Safety of Combined PD-1 Pathway Inhibition and Intracranial Radiation Therapy in Non-Small Cell Lung Cancer

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GLOSSARY OF ABBREVIATIONS

NSCLC	**Non-small cell lung cancer**
RT	**Radiation therapy**
ICI	**Immune checkpoint inhibitors**
PD-1	**Programmed cell death protein 1**
PD-L1	**Programmed death-ligand 1**
AEs	**Adverse events**
SRS	**Stereotactic radiosurgery**
PBI	**Partial brain irradiation**
WBRT	**Whole brain radiation therapy**
Gy	**Gray**
MRI	**Magnetic resonance imaging**
CT	**Computed tomography**
TRIC	**Treatment-related imaging change**
sxTRIC	**Symptomatic treatment-related imaging change**
CNS	**Central nervous system**
CTLA-4	**Cytotoxic T-lymphocyte-associated protein 4**
ECOG	**Eastern cooperative oncology group**

ABSTRACT

Introduction: Intracranial metastases are a common cause of morbidity and mortality in patients with advanced non-small cell lung cancer (NSCLC), and are frequently managed with radiation therapy (RT). The safety of cranial RT in the setting of treatment with immune checkpoint inhibitors (ICIs) has not been established.

Methods: We identified advanced NSCLC patients with brain metastases who received cranial RT and were treated with or without PD-1/PD-L1 inhibitors between January 2013 and September 2016. RT-related adverse events (AEs) were retrospectively evaluated and analyzed according to ICI treatment status, cranial RT type, and timing of RT with respect to ICI.

Results: Of 163 patients, 50 (31%) patients received ICIs while 113 (69%) were ICI-naive. Overall, 94 (58%), 28 (17%) and 101 (62%) patients received stereotactic radiosurgery (SRS), partial brain irradiation (PBI), and/or whole brain RT (WBRT), respectively. Fifty percent of patient received >1 radiation course. We observed no significant difference in rates of all-grade AEs and grade ≥3 AEs between ICI-naive and ICI-treated patients across different cranial RT types (grade ≥3 AEs: 8% ICI- vs. 9% ICI+ for SRS [P=1.00]; 8% ICI- vs. 10% ICI+ for WBRT [P=0.71]). Additionally, there was no difference in AE rates based on the timing of ICI administration with respect to RT.

Conclusions: Treatment with ICI and cranial RT was not associated with a significant increase in RT-related AEs, suggesting that use of PD-1/PD-L1 inhibitors in patients receiving cranial RT may have an acceptable safety profile. Nonetheless, additional studies are needed to validate this approach.

INTRODUCTION

Intracranial metastases are a common and devastating complication of lung cancer.[1] Approximately 40% of patients with advanced non-small cell lung cancer (NSCLC) develop intracranial metastases during their disease course, of which the majority, approximately 70%, go on to receive intracranial radiation therapy (RT).[2] Recently, multiple immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have entered the clinic and have quickly reshaped management strategies for patients with advanced NSCLC.[3,4,5] Within this evolving treatment paradigm, patients with brain metastases are increasingly considered for combined treatment using systemic immune checkpoint inhibition (ICI) and cranial RT; yet, there is limited data regarding the safety of this approach.[6]

Preclinical studies have provided some insight into the immunomodulatory effect of RT on the tumor microenvironment.[7] The pro-inflammatory consequences of RT are numerous: from DAMP release, to the production and recruitment of inflammatory cytokines, to changing tumor cell surface molecule expression, inducing enlargement of the tumor cell peptide pool, and generating tumor antigen-driven T cell selection and expansion.[8,9,10,11,12,13,14,15] And yet, the cellular cast change in the tumor microenvironment post RT invites both pro and anti-inflammatory forces.[16] Along with the influx of CD8+ T cells into the irradiated area, comes expansion of T regulatory cells and their myeloid immunosuppressive counterparts, myeloid-derived suppressor cells (MDSCs).[17,9,18,19] MDSCs not only suppress the anti-tumor activity of tumor antigen-specific CD8+ T cells, but directly promote tumor cell survival and metastasis by stimulating angiogenesis and tumor cell invasion of adjacent tissues.[20,21] Thus, the ultimate immune impact of RT depends on the balance of control of these opposing forces within the tumor microenvironment.

Immune checkpoints, such as CTLA-4 and PD-1/PD-L1, are one means by which tumors affect this balance of forces, suppressing T cell activity.[22] RT leads to upregulation of PD-L1 on immune and tumor cells, enabling this means of immune escape.[23,24,25,26] PD-1 pathway inhibition can counteract this RT-induced PD-L1 upregulation, and has been shown to reverse T cell exhaustion in the setting of RT.[15] Hence, the theoretical promise of combining RT and ICI: the potential to abrogate the suppressive side of RT's dichotomous effect on immunity, leaving only the stimulatory. Multiple preclinical studies have demonstrated the benefit of the combination of RT and ICI, both in terms of tumor volume reduction and overall survival.[24,27,28,29,30] Furthermore, characterization of the cellular makeup of the tumor microenvironment following ICI/RT reveals a significant increase in CD8+ T cells and a significant decrease in T regulatory cells and MDSCs as compared to what is observed after RT alone.[24,29] Using a mouse model of breast cancer treated with PD-L1 inhibition and RT, Deng et al. found that following combination therapy, CD8+ T cells induce apoptosis of MDSCs via TNF alpha release.[24] While this view into the inflammatory skewing of the tumor microenvironment induced by combined RT/ICI raises hope for a synergistic clinical effect, it also introduces concern for a theoretical increase in clinical toxicity.

This concern may be particularly pertinent in the CNS. Due to its limited regenerative capacity and inflexible compartment, brain tissue is uniquely vulnerable to excess inflammation.[31,32] While the CSF to plasma ratio of PD-1 pathway inhibitors in human subjects is unknown, the demonstrated efficacy of PD-1 pathway inhibition as monotherapy in NSCLC patients with brain metastases indicates that the impact of ICI can be felt in the CNS, be it via drug blood brain barrier penetration or remote manipulation of the CNS immune environment.[33,34,35] Of note, the latter mechanism is increasingly perceived as feasible as recent evidence suggests that the choroid plexus is a gateway for immune signal entry and the brain is no longer perceived as an "immune privileged" anatomic silo.[36,37,38]

Clinical data evaluating combined ICI/RT has thus far been limited in NSCLC, particularly in patients with brain metastases. Indeed, patients with active brain metastases have traditionally been excluded from prospective trials of ICIs.[3,4] Case reports have described clinical toxicity after combined ICI/CNS RT. [39] Alomari et al. described a NSCLC patient treated with combined anti-PD-1 and anti-CTLA4 therapy initiated one month after receipt of SRS, who developed confusion and radiographic CNS edema with midline shift. Pathology revealed reactive astrocytosis and a T lymphocyte infiltrate without malignant cells, implicating an immunologic process.[39] While this report suggests that a robust inflammatory response to combined therapy can generate significant symptoms, it should be noted that this was in the setting of combination PD-1/CTLA-4 blockade, an approach which may be more toxic than ICI monotherapy.[40]

The retrospective evidence examining rates of toxicity with combined PD-1 pathway inhibition/CNS RT in NSCLC has been very limited.[41] In a uniquely homogeneous study including exclusively RT to the brain, inhibition of the PD-1 pathway, and NSCLC patients, Ahmed et al. reported no neurologic toxicity in 17 NSCLC patients treated with SRS or fractionated RT to the CNS and PD-1 or PD-L1 inhibition, suggesting overall tolerability.[42] Beyond this small cohort we are left to extrapolate from retrospective studies including more heterogeneous primary cancers as well as more heterogeneous RT sites and immunotherapy agents. For example, a single institution, retrospective study by Colaco et al. assessed 180 total patients including 32 (18%) NSCLC patients treated with SRS and diverse systemic therapies (42 patients – 23% – received some type of ICI which included anti-PD-1, anti-CTLA-4, anti-CD137, Interferon, and Interleukin 2). This study reported a significantly increased rate of radiation necrosis/treatment-related imaging change in patients receiving immunotherapy as compared with targeted therapy or chemotherapy.[43] Of note, this study only analyzed radiographic endpoints and did not compare clinically symptomatic toxicity between groups.

Another retrospective study included 133 total patients, 71 (53%) with NSCLC, all treated with some type of ICI (79% received a PD-1 inhibitor).[44] Sites irradiated in this study were heterogeneous, though all RT was palliative and the majority (53%) was CNS-directed. This study did not assess neurologic toxicity specifically, but did note a trend toward increased any-grade immune-related toxicity when immunotherapy was administered within 14 days of RT.[44]

One related area where more retrospective data is available is the use of ICI and RT in patients with melanoma brain metastases.[6] Small retrospective studies in melanoma have reported mixed results with some describing potential toxicities of combined cranial RT/ICI including neurocognitive decline, radiation necrosis, and intratumoral hemorrhage, although the majority of these studies have focused on CTLA-4 rather than PD-1 inhibition.[45,46,47,48,49,50,51] Given the distinct histopathology of melanoma brain metastases and the unique toxicity of CTLA-4 inhibition, findings in melanoma may not translate to other malignancies including NSCLC.

Finally, with the caveat that, as discussed above, the CNS is a unique anatomic site with unique vulnerabilities, we can also look to studies assessing non-CNS directed RT in combination with PD-1 pathway inhibition in NSCLC for clues. Here, some prospective data is available. The recently resulted PACIFIC trial, a phase III trial comparing maintenance PD-L1 inhibition to placebo following chemotherapy/radiation for stage III NSCLC, demonstrated an overall tolerable safety profile for PD-L1 therapy in this setting, with comparable rates of grade 3-4 toxicity between groups.[5] Similarly, a secondary analysis of the KEYNOTE-001 trial found no increase in rates of grade 3 or higher pneumonitis in patients with a history of RT prior to pembrolizumab as compared to no prior RT.[52] And in the palliative setting, a retrospective study of lung cancer patients found comparable rates of immune-related adverse events including pneumonitis between PD-1/PD-L1 treated patients who did and did not receive thoracic RT.[53]

In light of the limited retrospective data and paucity of prospective data to guide clinical decision making as outlined above, the purpose of this study was to investigate the safety of cranial RT in NSCLC patients receiving ICIs; we retrospectively evaluated RT-related toxicity and radiographic intracranial inflammation in NSCLC patients with and without a history of treatment with PD-1 or PD-L1 inhibitors. Particular focus was given to the potential effect of sequencing and timing of cranial RT and ICI on treatment-related toxicities.

MATERIALS AND METHODS

Patient Population

We identified patients with NSCLC and brain metastases, treated with single agent PD-1 or PD-L1 inhibitor ('ICI+' cohort) at the Massachusetts General Hospital between August 2013 and September 2016. Patients were required to have a history of ≥1 course(s) of cranial RT, no history of non-lung malignancy metastatic to the brain, and ≥1 month of clinical follow-up after cranial RT and ICI start. For an ICI-naïve ('ICI-') comparator cohort, we identified NSCLC patients meeting the above eligibility criteria treated with cranial RT in the period immediately prior to regulatory approval/initiation of clinical trials of ICIs at our institution (January 2013-August 2013). Medical records were reviewed to extract data on clinicopathologic features, treatment histories, and patient outcomes. This study was approved by the institutional review board at our institution.

Radiation Therapy

All types of cranial RT (whole brain radiotherapy [WBRT], partial brain irradiation [PBI], and stereotactic radiosurgery [SRS]) were included to investigate a range of doses, volumes, and fractionation schedules. For SRS, photon or proton therapy was selected based upon clinical availability or patient preference. Photon SRS, as well as PBI and WBRT, were delivered with a linear accelerator. SRS was typically delivered in one fraction but ranged up to 5 fractions to

increase safety. PBI and WBRT were generally delivered in 10-15 fractions; one patient discontinued PBI after receiving 5 Gy due to unrelated clinical issues. Patients' most recent MRIs were fused with planning CTs to assist in the delineation of target structures.

Adverse Event Assessment

Toxicity was graded retrospectively by investigators in accordance with Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Motor deficits attributable to motor cortex directed RT were graded as 'Nervous system disorders – Other, specify.' To investigate whether the sequence or timing of ICI relative to RT affected the frequency or severity of cranial RT-related AEs, we performed a subgroup analysis according to RT/ICI timing groups. Patients were assigned to three RT/ICI timing groups: RT >4 weeks before ICI ("pre"), RT ≤4 weeks before or after ICI ("concurrent"), and RT >4 weeks after ICI ("post").[51] Patients who received multiple courses of RT with different temporal relationships to ICI were included in multiple groups as applicable; each AE was assigned to one group only.

Imaging Assessment

Brain imaging was retrospectively reviewed with input from radiation oncology and neuroradiology. Due to the retrospective nature of the study, the time interval between RT and post-treatment MRIs was not standardized. In general, however, patients underwent repeat MRIs within 6-12 weeks of completion of radiation treatment. Post-RT MRIs were evaluated for treatment-related imaging change (TRIC). TRIC was defined as post-RT MRI findings consistent with inflammation, with subsequent histopathologic confirmation of non-malignancy or with resolution on serial imaging without intervention (e.g. surgical removal, systemic therapy, or corticosteroid initiation/dose increase).[51,54,55,56] To avoid the subjectivity of distinguishing between 'expected' and 'excessive' post-RT imaging change and to maximize clinical relevance, we included only TRIC with associated symptoms ('sxTRIC') in our analysis.[43,51]

Statistical Analyses

Fisher's exact test was used to compare categorical characteristics between groups. Age and lines of therapy were compared using Wilcoxon rank sum test. All *P* values are based on a two-sided hypothesis with exact calculations performed using the SAS 9.4 statistical software (SAS Institute, Inc., Cary, NC).

RESULTS

Patient and Treatment Characteristics

We identified 163 NSCLC patients treated with cranial RT, of whom 50 received ICI ('ICI+') and 113 did not ('ICI-'). Baseline clinical and pathologic features are summarized in Table 1. In the overall study population, the median age of NSCLC diagnosis was 61 years (range, 31-97 years), and the majority of patients had a smoking history (77%) and adenocarcinoma histology (84%). Forty-five percent of the patients had brain metastases at initial NSCLC diagnoses. We found the burden of CNS disease to be comparable between study cohorts as assessed by percent of patients symptomatic at the time of brain metastases diagnosis (56% ICI- vs. 48% ICI+, P = 0.40) and size of largest lesion at the time of diagnosis of CNS involvement (median greatest diameter 16 mm ICI- vs. 13 mm ICI+. P = 0.21). While significantly more ICI- patients presented with a single brain metastasis at diagnosis of CNS involvement (49% ICI- vs. 30% ICI+, P = 0.04), rates of presentation with >3 brain metastases at diagnosis of CNS involvement did not differ significantly (27% ICI- vs. 20% ICI+, P = 0.34). Otherwise, ICI+ and ICI- cohorts had comparable baseline disease characteristics. Regarding history of systemic therapy, ICI+ patients received more lines of therapy during their disease course compared to ICI- patients (median 3 vs. 1, respectively; P <0.0001), and were more likely to have received cytotoxic chemotherapy (98% vs. 87%, respectively; P = 0.02), including platinum-doublet chemotherapy (94 vs. 81%, respectively; P = 0.03). The checkpoint inhibitors administered to ICI+ patients

included nivolumab (n = 39), pembrolizumab (n = 8), or atezolizumab (n = 4) (Supplementary Table 1). The median number of ICI cycles received was 9 (range, 1-95).

Overall, the 163 patients included in this study received 373 radiation treatments. Eighty-one [50%] patients received more than one RT course. Significantly more patients in the ICI+ cohort received multiple RT courses (>1 RT courses: 43% ICI- vs. 64% ICI+, P = 0.02). The median number of radiation treatments per patient was 2 (range 1-10) in the ICI+ cohort versus 1 (range 1-11) in the ICI- group. Overall, 94 patients received stereotactic radiosurgery (35 [70%] ICI+, 59 [52%] ICI-), 28 received partial brain irradiation (8 [16%] ICI+, 20 [18%] ICI-), and 101 received whole brain RT (29 [58%] ICI+, 72 [64%] ICI-). The number of SRS treatments per patient were greater in the ICI+ compared to the ICI- cohort (SRS courses: median 2 vs. 1, P = 0.0034; respectively) (Table 2). Additionally, a significantly greater percentage of ICI+ patients received SRS at any point (70% versus 52%, respectively; P = 0.0398). For patients with available RT plans (N=78), total dose, dose per fraction, and target size were comparable between ICI+ and ICI- cohorts with the exception of smaller targets for SRS in ICI+ (Supplementary Table 2). The majority of PBI (66%) was post-operative. Twenty-six percent of all RT was classified as re-irradiation, defined as RT directed at previously irradiated brain parenchyma (27% RT in ICI- vs. 25% of RT in ICI+, P = 0.72).

Frequency of systemic corticosteroid use within four weeks of RT including preventative and symptom-driven corticosteroid prescription was not significantly different between groups (65% ICI- vs. 62% ICI+, P = 0.72). While the duration of steroid courses did not differ significantly between groups (median 50 vs. 58 days of total steroid use in ICI- vs. ICI+ patients, respectively, P = 0.61), starting steroid dose was significantly higher in the ICI- group (median 14 mg vs. 8 mg dexamethasone daily in ICI- vs. ICI+ patients, respectively, P = 0.003).

Adverse Events

The median duration of follow-up from first RT treatment was 16 months (range, 1-140 months). Overall, cranial RT was well tolerated with predominantly grade 1 or 2 AEs (Figure 1 & Supplementary Table 3). No significant difference was observed in the rate of all-grade RT-related AEs between ICI+ and ICI- patients for any particular cranial RT type (Figure 1 & Supplementary Table 3). The incidence of grade ≥3 AEs was 8% to 13% across treatment groups, and did not differ significantly between ICI+ and ICI- cohorts.

Among ICI+ patients, the most commonly observed AEs included fatigue (76%), radiation dermatitis (48%) and cognitive disturbance (41%) following WBRT, and headache (26%) following SRS (Supplementary Table 4). The most frequently observed grade ≥3 AEs in ICI+ patients were headache (n = 2), anorexia (n = 2), and cognitive disturbance (n = 2) (Supplementary Table 5). The distribution of AEs was similar in the ICI- cohort, with fatigue as the most commonly observed AE after WBRT or PBI and headache most frequently observed after SRS. Commonly observed grade ≥3 AEs in the ICI- cohort were fatigue (n = 4), motor deficit (n = 3), seizure (n =2), and radiation necrosis (n = 2, pathology confirmed). One grade 4 AE was observed in an ICI- patient; this patient experienced CNS necrosis resulting in midline shift requiring emergent craniotomy.

Symptomatic TRIC was observed on brain MRI in 41 (25%) patients across both cohorts. In six patients, brain biopsy or resection specimens were available for histopathology review, which demonstrated inflammatory findings consistent with TRIC (see Figure 2 for representative images). Rates of sxTRIC were comparable between ICI+ and ICI- patients across cranial RT treatment types (sxTRIC: 34% ICI- vs. 31% ICI+ for SRS [P = 1.00]; 5% ICI- vs. 13% ICI+ for PBI [P = 0.50]; 11% ICI- vs. 17% ICI+ for WBRT [P = 0.51]. Median time from RT start to the first MRI documentation of sxTRIC was 5 months in both cohorts.

1.

Timing of Radiation Therapy and Immune Checkpoint Inhibition

Within the ICI+ cohort, RT was most frequently administered before (n = 31) or concurrently with (n = 20) ICI. Ten patients underwent cranial RT after ICI (Table 3). The median time between RT and ICI was 13 months for RT pre-ICI, 9 days for concurrent RT/ICI and 4 months for RT post-ICI. RT parameters including rates of re-irradiation and brain surgery prior to RT were consistent across timing groups. There were no significant differences in rates of any grade AEs or of grade ≥3 AEs based on the sequencing of RT/ICI. Rates of sxTRIC were also similar irrespective of RT/ICI timing.

DISCUSSION

PD-1 pathway blockade now represents a standard therapy for patients with advanced NSCLC. Importantly, initial clinical trials evaluating these agents routinely excluded patients with active brain metastases. With the recent regulatory approvals of four PD-1/PD-L1 inhibitors in NSCLC, clinicians are now faced with real-world clinical questions, such as whether cranial RT can be delivered safely in a background of PD-1 pathway blockade. To date, there are limited data available to inform these therapeutic questions.

Here, we present the largest series to date evaluating the safety of combined cranial RT and PD-1 pathway inhibition in NSCLC patients with brain metastases. Overall, the combination of ICI and RT was well tolerated, and the rate of grade ≥3 AEs reported here (8-13% among ICI+ patients) is consistent with the 0-20% incidence of grade ≥3 AEs reported previously in melanoma treated with ICI/CNS RT.[51,45,46,49] Of note, this is the first study to include a comparator cohort of ICI-naïve patients who received cranial RT. Using this comparative approach, we observed similar rates of RT-related toxicity between ICI+ and ICI- cohorts, suggesting that PD-1 pathway blockade may not substantially elevate the risks of radiation

compared to cranial RT alone. These results are consistent with recent prospective studies evaluating the toxicity of thoracic RT, where the addition of ICI was not observed to significantly increase treatment-related AEs.[5,53]

A recent sub-analysis of KEYNOTE-001 noted improved efficacy of pembrolizumab among patients receiving radiation prior to immunotherapy—supporting the notion that clinically relevant immune synergy between RT and ICI may occur, and may be timing dependent.[53] To investigate whether the frequency and/or spectrum of RT-related toxicities may differ depending on the relative timing and sequencing of RT with ICI, we conducted additional subgroup-analyses. Again, no difference was observed in rates of cranial RT-related AEs between groups; however, the total number of patients in each group was relatively small. Nonetheless, these findings provide preliminary support for the safety and tolerability of pursuing cranial RT in patients being treated with ICIs.

The comparable rates of AEs that we observed between treatment timing groups is largely consistent with the limited prior literature examining AEs by RT/ICI sequence, although it notably does not recapitulate the trend toward increased inflammation and toxicity with concurrent RT/ICI observed by several groups in NSCLC and melanoma.[44,51] For example, in the study conducted by Bang et al. looking at mixed tumor types including NSCLC treated with CTLA-4 and PD-1 inhibitors and all-site RT, a non-significant trend toward increased immune-related AEs with RT administration within 14 days of ICI was noted; however, of note, neurologic toxicity was not specifically assessed.[44] Similarly, in a study examining AEs by RT/ICI sequence among melanoma patients, a slightly higher incidence of central nervous system toxicity was observed in patients receiving cranial RT within one month of ICI; however, there were too few events to allow statistical analysis.[51]

In this study, lesions that were radiographically consistent with radiation necrosis or pseudo-progression were assessed collectively as TRIC. We did not observe any differences in symptomatic TRIC based on exposure to immunotherapy, or on timing of cranial RT with respect to ICI. However, it is worth noting that we did not evaluate for asymptomatic transient increases in lesion size—a post-RT phenomenon that has been associated with immunotherapy in other studies.[43,51,57] Thus, our findings do not contradict the notion of timing-dependent immune synergy, but rather suggest that this synergy may not have a significant clinical impact, at least with respect to toxicity.

This study has several important limitations. First, it was a single-institution, retrospective study evaluating heterogeneous RT modalities. To overcome this limitation, we used a near-contemporaneous control cohort and stratified toxicity outcomes according to RT modality. Secondly, the total sample size in this study was small, reflecting the recent clinical approval of PD-1 and PD-L1 inhibitors in NSCLC. Third, while the control cohort was treated within 8 months of the earliest-treated immunotherapy cohort patient, temporal separation does introduce practice pattern changes between cohorts (e.g. increasing use of SRS for management of brain metastases, as reflected in the greater number of SRS treatments per patient in the more recently treated ICI+ cohort). Improvements in practice patterns over time could also potentially obscure an increase in toxicity emerging with the addition of ICI.

Notably, though we found the two cohorts to be generally comparable with respect to baseline characteristics, the ICI+ group received more lines of systemic chemotherapy. To investigate this further, we evaluated ECOG performance status and burden of disease at diagnosis of brain metastases between the two cohorts, finding that both were comparable, with the exception of significantly more patients with limited CNS burden (i.e. a solitary brain metastasis) in the ICI- cohort, a difference that would likely accentuate rather than obscure any possible

increase in treatment-related toxicity in the ICI+ cohort. Nonetheless, given the non-randomized sampling, unanticipated differences between the patient cohorts could have introduced confounders.

Finally, in this study we were unable to assess several important potential modifiers of immune synergy. While the optimal regimen for maximizing RT immunogenicity has not been defined at present, it is suspected that RT parameters such as dose and fractionation do modulate the immune effect of RT.[63] However, due to incomplete access to RT plans we were unable to comprehensively assess the effects of RT dose and volume on adverse outcomes. Additionally, the status of predictive markers such as PD-L1, tumor infiltrating lymphocytes (TILs), and baseline tumor mutational load were unavailable for the majority of the patients included in this study. Increases in these markers have been associated with increased efficacy of PD-1 pathway inhibitors, and therefore could predict increased risk for immune hyper-stimulation and treatment-related AEs.[58, 3, 59,60,61,62]

Moving forward, prospective investigation will be necessary to further evaluate the toxicity profile of ICI/CNS RT in NSCLC patients and firmly establish whether or not an increased risk of AEs is incurred with this combination therapy. While there is currently no prospective data resulted to shed light on these questions, at least 57 prospective trials of combined RT and PD-1 or PD-L1 inhibition are ongoing at this time, including 16 looking at NSCLC, 12 of which are enrolling patients with metastatic disease – potential recipients of CNS RT.[7,63] In addition to eliminating confounding and issues of longitudinal practice change which restrict definitive conclusions here, prospective trials will be better suited to address questions about tumor and treatment variables that may modulate immugenicity (e.g. PD-L1, TILs, tumor mutational load, RT type, RT dose, RT fractionation, sequence and timing of RT/ICI) and thus allow clinicians to better understand and manipulate the efficacy/toxicity balance of combined ICI/RT.

SUMMARY

In summary, we found that cranial RT and PD-1 pathway inhibition in combination were overall well tolerated in the study population. No significant differences in rates of RT-related AEs were observed between PD-1 pathway inhibitor-naive and PD-1 inhibitor-treated patients. Furthermore, the sequence and timing of PD-1 pathway inhibitor administration with respect to RT did not appear to impact RT-related toxicity. Further prospective investigation is needed to establish the optimal timing of this increasingly utilized combination approach and to further validate and evaluate its safety and tolerability, including its impact on quality of life and long-term cognitive outcomes.

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1 **Table 1.** Baseline Patient Characteristics

Characteristic	Overall (N = 163)	ICI- (n = 113)	ICI+ (n = 50)	P-value
Age at NSCLC diagnosis (median, range)	61 (31-97)	62 (31-97)	61 (35-82)	0.74
Gender				0.60
Male (%)	36	37	32	
Female (%)	64	63	68	
History of smoking (%)	77	75	80	0.55
Histology				0.14
Adenocarcinoma (%)	84	88	76	
Squamous cell carcinoma (%)	12	10	16	
Other (%)	4	3	8	
ECOG performance status at diagnosis of brain metastasis* (median, range)	1 (0-4)	1 (0-4)	1 (0-3)	0.75
Brain metastases at NSCLC diagnosis (%)	45	44	46	0.84
Symptomatic at diagnosis of brain metastasis (%)	53	56	48	0.40
Number of brain lesions at diagnosis of brain metastasis (median, range)	2 (1-21)	2 (1-21)	2 (1-20)	0.40
Single brain lesion (%)	43	49	30	0.04
>3 brain lesions (%)	25	27	20	0.34
Diameter of largest lesion at brain metastasis diagnosis, mm (median, range)	16 (1-63)	16 (1-63)	13 (1-39)	0.21
Leptomeningeal disease at any time during disease course (%)	22	22	22	1.0
Total lines of systemic therapy during disease course (median, range)	2 (0-10)	1 (0-9)	3 (1-10)	<0.0001
Chemotherapy, any kind (%)	90	87	98	0.02
Platinum-doublet chemotherapy (%)	85	81	94	0.03
Targeted therapy [EGFR-, ALK- or ROS1-directed] (%)	22	23	20	0.67
Brain surgery at any point during disease course (%)	36	37	32	0.60

*Reported for patients with ECOG performance status documented within one month of brain metastasis diagnosis only (n = 110 ICI-, 45 ICI+).
Abbreviations: ICI, immune checkpoint inhibitor; NSCLC, non small cell lung cancer; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase.

Table 2. Cranial Radiation Therapy

Type of cranial radiation therapy	Overall (N = 163)	ICI- (n = 113)	ICI+ (n = 50)	P-value
Cranial radiation therapy, all modalities				
Cranial radiation treatments per patient (median, range)	1 (1-11)	1 (1-11)	2 (1-10)	0.0045
Patients receiving >1 radiation therapy course (%)	50	43	64	0.02
Stereotactic radiosurgery (SRS)				
Patients receiving SRS (%)	58	52	70	0.0398
SRS per patient (median, range)	1 (0-11)	1 (0-11)	2 (0-10)	0.0034
Partial brain irradiation (PBI)				
Patients receiving PBI (%)	17	18	16	1.00
PBI per patient (median, range)	0 (0-3)	0 (0-2)	0 (0-3)	0.88
Whole brain radiation therapy (WBRT)				
Patients receiving WBRT (%)	62	64	58	0.49
WBRT per patient (median, range)	1 (0-2)	1 (0-2)	1 (0-2)	0.54

Abbreviation: ICI, immune checkpoint inhibitors.

FIGURE 1

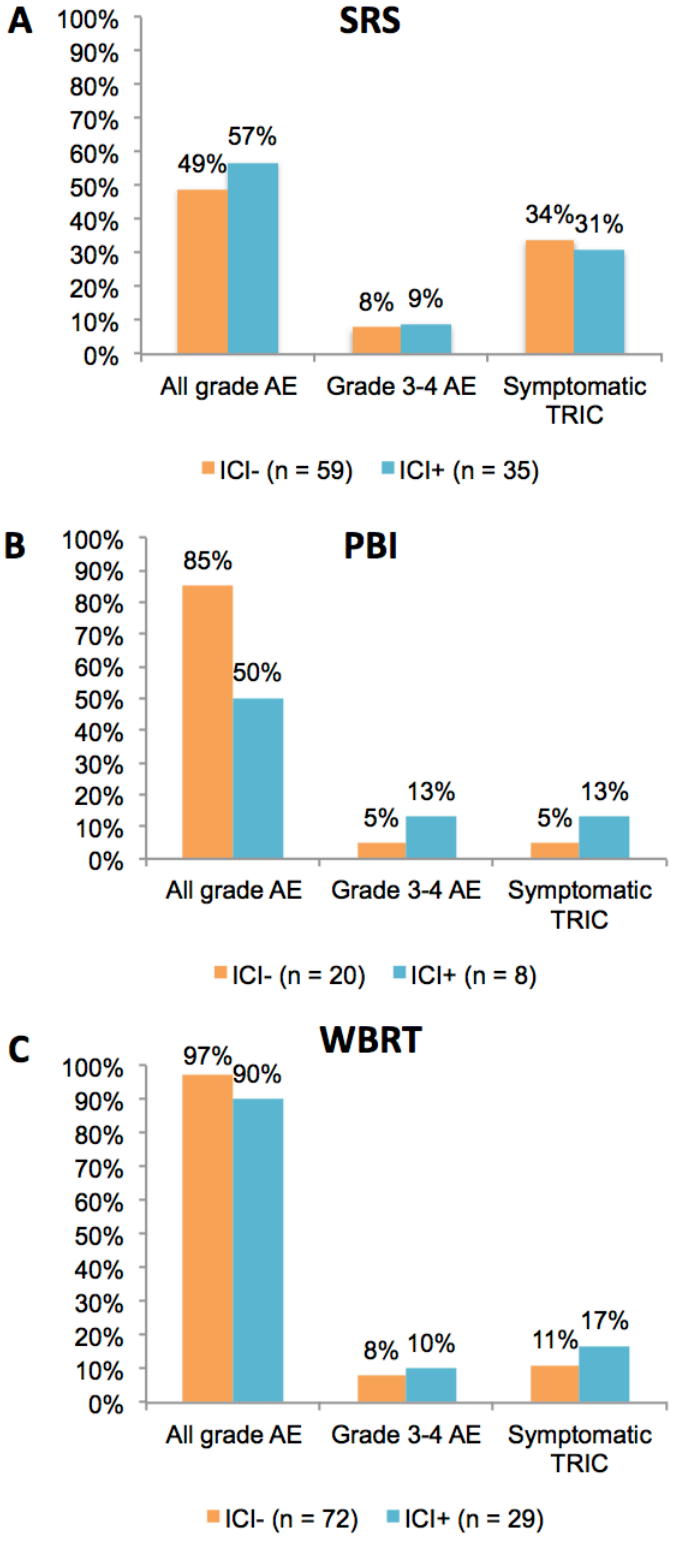

Figure 1. Cranial radiation therapy-related adverse events according to the receipt of immune checkpoint inhibitors, in patients who received (A) SRS, (B) PBI, or (C) WBRT as cranial RT. Abbreviations: SRS, stereotactic radiosurgery; AE, adverse event; TRIC, treatment-related imaging change; ICI, immune checkpoint inhibitors; PBI, partial brain irradiation; WBRT, whole brain radiotherapy.

FIGURE 2

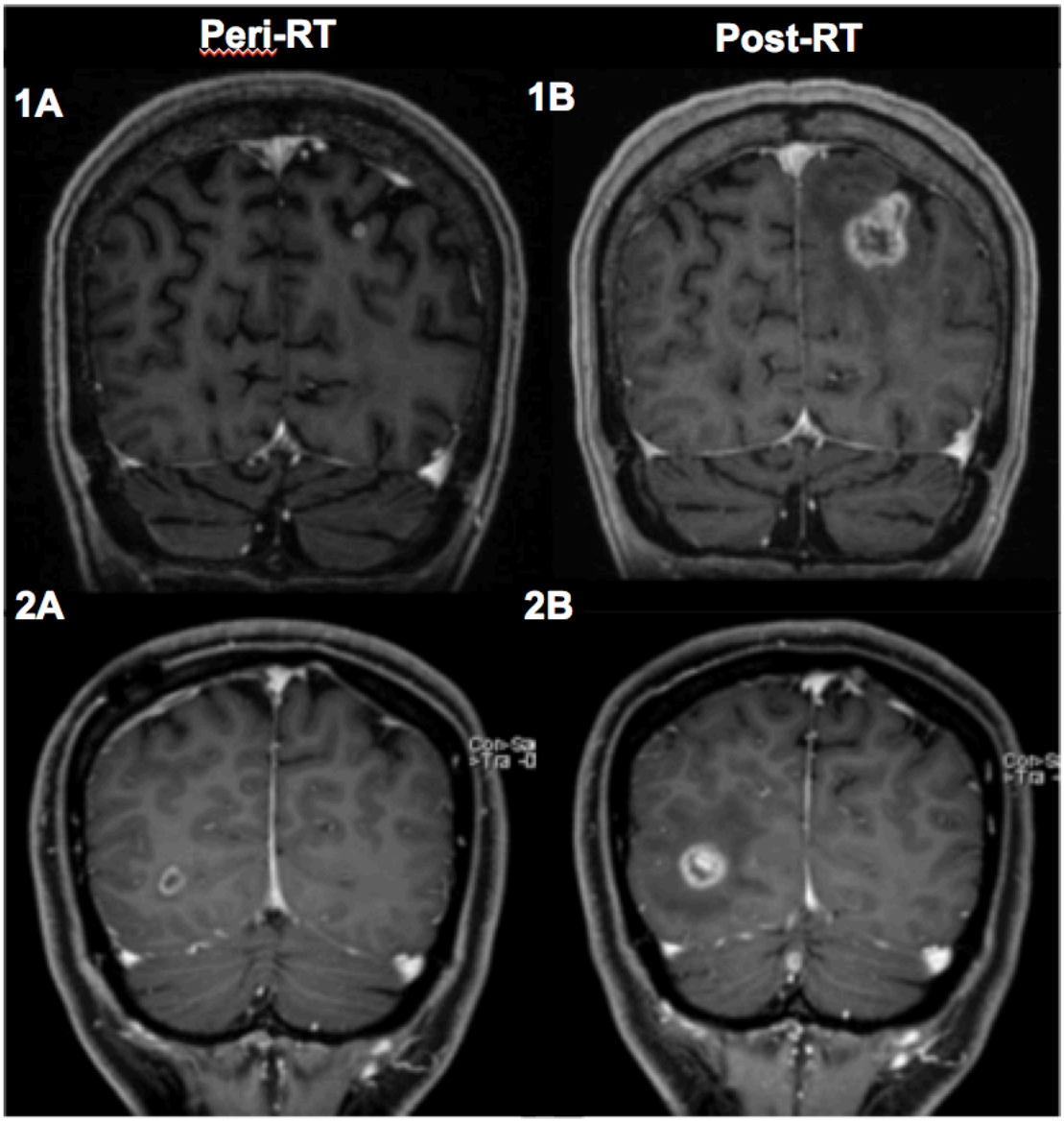

Figure 2. Representative axial post-contrast magnetic resonance images (MRI) of pathologically confirmed radiation necrosis in an immunotherapy-naïve (1A/B) and an immunotherapy-treated (2A/B) patient, respectively [MRI sequence: 1A/B, BRAVO; 2A, MP RAGE; 2B, STEALTH 3D FSPGR]

Table 3. Cranial Radiation Therapy-Related Adverse Events by Immune Checkpoint Inhibitor Timing

AE incidence by cranial RT Type	RT → ICI	ICI/RT	ICI → RT	P-value
Stereotactic radiosurgery	***n = 21***	***n = 14***	***n = 5***	
All grade AE (%)	57	64	20	0.27
Grade 3-4 AE (%)	10	7	0	1.00
Symptomatic TRIC (%)	29	36	20	0.90
Partial brain irradiation	***n = 5***	***n = 3***	***n = 1***	
All grade AE (%)	60	33	100	1.00
Grade 3-4 AE (%)	20	0	0	1.00
Symptomatic TRIC (%)	20	0	100	0.31
Whole brain radiation therapy	***n = 18***	***n = 6***	***n = 5***	
All grade AE (%)	89	100	80	0.53
Grade 3-4 AE (%)	6	33	0	0.17
Symptomatic TRIC (%)	17	33	0	0.51

Abbreviations: RT, radiation therapy; ICI, immune checkpoint inhibitors; RT → ICI**,** patients irradiated >1 month prior to receipt of ICI; ICI/RT, patients irradiated within 1 month of ICI receipt; ICI → RT, patients irradiated >1 month after receipt of ICI; AE, adverse event; TRIC, treatment-related imaging change.

Table S1. Immune Checkpoint Inhibitor (ICI) Characteristics	
ICI agents received by patient	n = 50* (n, %)
Nivolumab	39 (78)
Pembrolizumab	8 (16)
Atezolizumab	4 (8)
Duration on ICI, months (median, range)	3 (0-42)
Number of ICI cycles (median, range)	9 (1-95)
ICI line of therapy (median, range)	2 (1-7)

*One patient received non-concurrent courses of nivolumab and pembrolizumab.

Table S2. Cranial Radiation Therapy Parameters

	Overall	ICI-	ICI+	P-value
Total number of radiation treatments	***373***	***231***	***142***	
# Stereotactic radiosurgery treatments	***231***	***132***	***99***	
Total dose, Gy (median, range)*	18 (10-25)	18 (16-25)	18 (10-22)	0.0284
Dose per fraction, Gy (median, range)*	18 (4-24)	18 (4-24)	18 (4-20)	0.22
GTV/CTV, cc (median, range)*	0.4 (0.01-34)	0.5 (0.02-34)	0.2 (0.01-7)	0.0078
# Partial brain irradiation treatments	***35***	***23***	***12***	
Total dose, Gy (median, range)	30 (5-40)^	30 (5-40)^	30 (20-36)	0.99
Dose per fraction, Gy (median, range)	3 (2-6)	3 (2-6)	3 (2-6)	0.57
GTV/CTV, cc (median, range)*	11 (3-241)	14 (3-42)	6 (3-241)	0.97
# Whole brain radiation therapy treatments	***107***	***76***	***31***	
Total dose, Gy (median, range)*	35 (5-50)	35 (5-50)	31 (20-38)	0.75
Dose per fraction, Gy (median, range)*	3 (2-3)	3 (2-3)	3 (2-3)	0.0054

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*Dose, fraction, and GTV/CTV reported as available. For SRS: total dose & dose per fraction, n119 ICI-, n95 ICI+; GTV/CTV, n81 ICI-, n73 ICI+. For PBI: GTV/CTV, n14 ICI-, n7 ICI+. For WBRT: total dose, n75 ICI-, n29 ICI +; dose per fraction: n75 ICI-, n28 ICI+.
Abbreviations: ICI, immune checkpoint inhibitors; Gy, Gray; GTV, gross target volume; CTV, clinical target volume.
^The low end of the dose range for PBI represents a patient who was unable to complete the planned 30 Gy course due to unrelated clinical issues, discontinuing RT after receiving 5 Gy; the majority of PBI courses ranged in total dose from 20 to 40 Gy.

Table S3. Cranial Radiation Therapy-Related Adverse Events

AE incidence by cranial RT Type	ICI-	ICI+	P-value
Stereotactic radiosurgery	***n = 59***	***n = 35***	
All grade AE (%)	49	57	0.52
Grade 3-4 AE (%)	8	9	1.00
Symptomatic TRIC (%)	34	31	1.00
Partial brain irradiation	***n = 20***	***n = 8***	
All grade AE (%)	85	50	0.14
Grade 3-4 AE (%)	5	13	0.50
Symptomatic TRIC (%)	5	13	0.50
Whole brain radiation therapy	***n = 72***	***n = 29***	
All grade AE (%)	97	90	0.14
Grade 3-4 AE (%)	8	10	0.71
Symptomatic TRIC (%)	11	17	0.51

Abbreviations: ICI, immune checkpoint inhibitors; AE, adverse event; TRIC, treatment-related imaging change.

Table S4. All Grade Cranial Radiation Therapy-Related Adverse Events (>10% Incidence)

Adverse Event	ICI- (n = 113) n (%)	ICI+ (n = 50) n (%)
Stereotactic radiosurgery	***n = 59***	***n = 35***
Headache	13 (22)	9 (26)
Motor deficit	10 (17)	5 (14)
Dizziness	6 (10)	4 (11)
Cognitive disturbance	7 (12)	4 (11)
Seizure	11 (19)	4 (11)
Fatigue	9 (15)	4 (11)
Aphasia	2 (3)	4 (11)
Partial brain irradiation	***n = 20***	***n = 8***
Cognitive disturbance	1 (5)	2 (25)
Fatigue	9 (45)	1 (13)
Alopecia	6 (30)	1 (13)
Headache	5 (25)	1 (13)
Scalp pain	0 (0)	1 (13)
Paresthesia	0 (0)	1 (13)
Seizure	2 (10)	1 (13)
Motor deficit	1 (5)	1 (13)
Radiation dermatitis	3 (15)	0 (0)
Whole brain radiation therapy	***n = 72***	***n = 29***
Fatigue	60 (83)	22 (76)
Radiation dermatitis	40 (56)	14 (48)
Cognitive disturbance	33 (46)	12 (41)
Headache	30 (42)	10 (34)
Alopecia	40 (56)	8 (28)
Nausea	26 (36)	8 (28)
Dizziness	9 (13)	6 (21)
Anorexia	21 (29)	5 (17)
Seizure	8 (11)	2 (7)
Blurred vision	13 (18)	1 (3)
Ataxia	8 (11)	0 (0)

Abbreviation: ICI, immune checkpoint inhibitors.

Table S5. Grade 3 or 4 Cranial Radiation Therapy-Related Adverse Events

Adverse Event	ICI- n (%)	ICI+ n (%)
Stereotactic radiosurgery	***n = 59***	***n = 35***
Headache	0 (0)	2 (6)
Radiation necrosis	2 (3)	1 (3)
Dizziness	0 (0)	1 (3)
Ataxia	0 (0)	1 (3)
Motor deficit	3 (5)	0 (0)
Seizure	1 (2)	0 (0)
Urinary frequency*	1 (2)	0 (0)
Partial brain irradiation	***n =20***	***n = 8***
Cognitive disturbance	0 (0)	1 (13)
Cranial neuropathy	1 (5)	0 (0)
Whole brain radiation therapy	***n = 72***	***n = 29***
Anorexia	0 (0)	2 (7)
Cognitive disturbance	0 (0)	1 (3)
Fatigue	4 (6)	0 (0)
Seizure	2 (3)	0 (0)
Nausea	1 (1)	0 (0)
Motor deficit	1 (1)	0 (0)

*Urinary frequency secondary to diabetes insipidus after pituitary radiation.
Abbreviation: ICI, immune checkpoint inhibitors.

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