Short Communication

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Melanoma Management

Durability of response in metastatic melanoma patients after combined treatment with radiation therapy and ipilimumab

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Practice points

- The combination of immunotherapy and radiation may result in increased clinical response rates in metastatic melanoma patients.
- The rate of initial complete response and its durability appear to be correlated with at least a grade 2 hypophysitis requiring long-term steroid use.
- Treatment-related hypophysitis may be an indicator of durable response following the use immunotherapy agents in melanoma.
- Secondary analysis of previously reported prospective trials with melanoma patients treated with immunotherapy will be helpful to determine if this observed correlation is present in a larger study cohort.

Aim: We previously reported a prospective trial evaluating the safety and efficacy of combining ipilimumab and radiation therapy in patients with metastatic melanoma. Herein, we provide a long-term update on patients with complete response (CR) or partial response (PR). **Patients & methods:** We continued to follow these patients with serial imaging including computed tomography, PET or MRI. **Results:** Two of the three patients with CR are still alive and without evidence of melanoma but with chronic treatment-induced hypophysitis. The third patient died of hepatocellular carcinoma, but with no evidence of melanoma. Among the three patients with PR, two achieved CR after pembrolizumab monotherapy. **Conclusion:** This long-term follow-up reveals the striking durability of the CRs, which appears to correlate with a grade 2–3 hypophysitis.

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Keywords: hypophysitis • immunotherapy • melanoma • radiation therapy

Immunotherapy has become an important tool in the armamentarium of oncologists and is referred to as the fifth clinical pillar of cancer therapy, along with radiotherapy, surgery, chemotherapy and targeted therapy [1]. Melanoma represents a highly immunogenic cancer for which treatment in the metastatic setting has greatly benefited from immunotherapy with checkpoint blockade. With the advent of ipilimumab (anti-CTLA-4 antibody), nivolumab/pembrolizumab (anti-PD-1 antibody) and anti-PD-L1 agents, there have been increasing numbers of reports of clinical response in metastatic melanoma patients [2]. In the first prospective Phase I clinical trial reported by Twyman-Saint Victor *et al.* evaluating the combination of radiation therapy (RT) with ipilimumab in patients with metastatic melanoma, patients underwent irradiation of a single lesion using a hypofractionated radiation regimen, with four cycles of ipilimumab. Subsequent evaluation of unirradiated sites revealed no complete responses

(CR) but an 18% rate of partial response (PR), with stable disease (SD) in 18% of the patients [3]. In a prospective trial evaluating clinical response in patients with metastatic melanoma treated with the combination of RT and ipilimumab, we reported a CR rate of 13.6% at a median follow up of 55 weeks (range 32–65 weeks weeks), a similar 13.6% rate of PR without progression at a median of 40 weeks (range 29–53 weeks) and SD in 22.7% of patients [4].

Herein, we report the durability of the clinical responses achieved in our earlier clinical trial by providing a long-term update on disease recurrence, overall survival and long-term toxicity after a median follow up of 233.5 weeks (range 78–272 weeks) in patients with initial complete or partial responses. This represents the longest follow up of metastatic melanoma patients treated in a prospective trial with a combination of RT and ipilimumab with resultant CRs and PRs.

Patients & methods

In the initial trial, 22 patients with progressive metastatic melanoma received four cycles of ipilimumab and palliative RT to one to two sites of disease within 5 days of starting ipilimumab. Follow-up imaging was performed 2–4 weeks after the fourth cycle of ipilimumab and every 3 months until disease progression. The Response Evaluation Criteria in Solid Tumors was used to evaluate response to the combination therapy. At the completion of the Phase I trial, patients who achieved CR or PR (Table 1) continued to have regular follow up with clinical and radiographic exams with the interval of follow-up visits at the discretion of the attending physician. Imaging modalities utilized to monitor response included computed tomography, PET and MRI.

Results

At the completion of the initial Phase I trial, out of the 22 patients in the cohort, 11 (50%) had clinical benefit, ranging from SD to partial or CRs, after a median follow up of 55 weeks (range 32–65 weeks). In the setting of progressive metastatic disease prior to the trial, even stabilization of disease was felt to be clinically beneficial, and these patients were without disease progression for a median of 39 weeks. Among the patients with CR or PR, clinical responses were ongoing after a median follow up of 233.5 weeks (range 78–272 weeks; Table 2).

Patients with CR

Among the initial cohort of 22 patients, three (13.6%) achieved a CR at a median follow-up of 55 weeks (range 32–65 weeks). These patients completed all four cycles of ipilimumab and RT, and all three experienced a grade 2 or 3 hypophysitis (Table 3).

Patient 15

A year after the completion of radiation, follow-up imaging showed new liver lesions, and subsequent biopsy revealed hepatocellular carcinoma, but no evidence of melanoma. The patient succumbed to hepatocellular carcinoma after 78 weeks of follow-up, corresponding to a CR duration of 27 weeks.

Patient 17

At the last follow-up, 269 weeks after treatment, the patient remains in CR (226+ weeks) with no evidence of disease on PET/CT (Figure 1A). In addition to the ongoing side effects from the treatment-related grade 3 hypophysitis, the patient had evidence of radiation necrosis due to radiosurgery for the brain metastasis that was administered prior to enrolling in the clinical trial.

Patient 20

After a follow-up of 221 weeks, on the latest PET/CT the patient remained in CR (193 + weeks) with ongoing side effects from a grade 2 hypophysitis (Figure 1B).

Patients with PR

Three (13.6%) patients initially had PRs without disease progression at a median of 40 weeks (range 29–53 weeks). Within this group, one developed a grade 2 hypophysitis (Table 3).

Patient 12

At the completion of the four cycles of ipilimumab and radiation, this patient continued ipilimumab monotherapy for a year due to disease progression and was subsequently switched to pembrolizumab monotherapy, receiving 28

Table 1. Characteristics of patients with complete or partial responses during the initial Phase I trial.

Patient no.	Clinical response	Sex	Age (years)	Metastatic sites[†]	Baseline LDH (U/l)	M-Stage (AJCC 8th)	Previous treatment	Site irradiated	RT dose, fractionation and technique	Side effects (grade)
15	CR	M	83	Lung (left upper lobe, lingula, right middle lobe), occipital calvarium	194	M1b (0)	Resection, RT	Left upper lobe	50 Gy/4 fx, SBRT	Hypophysitis (2) Diarrhea (1)
17	CR	F	68	Lung (left upper lobe, left lower lobe), brain	195	M1d (0)	Resection and SRS	Left upper lobe	24 Gy/3 fx, SBRT	Hypophysitis (3) Alopecia (1)[‡]
20	CR	M	66	Scalp lesions (right posterior occipital, inferior right, superior right), neck	164	M1a (0)	Resection, interferon, IL-12	Right posterior occipital scalp and right neck	40 Gy/10 fx, IMRT	Hypophysitis (2) Alopecia (1)[‡] Rash (2)
12	PR	F	69	Lung (left upper lobe), liver, left breast, left supraclavicular lymph nodes	332	M1c (0)	Resection	Left upper lobe	45 Gy/15 fx, IMRT	Rash (2)
18	PR	M	46	Pancreas, supraclavicular lymph nodes, chest wall nodules, left adrenal, gallbladder, paracolic gutter	224	M1c (0)	Resection, debulking	Pancreas	24 Gy/3 fx, SBRT	Hypophysitis (2)
19	PR	M	73	T1 paraspinous mass, paratracheal lymph nodes, lung (left upper lobe), left adrenal, right kidney	176	M1d (0)	Resection, SRS	T1 paraspinous mass	20 Gy/5 fx, 3D	Fatigue (1) Hypothyroidism (2)

[†]All patients had cutaneous melanoma subtype.
[‡]Radiation related.
CR: Complete response; Fx: Fraction; Gy: Gray; IMRT: Intensity modulated radiation therapy; PR: Partial response; RT: Radiation therapy; SBRT: Stereotactic body radiation therapy; SRS: Stereotactic radiosurgery.

Table 2. Summary of current disease status of patients with initial complete or partial response after a median follow up of 233.5 weeks (range 78–272 weeks).

Initial clinical response	Patient (n)	Sex	Follow-up (weeks)	Disease status at last follow-up	Current systemic therapy	Deceased or Alive	Duration of CR (weeks)
CR	15	M	78	NED for melanoma	NA	Deceased[†]	27
	17	F	269	Ongoing CR	None	Alive	226 +
	20	M	221	Ongoing CR	None	Alive	193 +
PR	12	F	272	Ongoing CR	None	Alive	63 +[#]
	18	M	206[‡]	Progression[§]	Unknown[‡]	Unknown[‡]	NA[‡]
	19	M	246	New sacral lesion concerning for melanoma vs prostate cancer[¶]	Pembrolizumab (28 cycles)	Alive	69 +[#]

[†]Death related to hepatocellular carcinoma.
[‡]Patient lost to follow up.
[§]Resection for site of disease progression but no systemic therapy due to stable disease at other sites.
[¶]Recent diagnosis of metastatic prostate cancer, with a new sacral lesion concerning for melanoma vs prostate cancer (the latter is likely due to rising prostate specific antigen [PSA] despite androgen suppression).
[#]Indicates the duration of the complete response following pembrolizumab monotherapy in patients 12 and 19, who initially had a PR at the completion of the trial. '+' indicates ongoing response at the time of preparation of this manuscript.
CR: Complete response; NA: Not applicable; NED: No evidence of disease (melanoma); PR: Partial response.

Table 3. Incidence of treatment-induced hypophysitis in the different clinical response groups.

Initial clinical response	Patients with clinical response (n)	Patients with hypophysitis (n)	Rate of hypophysitis (%)
Complete response	3	3	100
Partial response	3	1	33
Stable disease	5	0	0
Progressive disease	11	0	0

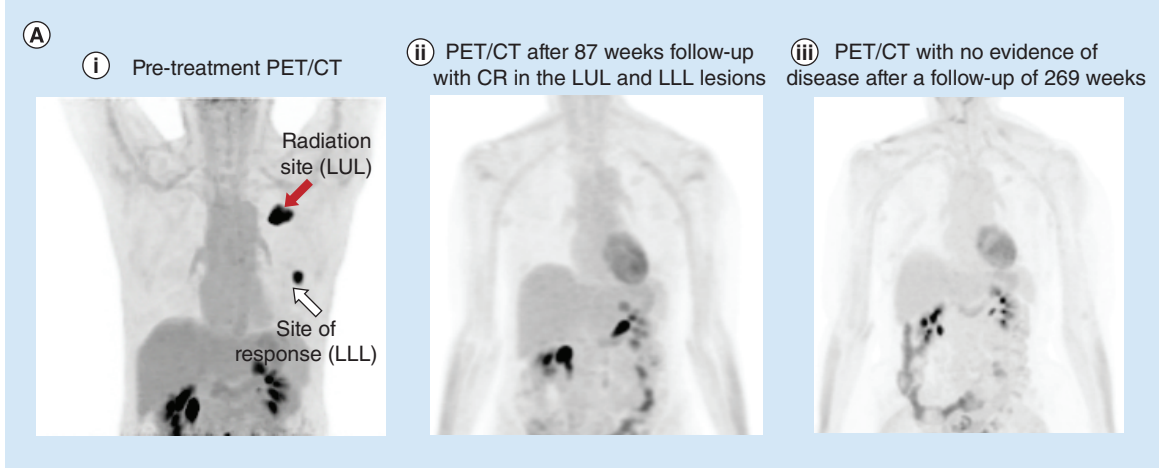

Figure 1. Radiographic evidence of ongoing complete response. (A) Patient 17: pretreatment PET/CT showing the two sites of disease. Posttreatment, CR achieved with regression in the left lower lung lobe lesion (white arrow) following palliative RT to the left upper lung lobe lesion (red arrow). No evidence of disease on most recent PET/CT after follow-up of 269 weeks. **(B)** Patient 20: CR achieved with regression of other scalp lesions following RT to the right occipital scalp and neck lesions with ongoing CR after a follow-up of 221 weeks.
CR: Complete response; RT: Radiation therapy.

cycles with a resultant CR. On the most recent follow-up imaging, the patient remains in CR after a follow-up of 272 weeks, representing the longest follow-up period in this study (Figure 2).

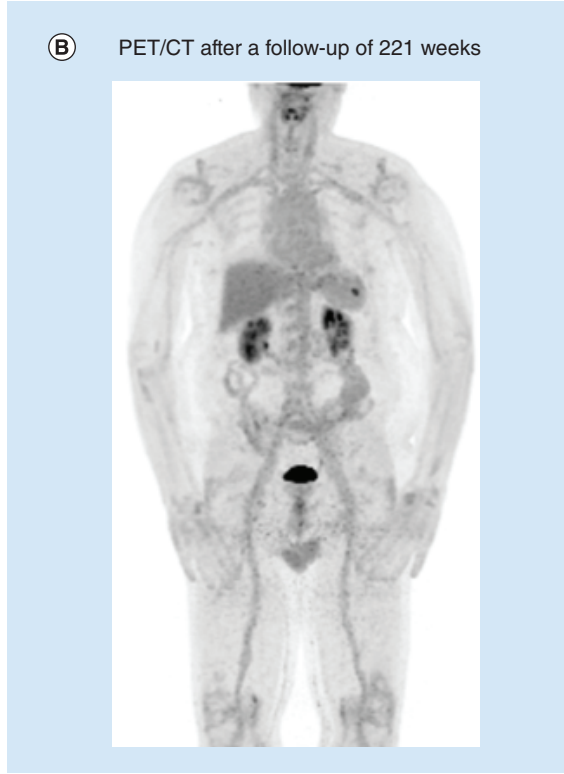

Figure 1. Radiographic evidence of ongoing complete response (cont.). (A) Patient 17: pretreatment PET/CT showing the two sites of disease. Posttreatment, CR achieved with regression in the left lower lung lobe lesion (white arrow) following palliative RT to the left upper lung lobe lesion (red arrow). No evidence of disease on most recent PET/CT after follow-up of 269 weeks. **(B)** Patient 20: CR achieved with regression of other scalp lesions following RT to the right occipital scalp and neck lesions with ongoing CR after a follow-up of 221 weeks.
CR: Complete response; RT: Radiation therapy.

Patient 18

This patient developed a small bowel obstruction due to disease progression after a follow-up period of 180 weeks, for which surgical resection was performed. Although other lesions were noted, due to their stability in size, the patient did not receive any adjuvant therapy and was lost to follow up after a follow-up of 206 weeks.

Patient 19

Following disease progression at the completion of the clinical trial, this patient was started on dabrafenib and trametinib, with continued disease progression. However, CR was achieved after initiation of pembrolizumab monotherapy, which is ongoing with 28 cycles administered thus far. The patient was diagnosed with a biopsy proven metastatic prostate cancer 3 years after the completion of the trial and is currently on hormonal therapy with leuprolide acetate and enzalutamide. On the most recent PET/CT after a follow-up of 236 weeks, a new left sacral lesion was noted, concerning for metastatic melanoma or prostate cancer. Although biopsy was not performed, metastatic prostate cancer was deemed most likely, in the setting of a rising prostate-specific antigen (PSA).

Discussion

To date, numerous case reports of clinical responses have been described in melanoma patients treated with the combination of radiation and immunotherapy. We initially reported a CR in a 57-year-old man with metastatic melanoma to the liver treated with ipilimumab and palliative radiation (54 Gy in 3 fractions), after a 12 month follow-up [5]. The first prospective clinical trial evaluating the safety and efficacy of the combination of palliative radiation and ipilimumab in metastatic melanoma patients reported some clinical benefit, with 18% PRs and 18% of patients with SD. No CR, no dose limiting toxicity and no grade 4 treatment-related toxicities were reported, but there were various grade 3 toxicities including anemia and colitis, though no hypophysitis [3]. In contrast, in our study, three patients achieved a CR, all of whom also experienced a grade 2–3 hypophysitis, indicative of vigorous immune system activation, however, no dose-limiting toxicity was noted. Indeed, similar immune-related hypophysitis, requiring chronic steroid use was noted in the aforementioned patient with metastatic melanoma to the liver who currently remains in CR, more than 7 years after completion of the combination therapy [5,6]. Interestingly, we noted that all three patients with CR had at least a grade 2 hypophysitis, compared with one out of three patients in the PR group and none in the stable and progressive disease cohorts (Table 3). Since the

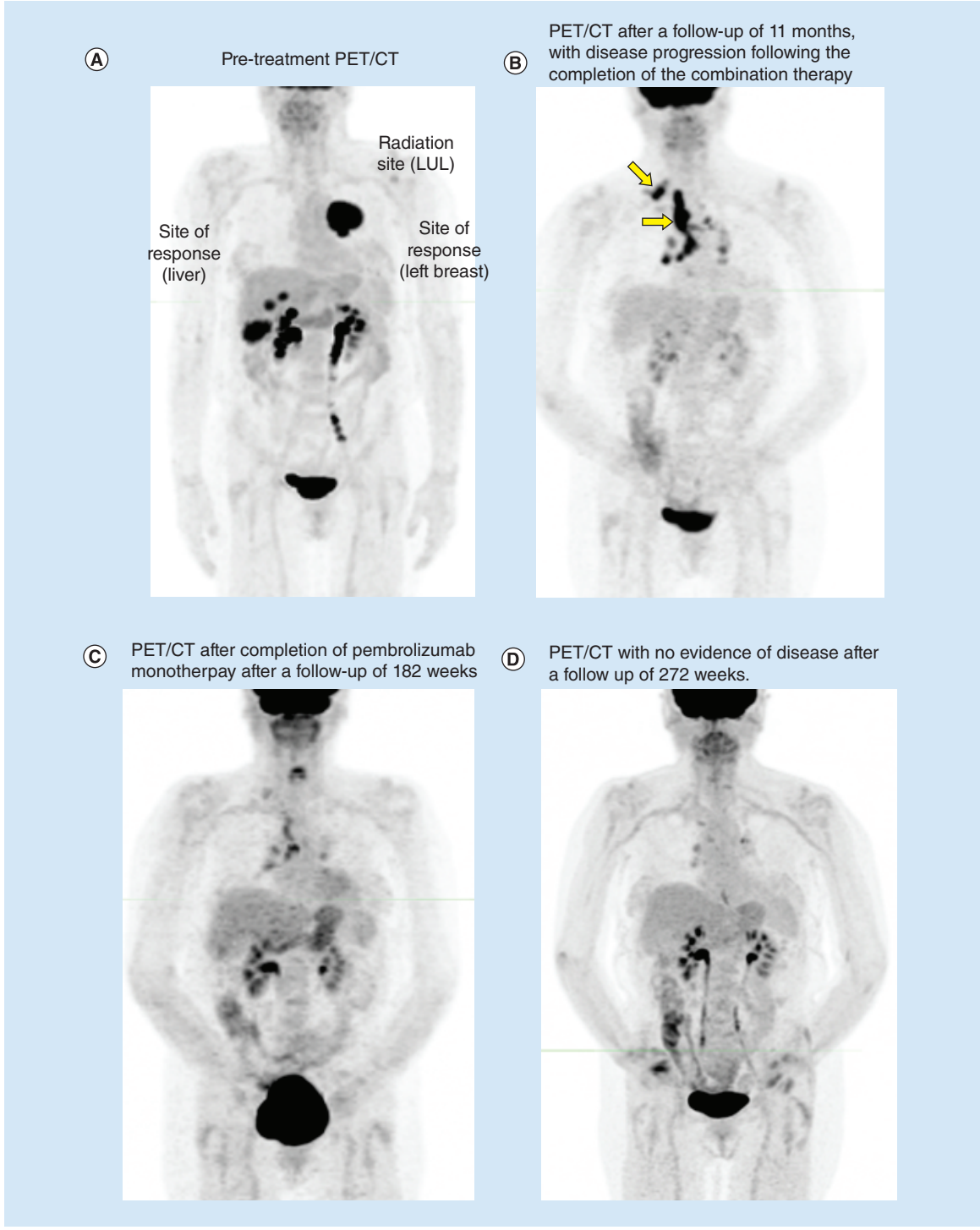

Figure 2. PET/CT demonstrating a complete response after pembrolizumab monotherapy following a partial response after the combination of radiation and ipilimumab after 272 months follow-up (patient 12). Sites of disease prior to the combination of RT and ipilimumab. Site of radiation in the left upper lung lobe. Sites of clinical response in the left breast and liver. Disease response in the liver and left breast, disease progression after 11 months, with new mediastinal and left supraclavicular lesions. Significant disease improvement after the completion of pembrolizumab monotherapy (28 cycles) after disease progression. Ongoing CR without evidence of disease on PET/computed tomography after the completion of pembrolizumab monotherapy following disease progression after RT and ipilimumab, and no current systemic therapy after a follow-up of 272 weeks.
CR: Complete response; RT: Radiation therapy.

completion of the prospective clinical trials described above, there have been numerous Phase I prospective studies evaluating the combination of ipilimumab and anti-PD-1/PD-L1 with RT. Primarily with stereotactic ablative radiotherapy in metastatic melanoma patients. In addition to exploring the optimal dose and fractionation, these trials also evaluated the timing of radiation and initiation of ipilimumab [7–10]. Tang *et al.* reported a 23% rate of clinical benefit including PR and SD but no CR. Furthermore, one out of 35 patients experienced a grade 3 hypophysitis [10]. A similar rate of clinical benefit (23%) as defined by PR and SD was also reported by Sundahl *et al.* However, no treatment-induced hypophysitis was observed [7]. Although durable clinical responses have been correlated with the severity of adverse events in metastatic melanoma patients treated with ipilimumab, and in stage III melanoma patients treated with other checkpoint inhibitors such as pembrolizumab, to our knowledge, no such correlation has been reported between a durable clinical response and adverse events in patients treated with the combination therapy of RT + ipilimumab [11,12]. Immune checkpoint inhibitors can affect all organs and lead to immune-related toxicities, but with anti-CTLA-4 agents such as ipilimumab, hypophysitis appears to be one of the more common toxicities with an incidence rate as high as 17% [13,14]. High index of clinical suspicion in patients receiving checkpoint inhibitors and presenting with severe fatigue, muscle weakness and headache should prompt laboratory tests evaluating the adrenal, thyroid and gonadal axes [14,15]. During our initial study, any of the aforementioned symptoms resulted in laboratory tests including adrenocorticotropic hormone, cortisol, thyroid stimulating hormone, thyroid hormone, luteinizing- and follicle-stimulating hormones. In addition to being symptomatic, patients diagnosed with hypophysitis in our cohort had low adrenocorticotropic hormone and cortisol, prompting steroid replacement therapy. Although MRI is the preferred imaging modality for the diagnosis of hypophysitis, a normal MRI does not exclude hypophysitis in a symptomatic patient [15]. As such, MRI was not routinely done in our cohort for the diagnosis of hypophysitis.

Herein, we report the durability of clinical response in patients who achieved a CR after an initial follow-up period of 55 weeks. After a median follow-up of 233.5 weeks (range 78–272 weeks), two out of three of these CRs were ongoing with no evidence of disease. Although the rate of CR in published trials is low, responses can be very durable as demonstrated in our study cohort. To our knowledge, this nearly 5-year disease-free survival represents one of the most durable reports of clinical response in metastatic melanoma patients treated with the combination of ipilimumab and radiation on a prospective clinical trial. Furthermore, among the three patients who initially achieved a PR without disease progression at a median of 40 weeks (range 29–53 weeks), two subsequently developed a CR following pembrolizumab monotherapy. The initial response and its durability appear to correlate with treatment-related hypophysitis. The small size of our cohort is a significant limitation of this study, thus a secondary analysis of previously reported prospective trials evaluating the use of immunotherapy in melanoma would be useful to validate the observed correlation between hypophysitis and durability of response we have noted.

Conclusion

This update on our previously published prospective clinical trial on the combination of palliative RT with ipilimumab in patients with metastatic melanoma reveals a durable response in three out of 22 patients who achieved a CR. These patients remained in remission with no evidence of disease recurrence after a median follow-up of 233.5 weeks (range 78–272 weeks). These CRs appear to correlate with a grade 2–3 hypophysitis, indicative of a robust immune response. In addition, two out of three patients achieving PR eventually developed CR after monotherapy with pembrolizumab. These results demonstrate that a subset of patients treated with ipilimumab and RT have durable responses that can last years. It will be interesting to compare these results with those from ongoing trials with anti-PD-1 monotherapy, or anti-PD-1 and anti-CTLA-4, combined with RT in terms of response rate, long-term efficacy and immune-related adverse events.

Future perspective

Undeniably, immunotherapy has revolutionized cancer treatment and extensive research has been conducted to harness its benefit in combination with other therapies especially RT. Due to the synergistic effect existing between immunotherapy and radiation, we expect a further increase in clinical trials and studies aiming at elucidating the mechanisms of the abscopal response. We also anticipate the development of predictive biomarkers which will be crucial in selecting patients who are likely to benefit from such combination therapy, and to identify individuals who may develop severe or life-threatening toxicities.

Author contributions

SJ Knox was the PI of the original study, and was responsible for the study design, study conduct, data collection and analysis. QH Sodji, SM Hiniker and SJ Knox were responsible for the study design, data collection, analysis and writing of the manuscript. PM Gutkin was involved in data collection. SM Swetter and SA Reddy were involved in data collection, patient's follow-up and writing of the manuscript. All authors reviewed the final version of the manuscript.

Financial & competing interests disclosure

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

This study was reviewed and approved by the Stanford University Institutional Review Board and the Stanford Cancer Institute Scientific Review Committee. Written consent was obtained from all patients.

Data sharing statement

Data and materials are available by request to corresponding authors.

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