Analysis of the Abscopal Effect With Anti-PD1 Therapy in Patients With Metastatic Solid Tumors

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Summary: Abscopal effect is a rare phenomenon characterized by tumor regression of untreated metastatic lesions after a local therapy (eg, radiotherapy). We studied the probability of abscopal effect with radiotherapy associated with anti-programmed death cell 1 (PD1) therapy after progression on anti-PD1. This study is a retrospective analysis of patients treated with nivolumab or pembrolizumab for melanoma, non–small cell lung cancer (NSCLC) and renal cancer at Antônio Ermírio de Moraes Oncology Center, Brazil. To be eligible for this analysis, patients must have had unequivocal evidence of disease progression on anti-PD1 therapy and subsequent radiotherapy for any tumor site while still receiving anti-PD1. The abscopal effect was characterized as a response outside the irradiated field after radiotherapy plus anti-PD1. Sixteen patients were evaluated, including 12 metastatic melanoma, 2 metastatic NSCLC, and 2 metastatic renal cell carcinoma. The median time to disease progression on anti-PD1 was 3 months. The radiotherapy field included lung, lymph nodes, and bones, with a median total dose of 24 Gy (1–40 Gy), usually in 3 fractions (1–10 fractions). Three patients with melanoma developed an abscopal effect at a rate of 18.7% (25% among melanoma patients). Of note, one of them achieved a remarkable complete response lasting >6 months. Three patients with melanoma obtained a significant local response after radiotherapy, despite no response in distant metastases. Eleven patients presented disease progression after radiotherapy. No increased toxicity was observed. In conclusion, no patients with NSCLC or renal cancer showed abscopal effect, but 25% of patients with melanoma showed regression of nonirradiated lesions when anti-PD1 was continued after radiation to a tumor site that had progressed on anti-PD1 monotherapy.

Key Words: abscopal effect, anti-PD1, radiotherapy, melanoma, metastatic solid tumors

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Immunotherapy in cancer has been studied for many years, and, until recently, the results were not considered good enough for wide adoption. Together with new strategies, particularly a knowledge of immune checkpoint inhibitors allowed the development of new agents with remarkable antitumor effects in metastatic melanoma as well as in other types of cancer, including non–small cell lung cancer (NSCLC), Hodgkin's lymphoma, and renal cell carcinoma.[1–10] The outstanding benefit with these new agents includes marked and delayed response not only in naive-treatment patients[1–3] but also in the treatment-refractory ones.[5–10] In particular, they potentially induce prolonged survivals in a proportion of patients.[4–11]

Recently, United States Food and Drug Administration approved anti-programmed death cell-1 (PD1) therapy for advanced melanoma, NSCLC, classical Hodgkin lymphoma and renal cancer. Food and Drug Administration also approved the anti- programmed death-ligand 1 (PDL1) atezolizumab for urothelial cancer. In one phase III trial, anti-PD1 therapy showed greater efficacy compared with ipilimumab, with increase of overall survival[1]: the estimated 12-month survival rates were 68.4% and 58.2% for pembrolizumab every 3 weeks and ipilimumab, respectively (hazard ratio, 0.69; $P = 0.0036$).[1] Anti-PD1 therapy also showed superior efficacy over chemotherapy as first-line therapy and after progression on ipilimumab in metastatic melanoma,[2,5,6] as well as after progression to first-line chemotherapy in NSCLC.[7,8]

Despite those advances, many patients still have disease progression on checkpoint inhibitors, and further therapies are not so efficacious, unless patients' tumor harbors an actionable mutation. Therefore, to control symptoms, many strategies might be needed, including radiation therapy. In 2012, Postow et al[12] reported a case in which a patient who had failed therapy with ipilimumab received palliative radiotherapy and had, besides a local response, reduction of nonirradiated lesions, that is, the abscopal effect.

The abscopal effect is a rare phenomenon characterized by tumor regression of untreated metastatic lesions after a local therapy. Considering radiotherapy, it is observed as the reduction of lesions outside the radiation field after treatment of a lesion or region. It was first described by Mole[13] in 1953, and later it was better characterized by Andrews.[14] Its exact mechanism is unknown, but preclinical models suggest that it results from immunogenic cell death induced by local radiotherapy[15,16] and results in improvement of immune function.[17] The real incidence of abscopal effect has not been well evaluated in clinical trials, with no clinical studies analyzing the frequency of abscopal effect after radiotherapy alone. The combination of irradiation with immunotherapy may increase the occurrence of abscopal effect,[18–20] with rates of 25%–52% with immune checkpoint inhibitors.[18,19] Moreover, the abscopal response seems to be more likely to occur in more immunogenic tumors such as melanoma, although some preclinical trials have demonstrated some benefit in other tumors.[21]

We retrospectively studied the experience of our center with respect to the role of radiotherapy given concomitantly to anti-PD1 therapy after unequivocal evidence of progression on anti-PD1 to evaluate the probability of occurrence of the abscopal effect.

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PATIENTS AND METHODS

We performed a retrospective analysis of patients who underwent anti-PD1 therapy for any metastatic cancer and were treated at the Antonio Ermirio de Moraes Oncology Center in Brazil from September 2013 to November 2015. The anti-PD1 used was nivolumab 3 mg/kg given intravenously every 2 weeks or pembrolizumab 2 mg/kg given intravenously every 3 weeks.

The selection criteria included occurrence of unequivocal disease progression during anti-PD1 therapy and subsequent radiotherapy for any tumor site while still receiving anti-PD1. Disease progression was defined according to RECIST (Response Evaluation Criteria in Solid Tumors) criteria version 1.1. Radiotherapy was generally performed in an attempt to elicit an abscopal effect as further options of systemic treatment for those patients were limited. The criteria for the choice of the lesion to be irradiated were: a symptomatic lesion requiring palliative radiotherapy and/or the lesion with low risk of toxicity from radiotherapy.

The exclusion criteria included the following: concomitant use of ipilimumab or BRAF/MEK inhibitor with anti-PD1 therapy; radiotherapy performed during objective response or stable disease with anti-PD1 or before any response evaluation; and change of therapy for metastatic disease after initial progression on anti-PD1 with no radiotherapy performed. Previous use of ipilimumab or BRAF/MEK inhibitor was not an exclusion criterion.

The abscopal effect was characterized as a response in distant metastases (outside the irradiated field) after radiotherapy plus anti-PD1 in those patients who previously progressed on anti-PD1. Response was evaluated by the qualitative assessment of the investigator through computed tomography or positron emission tomography.

This study was approved by Ethics Committee of Real e Benemérita Instituição Portuguesa de Beneficência, Brazil.

RESULTS

From all patients treated with anti-PD1 therapy at our institution, 16 patients met the criteria of disease progression on anti-PD1 alone followed by radiotherapy while maintaining anti-PD1 treatment.

Among the 16 eligible patients, 65.5% were male, and the median age was 56 years (41–87 y). Twelve patients (75%) were diagnosed with metastatic melanoma: 10 had cutaneous melanoma, 1 had mucosal melanoma, and 1 had choroidal melanoma. Four of them (33.3%) were BRAF-mutated. Two patients had metastatic NSCLC (both adenocarcinoma) and 2 had metastatic clear cell carcinoma of the kidneys.

The median lines of treatment received before anti-PD1 therapy was 2, and the majority of patients received nivolumab (12 patients), while 4 patients received pembrolizumab. The median time to disease progression on anti-PD1 was 3 months (2–9 mo) after a median of 5 cycles.

The site of radiotherapy varied according to possible morbidity, and patients' need of palliation. The majority was performed for lesions localized in lung, lymph nodes, and bones. The median total dose was 24 Gy (1–40 Gy), and the doses were, in general, given in 3 fractions (1–10 fractions).

The results following radiotherapy are showed in Table 1. The median duration of follow-up was 8 months. Eleven patients presented disease progression after radiotherapy while maintaining anti-PD1 treatment; consequently, no abscopal effect was observed. Among these, 6 patients were diagnosed with melanoma, and only 1 patient

TABLE 1. Description of Outcomes After Radiotherapy

Patient	Tumor	Duration of Anti-PD1 Before PD (wk)	Reason for RT	Target of RT	Local Response	Distant Response	Time to Abscopal Response After RT (wk)	Alive	Survival after Anti-PD1 (mo)
1	Melanoma	10	Palliation	Retroperitoneal LN	Yes	Yes	4	Yes	9
2	Melanoma	30	Abscopal	Lung, vertebrae	Yes	Yes	6	Yes	8
3	Melanoma	20	Palliation	Gluteal lesion	Yes	Yes	4	Yes	6
4	Melanoma	10	Palliation	Retroperitoneal LN	Yes	No (SD)	NA	Yes	9
5	Melanoma	14	Palliation	Thoracic mass	Yes	No (SD)	NA	Yes	11
6	Melanoma	4	Palliation	Supraclavicular LN	Yes	No (SD)	NA	Yes	7
7	Renal cancer	15	Abscopal	Lung	No	No (SD)	NA	Yes	7
8	Melanoma	15	Palliation	Brain	No	No (PD)	NA	Yes	10
9	Melanoma	8	Palliation	Lung	No	No (PD)	NA	Yes	5
10	Melanoma	6	Palliation	Vertebrae	No	No (PD)	NA	No	8
11	Melanoma	10	Palliation	Retroperitoneal LN	No	No (PD)	NA	No	5
12	Melanoma	10	Palliation	Abdominal lesion	No	No (PD)	NA	Yes	6
13	Melanoma	16	Palliation	Breast	No	No (PD)	NA	No	8
14	NSCLC	15	Palliation	Abdominal lesion	No	No (PD)	NA	No	3
15	NSCLC	15	Abscopal	Lung	No	No (PD)	NA	Yes	7
16	Renal cancer	44	Palliation	Iliac bone	No	No (PD)	NA	Yes	27

LN indicates lymph node; NA, not applicable; NSCLC, non–small cell lung cancer; PD, progressive disease; RT, radiotherapy; SD, stable disease.

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continued receiving nivolumab due to clinical benefit, with amelioration of symptoms. In other patients, systemic therapy was changed to chemotherapy, ipilimumab, or BRAF/MEK inhibitors. In the patient with renal cell carcinoma, the therapy was changed to ipilimumab with no response; this was followed by further change to pegylated interferon plus bevacizumab, which generated a response to date. With respect to the patients diagnosed with metastatic NSCLC, one of them started on ipilimumab plus pembrolizumab at disease progression, and the other one died due to cancer.

In 3 patients, all of them diagnosed with advanced cutaneous melanoma, a significant local response was obtained after radiotherapy that was characterized by significant reduction of local tumor, despite no response in distant metastases (in which only a stable disease was observed). Therefore, anti-PD1 therapy was continued without change of systemic therapy to date.

In another 3 patients, local and distant tumor reductions were observed after radiotherapy; this therefore met the definition of the abscopal effect in 18.7% of the patients (Figs. 1, 2). All of the patients who experienced abscopal response were diagnosed with metastatic melanoma: 2 cutaneous melanoma and 1 choroidal melanoma. Therefore the estimated rate of abscopal effect when evaluating only patients with melanoma was of 25%. In those 3 patients, there was disease progression on anti-PD1, which was confirmed by clinical symptoms and radiological findings, followed by further distant response after local radiotherapy. One of them (diagnosed with metastatic cutaneous melanoma) presented progressive disease associated with clinical worsening after 5 cycles of nivolumab. After radiotherapy, he achieved a remarkable complete response which lasted >6 months (Fig. 1), with no evidence of disease to date.

In 1 patient with metastatic renal cell carcinoma, the irradiation after progression on anti-PD1 yielded a stable disease with clinical benefit with anti-PD1 for 4 months after radiotherapy so far.

The median survival of all 16 patients from beginning of anti-PD1 and to date was 7.4 months and included 4 deaths in the group of non abscopal response. In the 3 patients that exhibited the abscopal effect, the range of survival was 6–9 months, but all of them are still on response and receiving anti-PD1 with benefit to date. No grade 3/4 toxicities were observed with anti-PD1 alone or following radiotherapy.

DISCUSSION

The abscopal effect seems to occur through a systemic immune stimulation performed by radiotherapy. Studies have suggested that radiation improves antitumoral response to immunotherapy through several mechanisms: enhancement of major histocompatibility complex class I, calreticulin, and factor for apoptosis signals surface expression; release of high mobility group box 1; activation of dendritic cells; enhancement of cross-presentation of tumor antigens; increase of density of tumor-infiltrating lymphocytes; modulation of expression of immune checkpoint molecules; and modulation of Treg populations.[17] However, despite stimulation of immune response, radiotherapy alone is in general insufficient to induce the abscopal effect. Therefore, association of irradiation with immune checkpoint inhibitors has been evaluated in an attempt to elicit an abscopal response.

Some preclinical experiments have shown the role of checkpoint inhibitors as radiosensitizer therapies with at least local tumor control[21,22] and some with improved survival.[22,23] In that scenario, the systemic antitumor immune stimulation is suggested by studies using murine models in which immunologic memory was observed: irradiation combined to cytotoxic T-lymphocyte associated antigen 4 or PD1 inhibitors produces only initial local control of tumor, but the mice reject the tumor after secondary challenge of tumor reinjected in flank, despite no additional therapy.[22,23]

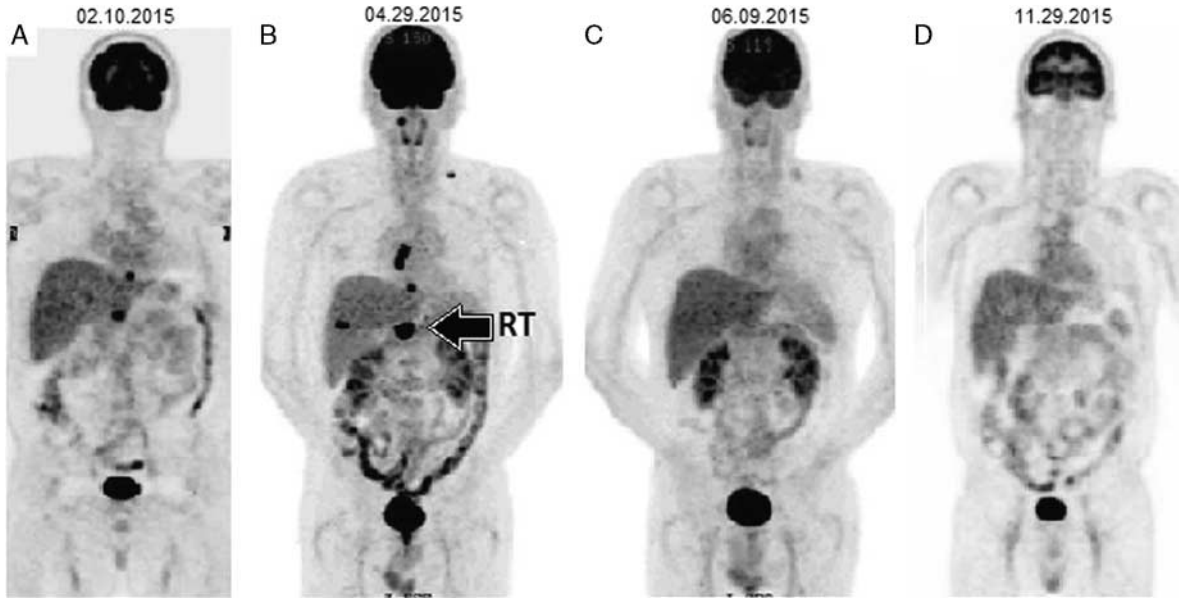

FIGURE 1. A 55-year-old man with metastatic melanoma of unknown primary site who started on nivolumab 3 mg/kg IV q2 weeks (A) and experienced symptomatic progression (lumbar pain) after 5 cycles of nivolumab (B). The patient had previously failed ipilimumab and BRAF/MEK inhibitors. The retroperitoneal node was irradiated with palliative intent (B) and the patient had complete resolution of all sites of disease (C and D) (arrow: site of radiotherapy).

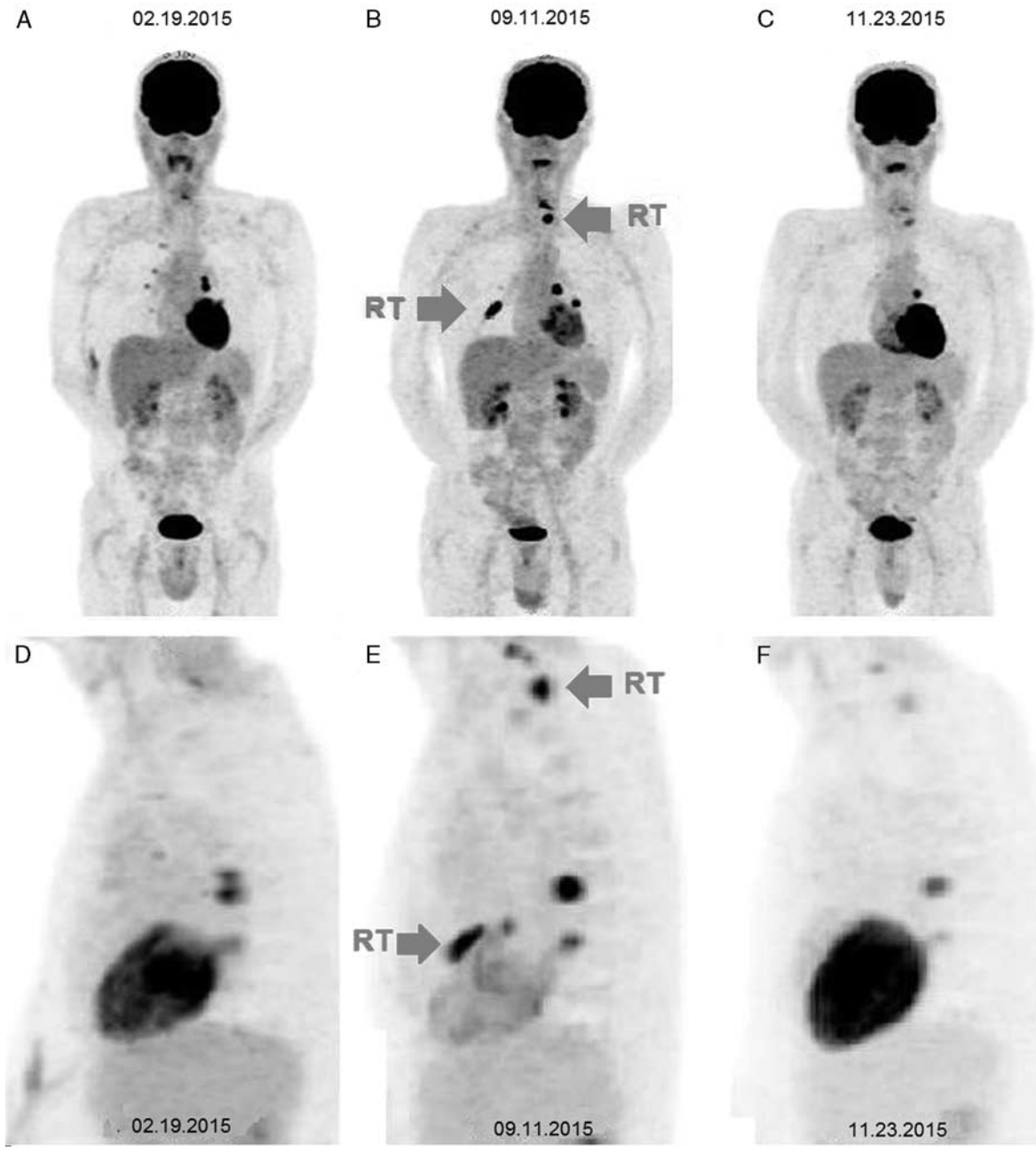

FIGURE 2. A 54-year-old man with metastatic melanoma of unknown primary site who started on nivolumab 3 mg/kg IV q2 weeks (A and D) and experienced cervical spine pain after 15 cycles of nivolumab (B and E). The patient had previously progressed on ipilimumab. His tumor was BRAF wild type. The cervical metastasis as well a pulmonary nodule were irradiated (B and E). Two other pulmonary foci of metastases had significant reduction in size and standardized uptake value uptake (C and F) (arrow: site of radiotherapy).

In the first preclinical experiment of anti-cytotoxic T-lymphocyte associated antigen 4 combined with radiotherapy, a model of poorly immunogenic metastatic mouse mammary carcinoma 4T1 was studied, and the group which received ipilimumab plus radiotherapy had a statistically significant survival advantage over radiotherapy alone or ipilimumab alone with reduction of local and distant lung tumor.[21]

In the clinical setting, despite being rare, the benefit of combination of immune checkpoint inhibitors and radiotherapy has also been observed. A report of a patient with metastatic melanoma who underwent maintenance with ipilimumab and concurrent palliative radiotherapy (28.5 Gy) at disease progression resulted in regression of non-irradiated metastases that showed benefits for at least 10 months.[12] Many other reports also observed benefit of radiotherapy combined to ipilimumab in metastatic melanoma or NSCLC, including patients with complete responses.[24–26]

Of note, a series enrolling 21 patients with advanced melanoma who progressed after ipilimumab and then underwent radiotherapy for cranial or extracranial sites

observed an abscopal response in 11 patients (52%), including 9 with partial responses and 2 with stable disease.[18] The median time from radiotherapy to an abscopal response was 1 month (range, 1–4), and median overall survival was superior in patients that exhibited the abscopal effect compared with nonresponders (22.4 vs. 8.3 mo, respectively).[18]

Another series included 47 metastatic melanoma patients who underwent radiotherapy following ipilimumab. A reduction of lesions was observed in 7 patients (11%) before radiation therapy compared with 16 (25%) after radiation therapy; in 11 of the latter (69%), an increase of lesions had been observed before radiotherapy ($P = 0.03$). The radiation fraction size ≤ 3 Gy was associated with favorable lesion response ($P = 0.014$).[19]

Some case reports also suggest that the benefit of adding radiotherapy to ipilimumab may not be exclusive to melanoma. In a case report, a striking systemic response was observed in a patient with metastatic NSCLC who started on ipilimumab plus radiotherapy for a liver metastasis.[25] Despite the possible questioning about the response being due to an abscopal effect or just to the delayed systemic activity of ipilimumab, the significant response obtained was remarkable. However, these results require confirmation in prospective clinical trials.

As anti-PD1 therapies are a more recent treatment in clinical trials and daily practice compared with ipilimumab, there is not much clinical data regarding abscopal effects with anti-PD1. A preclinical study of murine glioma treated with anti-PD1 and radiotherapy showed superior survival compared with controls, anti-PD1, or radiotherapy alone (53, 25, 27, and 28 d, respectively, $P < 0.05$) with an increase of tumor infiltration of $CD8^+$ T lymphocyte.[23] An immunologic memory was also observed, as the mice were able to reject secondary challenge of glioma cells injected in the flank.[23] A preclinical study also suggests abscopal benefit with anti-PDL1 therapy.[27]

Aside from immune checkpoint inhibitors, other strategies have been studied to obtain abscopal responses. A trial included 41 patients with metastatic solid tumors who had stable or progressive disease to single-agent chemotherapy or hormonal therapy and therefore started on concurrent radiotherapy and a granulocyte-macrophage colony-stimulating factor.[28] An abscopal response occurred in 11 patients (26.8%) that were diagnosed with NSCLC, breast cancer, and thymic cancer. Other trial evaluated 12 patients with metastatic melanoma or renal cell carcinoma to receive radiotherapy, followed by high-dose interleukin-2.[20] Eight of 12 patients (66.6%) achieved an objective response, with 1 complete response: 5 of 7 patients with melanoma, and 3 of 5 with renal cancer. The response rate was significantly higher than expected on the basis of historical data, suggesting a possible abscopal effect associated to a greater frequency of proliferating $CD4^+$ T cells.[20]

Questions arise about the optimal time to begin radiotherapy to obtain an abscopal response. It is not yet known whether the use of those therapies sequentially is better than concomitantly. Some preclinical and clinical trials that evaluate the abscopal effect offer radiotherapy concurrent with checkpoint inhibitors during objective response to immunotherapy or before any evaluation of response. It is difficult to distinguish how much of the tumor response is due to systemic therapy alone or to combination therapy. To exclude that bias, in our study we selected only patients who had unequivocal evidence of disease progression on anti-PD1 and then underwent irradiation while on anti-PD1 therapy. Besides, we considered only objective responses after radiotherapy to be characteristic of the abscopal effect, excluding stable disease. This more stringent criteria is probably the reason why the rate of the abscopal effect observed in our study was lower when compared with some other trials.

In our study, we observed a remarkable durable, complete response after radiotherapy, that is, the abscopal effect, in one of our patients with metastatic cutaneous melanoma who had previously progressed with anti-PD1 as confirmed by radiological and clinical findings. That suggests a significant role of radiotherapy as an attempt to elicit an abscopal effect before changing systemic therapy. However, one could question whether the distant response after radiotherapy would simply represent a late response to systemic therapy with checkpoint inhibitors. Although it would be possible, we should remark that the phenomenon of pseudo-progression is rare with anti-PD1 therapies. A study by Hodi et al[29] evaluated 324 patients with melanoma with follow-up superior to 28 weeks, and observed a rate of 4.6% for early pseudo-progression (at 12 wk after beginning of anti-PD1) and 2.8% for delayed pseudo-progression (after 12 wk). Therefore, the frequency of pseudo-progression is too low to clearly justify the initial progression observed in our 3 patients (18.7%) with abscopal effect. Furthermore, clinical worsening associated with radiologic progression is highly suggestive of real disease progression, not pseudo-progression. As pointed out before, our patients that exhibited the abscopal effect presented progressive disease demonstrated by clinical and radiologic findings, followed by clear improvement after radiotherapy.

Another concern about the combination of checkpoint inhibitors and radiotherapy is toxicity. Some studies showed no increased toxicity of immunotherapy when given concurrently or sequentially to radiation therapy,[30] but to our knowledge no formal trial has addressed this issue so far. We have not observed unexpected toxicity with the addition of radiotherapy to immune checkpoint inhibitors.

In conclusion, in patients who appeared to be progressing on anti-PD1 therapies, we observed an abscopal response after administration of radiotherapy in 18.7% of patients with metastatic solid tumors (all of them with metastatic melanoma). Although encouraging, those results are still preliminary, and radiotherapy remains only indicated for palliation. However, radiotherapy may be an alternative to patients who already progressed on chemotherapy, ipilimumab, and anti-PD1 as an attempt to elicit an abscopal effect as further options of systemic treatment for those patients are limited. Only a randomized trial would truly enable an assessment of whether radiotherapy adds to ongoing checkpoint blockade in patients who progress on checkpoint blockade alone. This type of study is necessary to exclude pseudoprogression.

CONFLICT OF INTEREST/ FINANCIAL DISCLOSURES

A.C.B. and R.A.S. are both medical advisors and speakers of Bristol-Myers Squibb and Merck Sharp and Dohme. The remaining authors declared that there are no financial conflicts of interest with regard to this work.

REFERENCES

1. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med*. 2015;372: 2521–2532.
2. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Eng J Med*. 2015;372:320–330.
3. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or monotherapy in untreated melanoma. *N Eng J Med*. 2015;373:23–34.
4. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Eng J Med*. 2010;363:711–723.
5. Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. *Lancet Oncol*. 2015;16:908–918.
6. Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol*. 2015;16:375–384.
7. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non–small-cell lung cancer. *N Engl J Med*. 2015;373:123–135.
8. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med*. 2015;373:1627–1639.
9. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 Blockade with nivolumab in relapsed or refractory hodgkin's lymphoma. *N Engl J Med*. 2015;372:311–319.
10. Motzer RJ, Escudier B, McDermott D, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803–1813.
11. Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. *J Clin Oncol*. 2015;33:1889–1894.
12. Postow MA, Callahan MK, Barker CA, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Eng J Med*. 2012;366:925–931.
13. Mole R. Whole body irradiation therapy—radiobiology or medicine? *Br J Radiol*. 1953:234–241.
14. Andrews JR. *Radiobiology of Human Cancer Radiotherapy*, 2nd ed. Baltimore, MD: University Park Press; 1978.
15. Formenti SC, Demaria S. Systemic effects of local radiotherapy. *Lancet Oncol*. 2009;10:718–726.
16. Gameiro SR, Jammeh ML, Wattenberg MM, et al. Radiation-induced immunogenic modulation of tumor enhances antigen processing and calreticulin exposure, resulting in enhanced T-cell killing. *Oncotarget*. 2014;5:403–416.
17. Sharabi AB, Lim M, DeWeese TL, et al. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol*. 2015;16: e498–e509.
18. Grimaldi AM, Simeone E, Giannarelli D, et al. Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy. *Oncoimmunology*. 2014;3:e28780-1–e28780-9.
19. Chandra RA, Wilhite TJ, Balboni TA, et al. A systematic evaluation of abscopal responses following radiotherapy in patients with metastatic melanoma treated with ipilimumab. *Oncoimmunology*. 2015;4:e1046028-1–e1046028-7.
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*. 2012;4: 137ra74-1–137ra74-1-7.
21. Demaria S, Kawashima N, Yang AM, et al. Immune-mediated inhibition of metastases after treatment with local radiation and CTLA-4 blockade in a mouse model of breast cancer. *Clin Cancer Res*. 2005;11(pt1):728–734.
22. Polistena A, Johnson LB, Ohiami-Masseron S, et al. Local radiotherapy of exposed murine small bowel: apoptosis and inflamation. *BMC Surg*. 2008;8:1–7.
23. Zeng J, See AP, Phalen J, et al. Anti-PD1 blockade and stereotatic radiation produce long-term survival in mice with intracranial gliomas. *Int J Radiat Oncol Biol Phys*. 2013;86: 343–349.
24. Hiniker SM, Chen DS, Reddy S, et al. A systemic complete response of metastatic melanoma to local radiation and immunotherapy. *Trans Oncol*. 2012;5:404–407.
25. Golden EB, Demaria S, Schiff PB, et al. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. *Cancer Immunol Res*. 2013;1:365–372.
26. Sullivan RJ, Lawrence DP, Wargo JA, et al. Case records of the Massachusetts General Hospital. Case 21-2013. A 68-year-old man with metastatic melanoma. *N Engl J Med*. 2013;369: 173–183.
27. Deng L, Liang H, Burnette B, et al. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest*. 2014;124:687–695.
28. 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*. 2015; 16:795–803.
29. Hodi FS, Hwu WJ, Kefford R, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *J Clin Oncol*. 2016;34:1510–1517.
30. Barker CA, Postow MA, Khan SA, et al. Concurrent radiotherapy and ipilimumab immunotherapy for patients with melanoma. *Cancer Immunol Res*. 2013;1:92–98.