

ORIGINAL RESEARCH

Activity and safety of radiotherapy with anti-PD-1 drug therapy in patients with metastatic melanoma

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ABSTRACT

The anti-PD-1 antibodies nivolumab and pembrolizumab are active in metastatic melanoma; however, there is limited data on combining anti-PD-1 antibody and radiotherapy (RT). We sought to review clinical outcomes of patients receiving RT and anti-PD-1 therapy. All patients receiving anti-PD-1 antibody and RT for metastatic melanoma were identified. RT and systemic treatment, clinical outcome, and toxicity data were collected. Fifty-three patients were included; 35 patients received extracranial RT and/or intracranial stereotactic radiosurgery (SRS) and 21 received whole brain radiotherapy (WBRT) (three of whom also received SRS/extracranial RT). Patients treated with extracranial RT or SRS received treatment either sequentially (RT then anti-PD-1, $n = 11$), concurrently ($n = 16$), or concurrent “salvage” treatment to lesions progressing on anti-PD-1 therapy ($n = 15$). There was no excessive anti-PD-1 or RT toxicity observed in patients receiving extracranial RT. Of six patients receiving SRS, one patient developed grade 3 radiation necrosis. In 21 patients receiving WBRT, one patient developed Stevens–Johnson syndrome, one patient developed acute neurocognitive decline, and one patient developed significant cerebral edema in the setting of disease. Response in irradiated extracranial/intracranial SRS lesions was 44% for sequential treatment and 64% for concurrent treatment ($p=0.448$). Likewise there was no significant difference between sequential or concurrent treatment in lesional response of non-irradiated lesions. For progressing lesions subsequently irradiated, response rate was 45%. RT and anti-PD-1 antibodies can be safely combined, with no detectable excess toxicity in extracranial sites. WBRT and anti-PD-1 therapy is well tolerated, although there are rare toxicities and the role of either anti-PD-1 or WBRT in the etiology of these is uncertain.

Abbreviations: CR, complete response; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; LDH, lactate dehydrogenase; mAb, monoclonal antibody; PD-1, programmed death receptor 1; PR, partial response; RT, radiotherapy; SJS, Stevens–Johnson syndrome; SRS, stereotactic radiosurgery; WBRT, whole brain radiotherapy

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Introduction

The anti-PD-1 antibodies nivolumab and pembrolizumab are active across a spectrum of malignancies including metastatic melanoma, non-small cell lung cancer, and renal cell carcinoma.^{1–4} In melanoma, overall survival (OS) of patients receiving anti-PD-1 antibody is significantly improved as compared to chemotherapy and ipilimumab.^{5,6} In the setting of advanced metastatic disease, radiotherapy (RT) is routinely used for symptomatic disease, or sites of threatened local morbidity. RT has been shown to modulate the immune response to tumors and there is much interest in harnessing the immunomodulatory effect of RT in order to augment the anticancer efficacy of immunotherapy.^{7,8}

RT may rarely result in tumor regression at sites distant to the irradiated field, an immune-mediated response termed the “abscopal effect.”⁹ The frequency of reported cases of the abscopal effect is rare with RT alone; however, preclinical data indicate that this response can be augmented when RT is

combined with an anti-CTLA4 antibody¹⁰ or an anti-PD-1 antibody.¹¹ This is paralleled by an increase in clinical reports of the abscopal effect in patients receiving RT and the anti-CTLA4 antibody ipilimumab,^{12,13} although the incidence of this effect is unknown. The triple combination regimen of RT, anti-CTLA4 antibody, and anti-PD-1 mAb has been shown to be synergistic in a preclinical study, and combining immunotherapy with RT therefore represents an attractive strategy for metastatic disease.¹⁴ However, there are concerns regarding potential toxicity given the complexities of interaction between RT and immunotherapy, with an outstanding need for safety data on combination treatment. This is of particular relevance in melanoma where the incidence of brain metastases at diagnosis is approximately 20%, and treatment often involves stereotactic radiosurgery (SRS) or whole brain radiotherapy (WBRT). While there is no safety data for WBRT in combination with anti-PD-1 antibody, there is only one case report of combination SRS and anti-PD-1 antibody.¹⁵ We sought to

evaluate both toxicity and prevalence of abscopal response in a cohort of patients with metastatic melanoma treated with anti-PD-1 antibody and palliative RT, with particular attention to safety in a cohort of patients receiving WBRT.

Results

Patient characteristics and treatment received

Fifty-three patients were included: 35 patients received extracranial RT and/or intracranial SRS and 21 received WBRT (three of whom also received SRS or extracranial RT). Of the 35 patients who received extracranial RT and/or intracranial SRS, 26 (74%) patients had M1c disease, 21 (60%) had a raised LDH, 6 (17%) were ECOG performance status 2 at baseline, and 13 (37%) had a history of brain metastases, reflecting a poor prognosis cohort (Table 1). Only 1 (3%) patient received anti-PD1 as first line systemic therapy, and 32 (91%) patients received prior ipilimumab with a median time from ipilimumab to anti-PD-1 antibody of 29 d (range 1–238 d) (Table 1). Nine patients

(26%) had an early switch from ipilimumab to anti-PD-1 antibody (prior to completion of four cycles of ipilimumab or prior to disease progression) due to the clinician's concerns regarding the patient's disease burden, tumor kinetics, and symptoms, based upon the concept that combining immunotherapies may have superior efficacy.¹⁶ These patients received a median of one infusion of ipilimumab (range 1–3) with a median interval of 21 d between ipilimumab and anti-PD-1.

Twenty-seven (77%) patients received pembrolizumab 2 mg/kg every three weeks, while seven (20%) patients received nivolumab 3 mg/kg every two weeks. One patient (3%) received pembrolizumab on a clinical trial and was subsequently switched to nivolumab after progressing on trial due to ongoing clinical benefit. At the time of assessment, median duration of anti-PD-1 antibody treatment was 6 mo. Of patients receiving extracranial RT and/or intracranial SRS, 11 (31%) received sequential RT followed by anti-PD-1 antibody with a median time of 11 d between commencing RT and anti-PD-1 antibody (range 1–21 d) and 16 (46%) patients received concurrent treatment with a median time of 7 d between commencing anti-PD-1 and RT (range –9 to 34 d). Within these cohorts one patient that was treated sequentially and six patients that were treated concurrently subsequently received further RT to progressive disease. A total of 15 (43%) patients received salvage RT to progressive disease (clinical progression in 1 patient, radiological confirmation of RECIST progression in 14 patients) a median of 121 d after starting anti-PD-1 antibody (range 49 to >800).

A total of 44 courses of palliative RT were evaluated; 24 (69%) patients received one course, 7 (20%) two courses, and 4 (11%) three or more courses. Standard palliative doses of RT were given to metastases in cutaneous or soft tissue (32%), bone (32%), SRS to brain metastases (14%), lymph node (18%), and leptomeningeal (2%) sites (Table S1). Doses of 8–30 Gy in 1–10 fractions were delivered using a conformal technique. One patient received 48 Gy in 20 fractions to a nodal metastasis.

Twenty-one patients received WBRT and anti-PD-1, including three patients who received extracranial RT and/or intracranial SRS as well as WBRT. Ten patients (48%) had received prior ipilimumab, a median of 18.5 d prior to commencing anti-PD-1 antibody (Table 2). The median WBRT dose received was 30 Gy in 10 fractions. Six patients received simultaneous integrated boost (45 Gy in 10 fractions) to larger lesions. The median time to start of WBRT was 7 d after commencement of anti-PD-1 therapy (Table 2).

Safety of Extracranial RT and Intracranial SRS

Adverse events were classified as drug-related or RT-related on the basis of the known side effect profiles and mechanisms of action of each treatment. Within the cohort of 35 patients who received extracranial RT or SRS, four patients (11%) experienced a grade 3 or 4 related adverse event due to anti-PD-1 antibody, consistent with the published trial data.⁵ Three of these patients developed a grade 3 rash after receiving anti-PD-1 antibody closely preceded by ipilimumab. All other toxicities were as expected for anti-PD-1 antibody therapy (Table 3). Three patients (9%) developed grade 1 transaminase derangement that did not require steroid intervention, consistent with the anti-PD-1 antibody trial data.¹⁷

Table 1. Baseline characteristics at start of anti-PD-1 therapy.

Baseline characteristic	N = 35
Male, n (%)	24 (69%)
Age, median (range)	59 (22 to 83)
M stage, n (%)	
Stage IIIc	1 (3%)
M1a	4 (11%)
M1b	4 (11%)
M1c	26 (74%)
History of brain metastases, n (%)	13 (37%)
LDH > ULN, n (%)	21 (60%)
BRAF status, n (%)	
Wild-type	26 (74%)
V600 mutation	8 (23%)
Other	1 (3%)
ECOG at start of PD-1, n (%)	
0–1	29 (83%)
2	6 (17%)
Number of previous therapies, n(%)	
0	1 (3%)
1	21 (60%)
2 or more	13 (37%)
Previous therapy type, n (%)	
Ipilimumab	32 (91%)
Dabrafenib and trametinib	8 (23%)
Dabrafenib monotherapy	2 (6%)
Vemurafenib	3 (9%)
Trametinib monotherapy	2 (6%)
Chemotherapy	4 (11%)
Other	4 (11%)
Median time from ipilimumab to PD1, days (range)	29 (1–238)
Ipilimumab cycles, n (%)	
4 ^a	13 (37%)
3	8 (23%)
2	2 (6%)
1	8 (23%)
Switched from ipilimumab to PD-1 due to	
RECIST progression on scan	14 (40%)
Clinical progression	5 (14%)
Toxicity	1 (3%)
Planned early switch to PD-1	9 (26%)
Previous RT (prior to inclusion criteria), n (%)	17 (49%)
Site of prior RT, n (%)	
Intracranial	8
SRS	5
WBRT	5
Extracranial	12

^aOne patient received a further 2 cycles of ipilimumab (i.e., total six cycles).

Table 2. Baseline characteristics and treatment summary of WBRT cohort at the start of anti-PD-1 therapy.

Characteristic	
Total number of patients	21
Age, median (range)	63 (22 to 81)
ECOG at start of anti-PD-1	
0–1	14 (67%)
2 or more	7 (33%)
Median number brain metastases	7
Leptomeningeal disease, <i>n</i> (%)	2 (10%)
Prior ipilimumab (%)	10 (48%)
Time between prior ipilimumab and anti-PD-1 antibody, median days (range)	18.5 (1 to 545)
Time between anti-PD-1 antibody and WBRT, median days (range)	7 (–28 to 106)
Sequential	4 (19%)
Concurrent	11 (52%)
For progression on anti-PD-1 antibody	6 (29%)
Median dose (range)	
Gy	30 (20 to 30), integrated boost to 45 Gy
Fractions	10 (5 to 10)

Abbreviations: Gy, Gray; WBRT, whole brain radiotherapy.

Extracranial RT was well tolerated, although a direct comparison of adverse events with the published data was not possible due to the heterogeneity of RT sites and doses within this cohort. Two patients experienced grade 3 radiation dermatitis (one patient 36 Gy in six fractions to the scalp, one patient 25 Gy in five fractions to a subcutaneous lesion on the left lateral flank, see Fig. S2). Of the six patients who received SRS to brain metastases (total 17 lesions treated), one patient developed a grade 3 symptomatic radiation necrosis 3 mo after receiving sequential SRS (single fraction of 20 Gy) to a 20 mm brain metastasis. This patient also received WBRT (30 Gy in 10 fractions) 12 mo prior

Table 3. Treatment-related adverse events* in patients receiving extracranial RT for SRS to intracranial lesions.

AEs recorded during treatment	Any grade, <i>n</i> (%)	Grade 3–4, <i>n</i> (%)
AEs due to anti-PD-1 antibody (<i>n</i> = 35)		
Rash	8 (23)	3 (9)
Diarrhea	6 (17)	1 (3)
Endocrinopathy	6 (17)	
Pruritis	5 (14)	
Raised AST and/or ALT	3 (9)	
Arthralgia	2 (6)	
Xerostomia	2 (6)	
Vomiting	2 (6)	
Nausea	1 (3)	
Fever	1 (3)	
AEs during RT treatment or affecting RT field		
<i>Extracranial RT (n = 31)</i>		
Radiation dermatitis (all lesions, <i>n</i> = 65)	20 (57)	2 (6)
Mucositis (head and neck lesions, <i>n</i> = 12)	4 (11)	
Nausea	3 (9)	
Vitiligo	1 (3)	
<i>SRS (n = 6)</i>		
Alopecia (any grade)	2 (6)	
Radiation dermatitis	2 (6)	
Cerebral radiation necrosis (SRS lesions, <i>n</i> D17)	1 (3)	1 (3)

*All recorded adverse events (AEs) during treatment due to anti-PD-1 antibody are shown. All recorded adverse events occurring due to radiotherapy treatment or affecting the radiotherapy field are shown. Two patients had both SRS and extracranial RT.

Abbreviations: SRS, stereotactic radiosurgery.

to SRS. The patient was managed with surgical resection, corticosteroids, and a single dose of bevacizumab and was subsequently able to resume treatment with anti-PD-1 antibody.¹⁸

Safety of WBRT

Rates of low-grade toxicities following WBRT including headaches, nausea, and radiation dermatitis were as expected when compared the prior published data^{19–21} (Table 4). Clinically significant cognitive changes were observed in two patients (10%), neither of whom had hippocampal sparing due to the extent of disease. In one of these patients, there was a grade 3 acute neurocognitive decline characterized by aphasia and gait disturbance, occurring 2 mo after completion of WBRT while receiving concurrent ipilimumab and anti-PD-1 antibody. Causes of acute delirium and intracranial progression were excluded. After discussion with the family, there was an agreement to palliate. One patient on single agent anti-PD-1 therapy for 3 mo (ipilimumab >2 y prior) developed Stevens–Johnson Syndrome (SJS) on a background of concomitant phenytoin therapy 4 d after completion of WBRT for intracranial progression. One patient developed significant cerebral edema associated with rapid disease progression after receiving ipilimumab closely followed by anti-PD-1 antibody and concurrent WBRT (Fig. S3). This patient had rapidly progressive disease with miliary brain metastases. The patient developed symptoms of raised intracranial pressure within the first week of treatment, suggesting disease progression as the most likely cause for symptoms. However, the concurrent immune therapy and WBRT could not be excluded as contributing to the edema seen on imaging.

Efficacy in the sequential and concurrent cohorts

There was no difference in OS of patients treated with concurrent or sequential RT to extracranial lesions and/or intracranial

Table 4. Treatment related adverse events* during WBRT.

AEs recorded during treatment (<i>n</i> = 21)	Any grade, <i>n</i> (%)	Grade 3–4 ^a , <i>n</i> (%)
<i>AEs attributed to WBRT</i>		
Radiation dermatitis	15 (71%)	
Alopecia (any grade)	18 (86%)	
Headache	7 (33%)	
Nausea (during WBRT)	3 (14%)	1 (5%)
Vomiting (during WBRT)	2 (10%)	
Cognitive changes	2 (10%)	1 (5%)
<i>AEs attributed to WBRT and/or anti-PD1, possibly synergistic</i>		
Stevens–Johnson syndrome	1 (5%)	1 (5%)
Vitiligo in WBRT field only	1 (5%)	
<i>AEs attributed to anti-PD-1 antibody</i>		
Diarrhea	3 (14%)	
Pruritus	4 (19%)	
Rash	5 (24%)	2 (10%)
Hepatotoxicity	2 (10%)	
Endocrinopathy	3 (14%)	
Arthralgia	1 (5%)	

*All recorded adverse events occurring due to radiotherapy treatment or affecting the radiotherapy field are shown. All patients given WBRT and anti-PD-1 antibody prior to October 31, 2015 were included in assessment of toxicity.

Abbreviations: SRS, stereotactic radiosurgery.

^aThere was one grade 5 event, the investigator assessed as possibly treatment related.

Table 5. Lesion-specific response in sequential and concurrent cohorts, excluding patients who received RT to metastases progressing on anti-PD-1.

	Best response (%)				Lesion response rate (%)
	PD	SD	PR	CR	
Non-irradiated assessable lesion ^a					
Sequential (<i>n</i> = 21)	29	19	28	23	52
Concurrent (<i>n</i> = 51)	18	35	25	21	46
Irradiated assessable lesions ^b					
Sequential (<i>n</i> = 16)	19	38	38	6	44
Concurrent (<i>n</i> = 14)	21	14	50	14	64

^aUp to five non-irradiated RECIST target lesions were assessed for individual lesion response after treatment with anti-PD-1 antibody and RT.

^bAll irradiated lesions were assessed for best response post-radiotherapy while on treatment with anti-PD-1 antibody.

SRS (median 6.4 vs. 8.6 mo, respectively, $p = 0.7672$) (Fig. S1). Similarly, the RECIST overall response rates were similar in the concurrent and sequential cohorts (5/16 [31%] vs. 4/11 [36%] respectively, $p = 1$). The fractionation regimen and the presence of multiple sites of irradiation were not predictors of response. Time to maximum response was almost identical in patients treated concurrently (76.5 d) or sequentially (77.5 d).

The response rate (CR and PR) of irradiated lesions was 44% for the 16 lesions treated sequentially and 64% ($p = 0.448$) for 14 lesions treated concurrently (Table 5). Of note, the sequential cohort included a greater proportion of irradiated brain metastases (14/26 [54%] vs. 5/30 [17%]), and the concurrent cohort included a larger proportion of bone and soft tissue lesions (19/30 [63%] vs. 9/26 [35%]) than the sequential cohort. The response rate in non-irradiated target lesions was 52% and 46% in sequential and concurrent cohorts, respectively, and was not significantly different between the groups ($p = 0.878$). There was one confirmed case of pseudoprogression within this group of patients. This was the patient who underwent resection of an enlarging brain metastasis which had previously been treated with SRS, and histopathology revealed radiation necrosis.

Efficacy in the salvage radiotherapy cohort

In patients who received salvage extracranial RT and/or intracranial SRS for progressive disease ($n = 15$ patients) on anti-PD-1 therapy, lesion response to RT and anti-PD-1 antibody was assessed using the scan immediately prior to RT as baseline, and best response was assessed post-RT during ongoing anti-PD-1 antibody after the initial progression. Nine irradiated lesions (31% of lesions treated) were not evaluable as four patients died prior to follow-up imaging post-RT and three lesions could not be accurately assessed on CT imaging.

For the 30 progressing lesions that were irradiated (excluding nine lesions not evaluable), the lesional response rate was 45%. The irradiated site, dose, and fractionation regimen were not predictors of response when assessed using logistic regression. The 25 non-irradiated lesions (excluding eight lesions not evaluable due to patient death) progressing on anti-PD-1 antibody had a subsequent response rate of 15% post-RT; all of these “abscopal” responding lesions were observed in a single patient whose scan revealed progression at day 50 following commencement of anti-PD-1 in neck nodes (subsequently

irradiated) and subcutaneous sites (not-irradiated) (Fig. S4); thus, a later response to anti-PD-1 could not be ruled out. After an initial response to treatment, this patient subsequently progressed after 10 mo of anti-PD-1 therapy. Of note, the patient had completed four cycles of ipilimumab 2 mo prior to commencing anti-PD-1.

Discussion

This is the first case series in any cancer to assess toxicity and response in patients receiving combined anti-PD-1 antibody and extracranial RT or WBRT. The only prior published study assessed clinical outcomes in 26 patients treated with anti-PD-1 therapy and SRS to melanoma brain metastases, and found that combination therapy was well tolerated.¹⁵ Our study demonstrates that RT and anti-PD-1 antibodies can be safely combined, with no detectable excess toxicity in extracranial sites. WBRT and anti-PD-1 therapy are also well tolerated, although there are rare toxicities and the role of either anti-PD-1 or WBRT in the etiology of these is uncertain. The highest lesion-specific response was seen in irradiated lesions in patients receiving concurrent anti-PD-1 therapy with an overall lesion response rate of 64% and CR rate of 14%. This was higher than the expected response rate, although a definite abscopal effect was not observed in this study.

One of the six patients receiving SRS to brain metastases (17%) developed symptomatic radiation necrosis, consistent with the reported incidence of up to 50% determined radiologically in patients treated with SRS alone depending on risk factors including dose, fractionation, and concurrent chemotherapy.²² Symptomatic radionecrosis is reported to occur in approximately 10% of patients.^{23,24} Although several case reports have suggested a possible increased risk of radiation necrosis in patients treated with SRS and ipilimumab,²⁵⁻²⁷ there has been no definitive data to support this.²⁸ There was also no increase in incidence of radiation necrosis in a recent case report of 26 patients treated with SRS and anti-PD-1 antibody.¹⁵ This apparent increase in incidence of radiation necrosis in this study could just be due to the longer survival associated with anti-PD-1 therapy.^{5,29} Within the cohort of patients treated with WBRT together with anti-PD-1, cognitive changes were observed in 2 of the 21 patients. Neither of these patients had hippocampal sparing due to the extent of brain disease, and neurocognitive decline is a recognized toxicity observed in 30% of patients receiving WBRT.³⁰ One patient developed SJS one week after completion of WBRT (on anti-PD-1 for 3 mo prior) on a background of concomitant phenytoin therapy. As both RT and anti-convulsant therapy are known risk factors for SJS,³¹ the role of anti-PD-1 in this case is not clear.

RECIST response rates in patients receiving up-front sequential or concurrent RT and anti-PD-1 antibody were consistent with published trial data for anti-PD-1 antibody,⁵ making it difficult to assess for abscopal effects. Evaluation of the abscopal effect in a subset of patients progressing on anti-PD-1 antibody who received RT for disease progression revealed one patient who demonstrated regression of both non-irradiated progressing and new lesions, although the patient had only received seven weeks of anti-PD1 therapy at the time of

progression and commencement of RT. This may indicate an abscopal effect; however, it has also been established that new and progression lesions can occur in 3–4% of patients who subsequently respond to anti-PD-1 antibody without any additional anticancer treatments.⁶

Irradiation dose and fractionation were analyzed but not found to be significant predictors of response. Similarly, there was no significant difference in RECIST response and lesional responses in patients receiving irradiation and anti-PD-1 antibody sequentially or concurrently, although the response was numerically higher in concurrently irradiated lesions. The question of sequential versus concurrent dosing requires further study, as pre-clinical data suggest that the timing of RT in relation to immunotherapy may be important. In mouse colon and breast carcinoma models, sequential RT then anti-CTLA-4 blockade was less effective than concurrent,³² and sequential RT with anti-PD-L1 blockade was also less effective than concurrent scheduling in a mouse colon carcinoma model.³³ However, a retrospective analysis of patients receiving SRS and ipilimumab for melanoma brain metastases found no significant difference in OS according to schedule.³⁴

Optimal radiation dose and fractionation regimen also remains unknown. Data from breast and colorectal mouse models have indicated that a fractionated regimen may be superior to single dose,³² and may overcome RT-induced adaptive resistance by upregulation of PD-L1.³³ Fractionated radiation alone was shown to maintain low regulatory T cells (Tregs), while single high dose RT resulted in an increase in Treg representation.³⁵ An abscopal response was observed following fractionated high dose palliative RT to a paraspinal mass in a patient progressing on ipilimumab.¹² Similarly, fractionated regimens were associated with improved lesion response as compared with hypofractionated treatment in a series of patients receiving concurrent anti-CTLA4 antibody.³⁶

This case series provides valuable insight into safety and efficacy of sequential, combination, and salvage treatment with RT and anti-PD-1 antibodies. It appears unlikely that RT commonly invokes an abscopal response in melanoma

resistant to anti-PD-1 antibodies. The study is limited by a relatively small and heterogeneous population of patients, and rare toxicities may therefore not be detected. Formal prospective trials are needed and are underway in melanoma (NCT02374242, NCT02562625, NCT02407171), and other cancers (NCT02402920, NCT02684253, NCT02444741), which should evaluate this issue further. Furthermore, study regarding long-term effects of radiation and anti-PD-1 antibody, particularly radionecrosis, is an important next step.

Methods

Patients, treatment, and safety assessments

A retrospective analysis of all metastatic melanoma patients receiving palliative RT and anti-PD-1 antibody therapy, at Melanoma Institute Australia and the Crown Princess Mary Cancer Centre Westmead, was performed. The study was undertaken with Human Ethics Review Committee approval and patient's informed consent. All patients treated with extracranial RT or SRS to an intracranial lesion between November 2013 and March 2015 were assessed for both response to treatment and safety. These patients either received sequential RT prior to systemic therapy or concurrent external-beam or stereotactic RT with either pembrolizumab (2 mg/kg three weekly) or nivolumab (3mg/kg two weekly). In addition, all patients treated with WBRT and anti-PD-1 antibody between November 2013 and October 2015 were analyzed for safety alone, to provide a more extensive safety assessment in this cohort of patients.

RT and anti-PD-1 were delivered in three different schedules (Fig. 1): (a) sequentially, whereby RT was commenced and completed within 28 d prior to starting anti-PD-1 antibody; (b) concurrently, whereby RT was given early-during anti-PD-1 therapy to symptomatic lesions or lesions clinicians were concerned could become symptomatic if unresponsive to anti-PD-1 antibody; or (c) “salvage” RT for clinical or radiological progression noted more than six weeks after starting anti-PD-1 antibody (i.e., to resistant lesions). RT was delivered using a

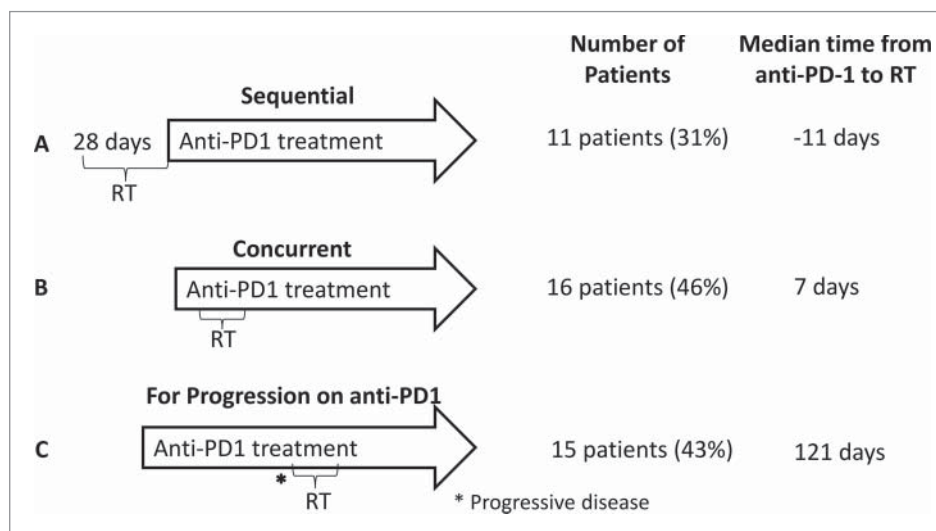


Figure 1. Summary of treatment schedules received by patients receiving extracranial RT or SRS. Patients received radiotherapy either (A) sequentially (commenced and completed within 28 d prior to starting anti-PD-1 antibody), (B) concurrently with anti-PD-1 antibody, or (C) for clinical or radiological progression noted more than six weeks after starting anti-PD-1 antibody.

conformal technique with photon energy in a standard palliative fashion. Hippocampal sparing WBRT was used in all cases except where disease burden prevented this. Safety was assessed through analysis of recorded adverse events during treatment and incidence compared with trial data for single agent anti-PD-1 antibody or RT.

Response assessments

Response assessment was performed in patients receiving extracranial RT or SRS to an intracranial lesion, and anti-PD-1 antibody. Overall response was assessed using RECIST 1.1.³⁷ A second response assessment, the “lesional response assessment,” involved identification of up to five target lesions, excluding the irradiated lesion, at baseline (prior to systemic therapy or RT), and followed throughout treatment. The irradiated lesions were followed separately. For both overall and lesional response assessments, response was classified as complete response (CR, disappearance or < 10 mm short axis for lymph nodes), partial response (PR, $\geq 30\%$ reduction), stable disease (SD, neither CR/PR/PD), or progressive disease (PD, $\geq 20\%$ increase in diameter and increase of ≥ 5 mm). Data cut-off for response was June 30, 2015.

Statistical analysis

Patient characteristics were expressed as relative frequencies (percentages) for discrete variables and median and range for continuous variables. OS was estimated using Kaplan–Meier analysis and expressed as a median value and survival curves analyzed using a log-rank test. Response rates in sequential and concurrent cohorts were assessed using Fisher’s exact test, and lesional response rates using a chi-squared test. Predictors of response were analyzed via logistic regression.

Disclosure of potential conflicts of interest

E. Liniker - Travel and accommodation to attend ESMO 2015 MSD Oncology

A.M. Menzies - Honoraria (Novartis, BMS, MSD), consulting/advisory role (MSD, Chugai), travel/accommodation (BMS)

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A. Hong - Honoraria (Novartis)

G.V. Long - Consultants advisor to Amgen, BMS, Novartis, MERCK MSD, Roche.

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