive cells.^{5,6}

SBRT precisely delivers high radiation doses in a limited number of treatments to a target. This approach is effective in early-stage non–small-cell lung cancer and is deployed for localized pancreatic and prostate cancer, as well as for metastatic disease, with control rates between 70% and 90%.⁷ This finding led to multiple, ongoing randomized trials in patients with limited metastases to determine if long-term survival is achievable after SBRT and systemic therapy.⁸

Increased tumor burden correlates with decreased efficacy of PD-1 immunotherapy.⁹ Tumor debulking by SBRT may enhance immunotherapy response. Moreover, preclinical observations demonstrate tumor infiltration of T cells after radiation, suggesting the potential for synergy with immunotherapies.¹⁰⁻¹²

Although there is potential for overlapping toxicities, radiation is commonly used with immunotherapy, even with a paucity of prospective data. To our knowledge, there are no reports evaluating the tolerability of SBRT to multiple tumors within the same patient when combined with PD-1 blockade. Herein, we present our phase I study of pembrolizumab immunotherapy with multisite SBRT delivered to at least two distinct metastases in patients with advanced solid tumors.

PATIENTS AND METHODS

Study Design

The primary objective was to determine the recommended SBRT dose to anatomic locations before pembrolizumab. Secondary objectives included grade 3 or higher adverse events, response rate (RR), irradiated tumor control, progression-free survival (PFS), overall survival (OS), and immune score gene-expression analysis. A cohort with reduced radiation dose was planned depending on rates of dose-limiting toxicity (DLT). Initially, six evaluable patients were to be enrolled per cohort and analyzed for ≥ 6 months of follow-up, with patients who dropped out of the study replaced to ensure at least six evaluable patients per cohort. However, the typical PFS time was 3 months and data arose during the trial that demonstrated most toxicity associated with PD-1 inhibition occurred within 90 days.¹³ We amended the primary end point (ie, toxicity) of the study from 6 months follow-up to 3 months. The study and amendments were approved by the University of Chicago institutional review board. This trial is registered on www.clinicaltrials.gov (ClinicalTrials.gov identifier: NCT02608385).

Toxicity data were collected using Common Terminology Criteria for Adverse Events, version 4.0, with assessment to determine attribution. DLT was defined as treatment-related grade 3 or higher toxicity (excluding asymptomatic biochemical abnormalities) within 3 months, starting from the first day of radiotherapy. Toxicity attribution was reviewed weekly.

Patients were placed in a single cohort according to location of irradiated metastases. The seven anatomic cohorts were peripheral lung, central lung, mediastinum/thoracic, liver, spinal, osseous, and abdominal/pelvic, as used in ongoing studies.¹⁴ Larger size and morbidity of the metastasis were prioritized when determining which irradiated metastasis would dictate cohort assignment.

Patients

Patients with Eastern Cooperative Oncology Group performance status ≤ 1 were eligible for enrollment if they were ≥ 18 years old with

metastatic solid tumor previously treated with standard-of-care therapy. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, was required with at least two tumors ranging from 0.25 mL to 65 mL that were amenable to SBRT. Metastatic tumors > 65 mL were partially treated with radiation. A prospectively followed non-irradiated target metastasis was not required.

Patients were required to have adequate organ function, including absolute neutrophil count $\geq 1,500/\mu\text{L}$, serum creatinine level ≤ 1.5 times the upper limit of normal (ULN), AST and ALT ≤ 2.5 times ULN (or ≤ 5 times ULN for patients with liver metastases), and albumin level ≥ 3.5 mg/dL. Notable exclusions included uncontrolled CNS metastases and history of noninfectious pneumonitis requiring steroids. Prior radiation therapy was permitted if the metastases to be targeted received minimal radiation (ie, $< 10\%$ of prior prescription dose). Patients previously treated with immunotherapies, including anti-PD-1, were eligible.

Radiation Technique

Patients were treated with multisite SBRT, as previously defined.¹⁴ For multisite SBRT, consensus has been established to limit the target metastasis size to 5 cm (ie, a 65-mL sphere) and the number of metastases targeted in a patient to four.¹⁴ Doses to organs at risk were stipulated in the protocol and two to four metastases were targeted. Owing to limitations of SBRT planning, not all metastases were targeted. When selecting metastases to be irradiated, symptomatic or clinically relevant metastases were prioritized. For tumors > 65 mL, a target volume was created within the gross tumor volume to limit the treated tumor to < 65 mL. SBRT dose varied by anatomic site: 45 Gy in three fractions for peripheral lung, liver, and abdominal/pelvic; 50 Gy in five fractions for central lung and mediastinal/cervical; 30 Gy in three fractions for osseous and spinal/paraspinal). If excess toxicity was observed, a reduced dose was specified.¹⁴ Treatment using photons with linear accelerators was delivered once daily on an every-other-day basis within 14 days.

Study Medication

Pembrolizumab 200 mg intravenously every 3 weeks was initiated within 7 days after the final SBRT fraction. Treatment continued until clinical or radiographic disease progression, dose-limiting toxicity, withdrawal from study, or death. Treatment beyond progression was allowed. No additional anticancer therapeutics were permitted during enrollment.

Follow-Up

Evaluation of study end points began from the start date of SBRT. Patients were evaluated clinically during radiotherapy and with each cycle of pembrolizumab. Computed tomography scans were scheduled after every fourth cycle of pembrolizumab, or earlier if clinically indicated. RECIST 1.1 was used to assess overall response. Irradiated, partially irradiated, and nonirradiated metastasis response was calculated on a per-patient basis, using RECIST techniques, by aggregating the largest axial diameter of the irradiated metastases and nonirradiated metastases separately. Tumor control was defined as any response other than progressive disease.

Gene-Expression Analysis

Pre-SBRT and post-SBRT tumor biopsy specimens from the same metastasis were collected within 7 days before or after SBRT. Total RNA was extracted using previously published techniques.^{4,15} At the time of study conception, we reviewed the literature for candidate genes that were consistently upregulated in tumors responding to immunotherapies. Treatment with ipilimumab¹⁶ was reported to increase expression of granzyme K (*GZMK*), lymphocyte-specific protein tyrosine kinase (*LCK*), toll-like receptor 8 (*TLR8*), and G-protein-coupled receptor 171 (*GPR171*). These were selected for analysis in our patient cohort. Gene expression values for *GMZK*, *LCK*, *TLR8*, and *GPR171* were normalized to the geometric mean of β -actin and 18S ribosomal RNA. An immune score

was defined as the median expression value of the normalized mRNA values for the four genes. Gene-expression measurements were correlated to treatment response for eight patients with pre- and post-SBRT biopsy tissue and at least one imaging follow-up.

Statistical Analysis

For each of the assigned seven anatomic cohorts, DLTs were assessed using continued toxicity assessment. Newly enrolled patients received radiation to their respective sites at the dose level deemed safe at the time of enrollment. If the cumulative DLT rate at 3 months was $\geq 33\%$ in six evaluable patients (ie, at least two of six) assigned to a particular cohort, the radiation dose would be reduced. Exact logistic regression analyses were planned to model the probability of DLTs; because no dose reductions occurred, however, these were not performed.

Descriptive statistics were used to summarize patient characteristics. Investigator-determined grade 3 or higher toxicity deemed possibly, probably, or definitely related to treatment was summarized.

Separate summaries of grade 2+ treatment-related toxicity and all adverse events by Common Terminology Criteria for Adverse Events category were tabulated. A paired *t* test was used to compare mean percent tumor-burden changes between irradiated and nonirradiated tumors within the same patient. The distributions of the percent changes and the within-patient differences were examined using histograms and normal quantile plots, and no strong departure from normality was observed. McNemar test was performed to compare control of irradiated versus nonirradiated metastases. PFS and OS curves were estimated using the Kaplan-Meier method. OS was calculated from date of first fraction of SBRT to date last known alive or death. PFS was calculated from date of first fraction of SBRT to date of progressive disease, death, or censored at last clinical follow-up. Preplanned assessment was performed on four

genes (*TLR8*, *GPR171*, *LCK*, and *GZMK*). The association of gene expression with treatment response was assessed using the Spearman correlation coefficient. JMP software, version 9.0 (SAS Institute, Cary, NC) and Stata, version 14.0 (StataCorp, College Stations, TX) were used for statistical analysis.

RESULTS

Patient Characteristics

Seventy-nine patients were enrolled between January 6, 2016, and March 3, 2017 (Fig 1). Three patients underwent pretreatment biopsies but declined clinically owing to disease and were not treated with SBRT or pembrolizumab. Three other patients were treated with SBRT alone (these patients experienced no treatment-related toxicity); therefore, they were excluded from this analysis.

Baseline characteristics of the 73 patients included are outlined in Table 1. Patients had a median number of five prior therapies (interquartile range [IQR], three to eight therapies). All patients were diagnosed with a stage IV metastatic solid tumor (Appendix Table A1 lists primary tumors).

Treatment

Nearly all patients (n = 69 of 73; 94.5%) had two metastases treated with SBRT, three of 73 (4.1%) had three metastases treated, and one of 73 (1.3%) had four metastases treated. Twenty-six (35.6%) patients had irradiated metastases confined to one

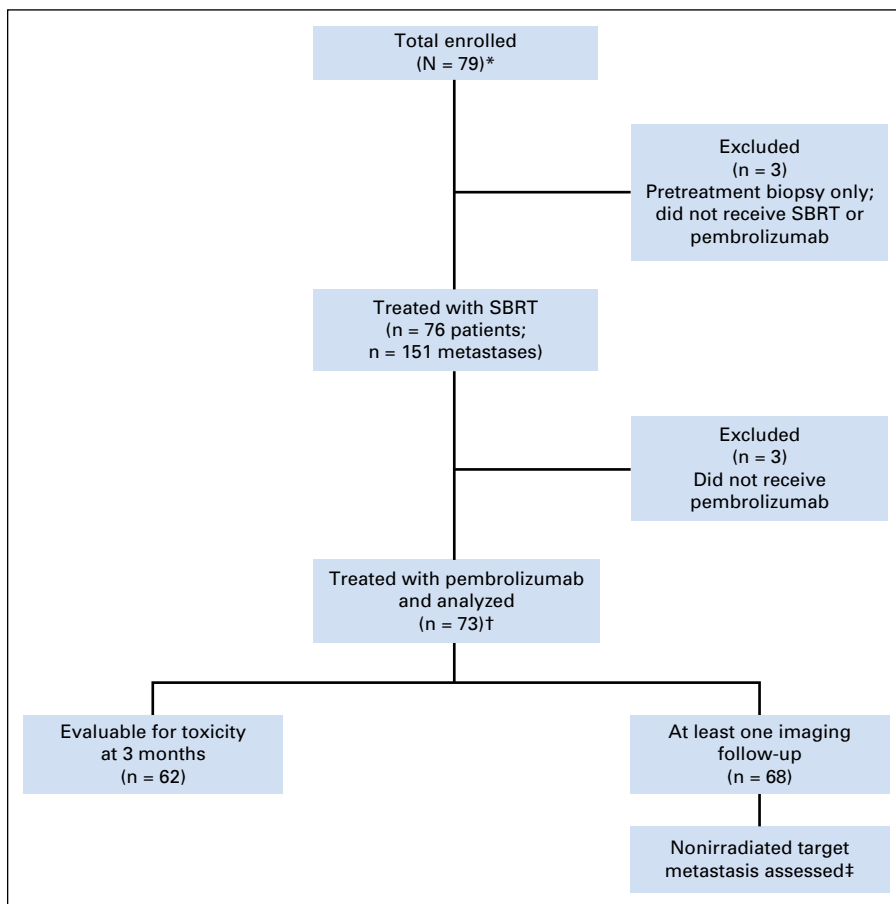


Fig 1. Protocol enrollment and analysis diagram. (*) A total of 12 patients had paired (both pre- and post-radiation) biopsy samples, six patients had preradiation biopsy samples, and six patients had postradiation biopsy samples. Of the patients with paired samples, eight had adequate follow-up to be included in this analysis. (†) Five patients had prior PD-1-axis blockade. (‡) A total of 52 patients had at least one measurable RECIST target metastasis that was not irradiated. SBRT, stereotactic body radiotherapy.

Table 1. Patient Characteristics

Characteristic	No.*	%*
Sex		
Female	44	60.3
Male	29	39.7
Age, mean, range (years)	62.0	19-89
ECOG performance status		
0	35	47.9
1	38	52.1
No. of distinct anatomic sites treated with SBRT in patient		
1	26	35.6
2	46	63.0
3	1	1.4
Smoking status		
Current	3	4.1
Former	32	43.8
Never	38	52.1
No. of prior therapies, median, IQR	5	3-8
Primary cancer		
Ovarian/fallopian tube cancer	9	12.3
Non-small-cell lung cancer	7	9.6
Breast cancer	6	8.2
Cholangiocarcinoma	6	8.2
Endometrial cancer	6	8.2
Colorectal cancer	5	6.8
Head and neck cancer	4	5.5
Other†	30	41.2
Baseline albumin, mean, range (g/dL)	3.9	1.8-4.5

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; SBRT, stereotactic body radiotherapy.
 *Unless otherwise indicated.
 †Tumors with < 5% accrual (Appendix Table A1 is a complete list of primary cancers).

anatomic location and 47 patients (64.4%) had irradiated metastases in two or more locations. Overall, there were 151 total metastases treated with SBRT (n = 30 peripheral lung, n = 23 central lung, n = 15 mediastinum/thoracic, n = 24 liver, n = 15 spinal, n = 16 osseous, and n = 28 abdominal/pelvic). Within 7 days of finishing radiotherapy, all 73 patients received at least one cycle of intravenous pembrolizumab (median, four cycles; IQR, two to seven cycles).

Toxicity

The primary end point of treatment-related DLT on the basis of anatomic cohort assignment is depicted in Table 2. Median

follow-up for treatment-related toxicity was 5.5 months (IQR, 3.3 to 8.1 months) for all patients and 7.1 months (IQR, 4.8 to 10.2 months) for living patients. Overall, there were no radiation-dose reductions, but six patients experienced severe treatment-related toxicity (n = 3 grade 3 pneumonitis, n = 2 grade 3 colitis, and n = 1 grade 3 hepatic toxicity). Sixty-two patients had at least 3 months of follow-up, corresponding to a DLT rate of 9.7%. All patients with a DLT had two metastases treated with SBRT. All planning constraints (including < 15% normal lung volume receiving 20 Gy) were met. Three patients had both metastases in the same anatomic location, and three patients had metastases in separate anatomic locations. Grade 2 and higher treatment-related toxicity by cohort and all adverse event data for the 62 patients with at least 3 months of follow-up are included in the Appendix Tables A2 and A3 (online only).

Treatment Response

To evaluate secondary efficacy end points, at least one imaging follow-up was available for each of 68 patients. The best RECIST responses were one complete response, eight partial responses, 21 patients with stable disease, and 38 with progressive disease, yielding an objective RR of 13.2% (nine of 68 patients). Waterfall plots for best overall RR using aggregate tumor diameter for RECIST target metastases, irradiated metastases, and nonirradiated RECIST target metastases are depicted in Figure 2. Out-of-field response using aggregate diameter of nonirradiated RECIST target metastases was 13.5% (seven of 52); however, using response defined by 30% reduction in any single, nonirradiated RECIST target metastasis, the nonirradiated RR was 26.9%.

The mean percent change in tumor diameter was -21.7% (standard deviation, 24.3%) for irradiated metastases versus 1.7% (standard deviation, 46.3%) for nonirradiated metastases (P = .0008). Tumor control (lack of progression at last follow-up) was compared between irradiated and nonirradiated metastases for the 52 patients with paired data. In 36 patients, neither the irradiated nor the nonirradiated metastases progressed; in one, the irradiated metastases progressed but the nonirradiated did not; in 15 patients, the nonirradiated metastases progressed but the irradiated did not; and in none did both progress (P = .0005).

Seventeen (25%) of the 68 patients with imaging follow-up had at least one metastasis measuring > 65 mL that was partially treated with SBRT. Median, initial, single-metastasis gross tumor

Table 2. Treatment-Related, Severe, Dose-Limiting Toxicity by Anatomic Cohort

Parameter	Anatomic Cohort							Total
	Lung-Peripheral	Lung-Central	Mediastinum/Thoracic	Liver	Spinal	Osseous	Abdominal/Pelvic	
Dose-limiting toxicity events, No./total No.	1/12	2/11	1/11	0/10	1/11	0/8	1/10	6/73
Toxicity for cohort patients evaluable at 3 months, No./total No. (%)	1/12 (8.3)*	2/10 (20.0)*	1/10 (10.0)†	0/8 (0)	1/8 (12.5)‡	0/5 (0)	1/9 (11.1)‡	6/62 (9.7)§

*Grade 3 pneumonitis (n = 3: one patient had two lung-central metastases irradiated, one patient had two lung-peripheral metastases irradiated, one patient had one lung-central metastasis and one bone metastasis irradiated).
 †Grade 3 hepatic toxicity (n = 1; one mediastinum/thoracic metastasis and one lung-peripheral metastasis irradiated).
 ‡Grade 3 colitis (n = 2; one patient with two abdominal/pelvic metastases irradiated, and one patient with one spinal metastasis and one osseous metastasis irradiated).
 §(n = 62; 11 were unevaluable for toxicity evaluation at 3 months).

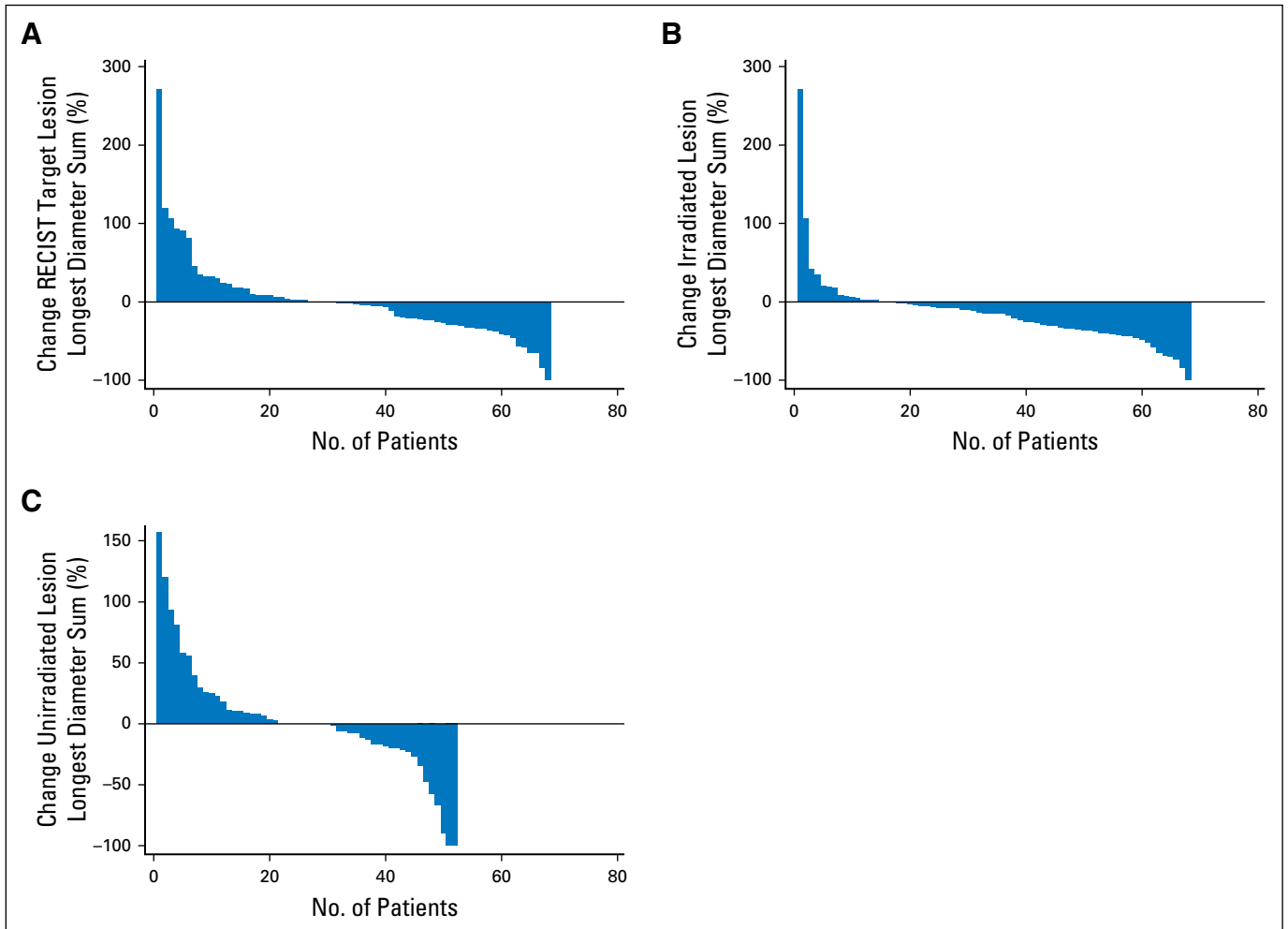


Fig 2. Best overall response waterfall plots. (A) Maximum percent change in the aggregate diameter of Response Evaluation Criteria in Solid Tumors (RECIST) target metastases. (B) Maximum percent change in aggregate diameter of irradiated metastases. (C) Maximum percent change in aggregate diameter of unirradiated RECIST target metastases.

volume for partial tumor irradiation was 116.6 mL (IQR, 90.7 to 219.7 mL) versus 7.2 mL (IQR, 2.6 to 14.8 mL) for the metastases treated with complete tumor irradiation ($P = .0001$). Comparison of patients with at least one tumor partially irradiated with patients whose tumors were completely irradiated showed no statistically significant difference in control at 3 months (88% for the partially irradiated patients ν 95% for the completely irradiated group; $P = .108$). Median OS was 9.6 months (95% CI, 6.5 months to undetermined) and median PFS was 3.1 months (95% CI, 2.9 to 3.4 months), as shown in Figure 3.

Immunologic Change Correlation with Treatment Response

To assess whether SBRT might result in favorable immunologic changes in the tumor microenvironment, expression of four preselected IFN- γ -associated genes was analyzed in post irradiation biopsy specimens. Increased gene expression was significantly correlated with responses in nonirradiated tumors ($P = .023$; Fig 4). Elevated immune scores were primarily driven by *GZMK* overexpression ($P = .011$; Fig 4B) and predicted greater decreases in the nonirradiated lesion size. By contrast, no association was observed

of preirradiation immune gene expression with irradiated or non-irradiated tumor responses. In addition, SBRT did not consistently increase IFN- γ -associated gene expression across patients.

DISCUSSION

In this study of multisite SBRT followed by pembrolizumab, similar rates of toxicity to SBRT or pembrolizumab monotherapy occurred, with high control rates of irradiated metastases and responses in nonirradiated metastases.⁷ The paradigm was well tolerated across anatomic sites with overall DLT < 10%. This rate is similar to the post hoc analysis of KEYNOTE-001 that showed 13% treatment-related toxicity in patients who previously received radiotherapy.¹⁷ Toxicity was generally low in our study; however, when toxicity was observed, it appeared to be in the region that was irradiated. This made it difficult to distinguish between toxicity of combination therapy versus radiation alone. A retrospective review of patients treated with palliative radiotherapy (RT) and anti-PD-1 showed a 4% grade 3 or higher immune-related adverse event rate, and toxicity was not related to anatomic location of RT.¹⁸ Clear

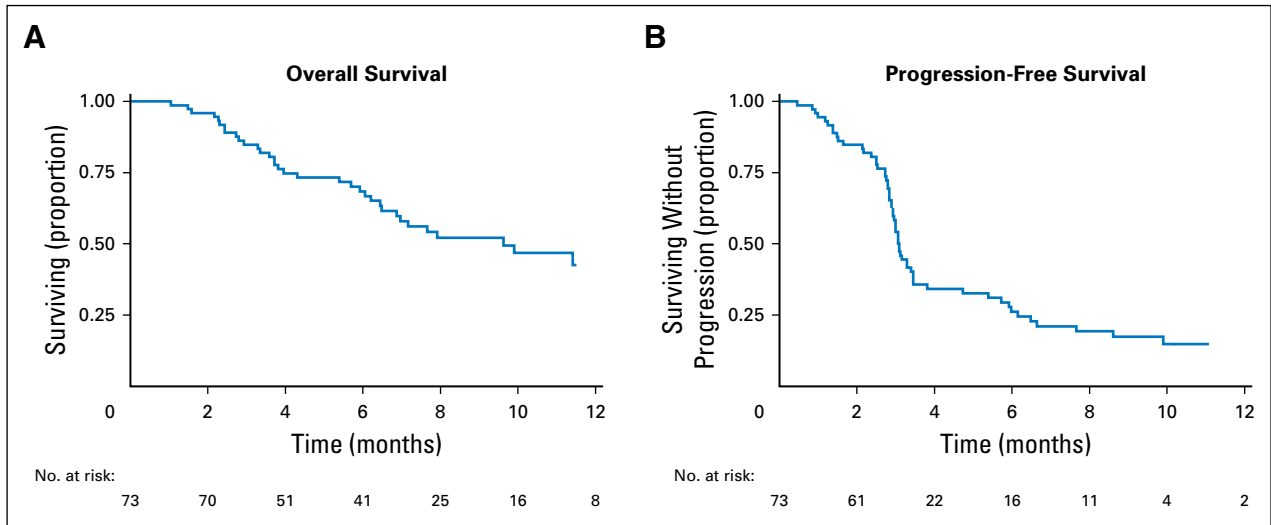


Fig 3. Kaplan-Meier curves of (A) overall and (B) progression-free survival.

distinctions of our study are the prospective design, higher radiation doses, and the consistent timing of radiation followed by PD-1 therapy. Our trial also used strict, normal, tissue-radiation planning parameters adopted from ongoing National Cancer Institute–sponsored trials to inform future analysis comparing our results with those of multisite SBRT alone.¹⁴

Our RECIST-based RR was 13.2% in a population of heavily pretreated patients. This population was unselected for PD-L1 expression, consisted of 27 cancer types, and was enriched in histologies not associated with significant RR to pembrolizumab. Our RR is similar to that of the multitumor basket study KEYNOTE-028 (range, 11% to 13% RR)¹⁹ in which patients were selected for high PD-L1 expression. We found no consistent clinical characteristics that were associated with treatment response. These results build on initial studies that incorporated SBRT and interleukin-2–based immunotherapy.²⁰ Our findings

support clinical and animal models demonstrating synergistic antitumor activity of RT and immunotherapy.²¹⁻²³ To our knowledge, this is the most robust prospective evaluation to demonstrate safety of SBRT combined with PD-1 immunotherapy and the first report of multisite SBRT combined with immunotherapy.

We hypothesized that radiation may augment PD-1 immunotherapy and we observed marked control of tumors. No significant changes from pre- to post-SBRT tumor biopsy specimens were seen in our predefined set of IFN- γ –associated genes. We noted, however, a significant correlation between the post-SBRT expression of the four-gene IFN- γ –related immune score and distant metastatic responses. We acknowledge our sample size was limited, the timing of a single biopsy procedure within 7 days after radiation was arbitrary, and only a limited set of genes has been analyzed. Nonetheless, our results indicate that additional studies

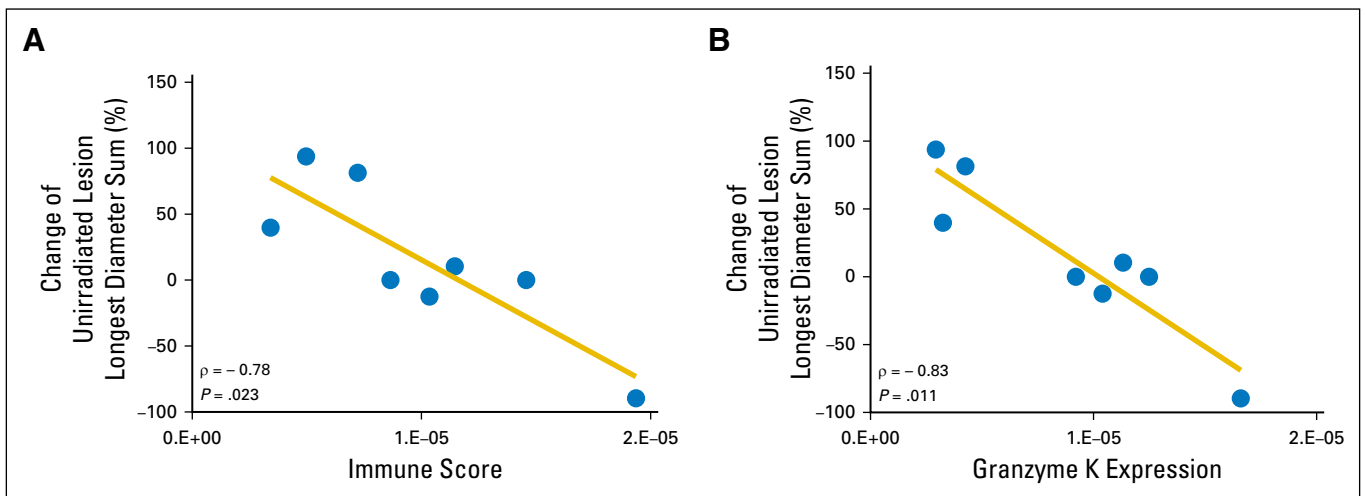


Fig 4. Posttreatment biopsy-specimen immune score correlation with unirradiated metastasis response. (A) Spearman rank analysis of poststereotactic body radiotherapy–irradiated tumor gene expression demonstrated significant correlations between the four-gene interferon- γ –related immune score and percent change in the unirradiated Response Evaluation Criteria in Solid Tumors target metastasis size in relation to baseline measurements. (B) Of the four genes, granzyme K expression in the irradiated metastasis demonstrated the strongest correlation with unirradiated metastasis response. Each dot represents an individual patient sample.

characterizing the immune-activating effects of SBRT predictive of immunotherapy response in clinical metastases are warranted.

The effects of SBRT and PD-1 blockade may be away from the radiation target (ie, abscopal) or close to the radiation target (ie, adscopal). Despite increased interest in the abscopal effect, no consensus definition exists.²⁴ Formenti²⁴ and others have defined an abscopal response as a reduction in the size of one nonirradiated metastasis by $\geq 30\%$.²⁵ We assessed abscopal response by aggregating the sum of the largest diameter for all of the nonirradiated RECIST target metastases ($\geq 30\%$ reduction indicating response), constituting a RR of 13%. When assessing a single nonirradiated RECIST target metastasis response $\geq 30\%$, the abscopal RR was 27%, similar to combined RT and granulocyte macrophage colony-stimulating factor.²⁵ These results are consistent with preclinical models of the abscopal response and support additional investigation of SBRT to improve checkpoint blockade.^{5,6}

Although some have combined nonablative RT doses with immunotherapy,²⁶ we used ablative SBRT doses developed through a US National Cancer Institute consensus working group.¹⁴ We anticipated an enhanced immune response with dose-escalated radiation.^{27,28} Also, there may be improved clinical outcomes to RT²⁹ and immunotherapy³⁰ with lower tumor burden. Although ongoing SBRT trials have limited patient enrollment to tumors with a 5-cm maximum diameter (ie, 65-mL sphere),¹⁴ we chose to partially irradiate larger tumors. We speculate that delivering SBRT to portions of tumors > 65 mL could provide cytoreduction while inducing effector T-cell trafficking throughout the remaining unirradiated portion of the lesion to enhance the local effects of PD-1 blockade. An exploratory subset analysis of partially irradiated tumors showed similar tumor control compared with total tumor irradiation, suggesting an adscopal immune effect of nontarget radiotherapy and pembrolizumab. Another consideration leading to this local control finding is that the low dose of radiation received to the nontargeted portion of the tumor may have been sufficient to elicit an immune response.

We acknowledge that our study has limitations. We treated a heterogeneous patient population with a variety of primary cancers not screened for PD-L1 status. Moreover, patients were exposed to

a high number of prior therapies and some patients died before the 3-month threshold for toxicity end point. Because there was no comparison of different SBRT doses, our study does not determine the radiation dose required to stimulate an optimal immune response.

In conclusion, the treatment paradigm was well tolerated, with clinical activity supporting a complementary role of SBRT and PD-1 immunotherapy. Expansion cohorts including large, partially irradiated tumors and additional analyses of tumor biopsy specimens are planned. Randomized studies are needed to determine whether combining pembrolizumab and SBRT potentiates efficacy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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REFERENCES

- Khoja L, Butler MO, Kang SP, et al: Pembrolizumab. *J Immunother Cancer* 3:36, 2015
- Herbst RS, Soria JC, Kowanetz M, et al: Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* 515:563-567, 2014
- Weichselbaum RR, Liang H, Deng L, et al: Radiotherapy and immunotherapy: A beneficial liaison? *Nat Rev Clin Oncol* 14:365-379, 2017
- Deng L, Liang H, Xu M, et al: STING-dependent cytosolic DNA sensing promotes radiation-induced type I interferon-dependent antitumor immunity in immunogenic tumors. *Immunity* 41:843-852, 2014
- Demaria S, Formenti SC: Radiation as an immunological adjuvant: Current evidence on dose and fractionation. *Front Oncol* 2:153, 2012
- Deng L, Liang H, Burnette B, et al: Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* 124:687-695, 2014
- Kirkpatrick JP, Kelsey CR, Palta M, et al: Stereotactic body radiotherapy: A critical review for nonradiation oncologists. *Cancer* 120:942-954, 2014
- Wong AC, Watson SP, Pitroda SP, et al: Clinical and molecular markers of long-term survival after oligometastasis-directed stereotactic body radiotherapy (SBRT). *Cancer* 122:2242-2250, 2016
- Huang AC, Postow MA, Orlowski RJ, et al: T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature* 545:60-65, 2017
- Lugade AA, Moran JP, Gerber SA, et al: Local radiation therapy of B16 melanoma tumors increases the generation of tumor antigen-specific effector cells that traffic to the tumor. *J Immunol* 174:7516-7523, 2005
- Schaue D, Comin-Anduix B, Ribas A, et al: T-cell responses to survivin in cancer patients undergoing radiation therapy. *Clin Cancer Res* 14:4883-4890, 2008
- Dovedi SJ, Cheadle EJ, Popple AL, et al: Fractionated radiation therapy stimulates antitumor immunity mediated by both resident and infiltrating polyclonal T-cell populations when combined with PD-1 blockade. *Clin Cancer Res* 23:5514-5526, 2017
- Weber JS, Hodi FS, Wolchok JD, et al: Safety profile of nivolumab monotherapy: A pooled analysis of patients with advanced melanoma. *J Clin Oncol* 35:785-792, 2017
- Al-Hallaq HA, Chmura S, Salama JK, et al: Rationale of technical requirements for NRG-BR001: The first NCI-sponsored trial of SBRT for the treatment of multiple metastases. *Pract Radiat Oncol* 6:e291-e298, 2016
- Harlin H, Meng Y, Peterson AC, et al: Chemokine expression in melanoma metastases associated with CD8+ T-cell recruitment. *Cancer Res* 69:3077-3085, 2009
- Ji RR, Chasalow SD, Wang L, et al: An immune-active tumor microenvironment favors clinical response to ipilimumab. *Cancer Immunol Immunother* 61:1019-1031, 2012
- Shaverdian N, Lisberg AE, Bornazyan K, et al: Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: A secondary analysis of the KEYNOTE-001 phase 1 trial. *Lancet Oncol* 18:895-903, 2017
- Bang A, Willhite TJ, Pike LRG, et al: Multicenter evaluation of the tolerability of combined

treatment with PD-1 and CTLA-4 immune checkpoint inhibitors and palliative radiation therapy. *Int J Radiat Oncol Biol Phys* 98:344-351, 2017

19. Ott PA, Bang YJ, Berton-Rigaud D, et al: Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: Results from the KEYNOTE-028 study. *J Clin Oncol* 35:2535-2541, 2017

20. Seung SK, Curti BD, Crittenden M, et al: Phase 1 study of stereotactic body radiotherapy and interleukin-2–tumor and immunological responses. *Sci Transl Med* 4:137ra74, 2012

21. Formenti SC, Demaria S: Radiation therapy to convert the tumor into an in situ vaccine. *Int J Radiat Oncol Biol Phys* 84:879-880, 2012

22. Sharabi AB, Lim M, DeWeese TL, et al: Radiation and checkpoint blockade immunotherapy:

radiosensitisation and potential mechanisms of synergy. *Lancet Oncol* 16:e498-e509, 2015

23. Vanpouille-Box C, Pilonis KA, Wennerberg E, et al: In situ vaccination by radiotherapy to improve responses to anti-CTLA-4 treatment. *Vaccine* 33:7415-7422, 2015

24. Formenti SC, Demaria S: Systemic effects of local radiotherapy. *Lancet Oncol* 10:718-726, 2009

25. Golden EB, Chhabra A, Chachoua A, et al: Local radiotherapy and granulocyte-macrophage colony-stimulating factor to generate abscopal responses in patients with metastatic solid tumours: A proof-of-principle trial. *Lancet Oncol* 16:795-803, 2015

26. Vanpouille-Box C, Formenti SC, Demaria S: Toward precision radiotherapy for use with immune checkpoint blockers. *Clin Cancer Res* doi: [10.1158/1078-0432.CCR-16-0037](https://doi.org/10.1158/1078-0432.CCR-16-0037) [epub ahead of print on July 27, 2017]

27. Schae D, Ratikan JA, Iwamoto KS, et al: Maximizing tumor immunity with fractionated radiation. *Int J Radiat Oncol Biol Phys* 83:1306-1310, 2012

28. Lee Y, Auh SL, Wang Y, et al: Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: Changing strategies for cancer treatment. *Blood* 114:589-595, 2009

29. Allibhai Z, Taremi M, Bezjak A, et al: The impact of tumor size on outcomes after stereotactic body radiation therapy for medically inoperable early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 87:1064-1070, 2013

30. Joseph RW, Ellassa-Schaap J, Wolchok JD, et al: Baseline tumor size as an independent prognostic factor for overall survival in patients with metastatic melanoma treated with the anti-PD-1 monoclonal antibody MK-3475. *J Clin Oncol* 32:3015, 2014 (suppl)

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Safety and Clinical Activity of Pembrolizumab and Multisite Stereotactic Body Radiotherapy in Patients With Advanced Solid Tumors

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Appendix

Primary Cancer Site	No.	%
Ovarian/fallopian tube cancer	9	12.3
Non–small-cell lung cancer	7	9.6
Breast cancer	6	8.2
Cholangiocarcinoma	6	8.2
Endometrial cancer	6	8.2
Colorectal cancer	5	6.8
Head and neck cancer	4	5.5
Pancreatic adenocarcinoma	3	4.1
Prostate cancer	3	4.1
Thyroid cancer (nonanaplastic)	3	4.1
Chondrosarcoma	3	4.1
Adenoid cystic carcinoma	2	2.6
Unknown primary	2	2.6
Appendiceal cancer	1	1.4
Basal cell carcinoma	1	1.4
Bladder cancer	1	1.4
Cervical cancer	1	1.4
Esophageal cancer	1	1.4
Hepatic biphenotypic carcinoma	1	1.4
Hepatocellular carcinoma	1	1.4
Merkel cell carcinoma	1	1.4
Mucoepidermoid carcinoma	1	1.4
Primary neuroendocrine tumor of the mediastinum	1	1.4
Renal cell carcinoma	1	1.4
Small bowel cancer	1	1.4
Anaplastic thyroid cancer	1	1.4
Vaginal cancer	1	1.4

CTCAE Category	Cohort (Metastasis Location)							Total
	Lung, Peripheral	Lung, Central	Mediastinum/Thoracic	Liver	Spinal	Osseous	Abdominal/Pelvic	
Endocrine disorders							1	1
Gastrointestinal disorders	1		2		1		2	6
General disorders and administration site conditions	1	1	1	1	1	1	1	7
Hepatobiliary disorders			1					1
Immune system disorders			1					1
Investigations			1	1				2
Musculoskeletal and connective tissue disorders							1	1
Renal and urinary disorders	1							1
Respiratory, thoracic, and mediastinal disorders	1	1	1					3

NOTE. Treatment-related severe toxicity grade 2 or higher and at least possibly related to treatment; n = 62 patients evaluable for toxicity. Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

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Table A3. All Adverse Events

CTCAE Category	Adverse Events*			
	Grade 1-2	Grade 3+	All Grades	Percentage
Blood and lymphatic system disorders	1	1	2	3.2
Cardiac disorders	2	3	5	8.1
Ear and labyrinth disorders	2	0	2	3.2
Endocrine disorders	5	0	5	8.1
Eye disorders	1	0	1	1.6
Gastrointestinal disorders	30	11	41	66.1
General disorders and administration site conditions	46	4	50	80.6
Hepatobiliary disorders	1	2	3	4.8
Immune system disorders	3	0	3	4.8
Infections and infestations	6	2	8	12.9
Injury, poisoning, and procedural complications	2	1	3	4.8
Investigations	8	1	9	14.5
Metabolism and nutrition disorders	23	3	26	41.9
Musculoskeletal and connective tissue disorders	24	6	30	48.4
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	2	1	3	4.8
Nervous system disorders	19	3	22	35.5
Psychiatric disorders	7	2	9	14.5
Renal and urinary disorders	4	0	4	6.5
Reproductive system and breast disorders	2	0	2	3.2
Respiratory, thoracic, and mediastinal disorders	23	7	30	48.4
Skin and subcutaneous tissue disorders	13	1	14	22.6
Vascular disorders	5	3	8	12.9

Abbreviation: CTCAE, Common Terminology Criteria for Adverse Events.

*Patients evaluable for toxicity: n = 62.