Immunotherapy and Stereotactic Radiosurgery for Management of Patients With Lung Cancer Brain Metastases

Abstract

Purpose: Despite the emerging role of PD-1 pathway inhibitors for patients with advanced lung cancer, there is a paucity of data on the activity of these agents among patients with brain metastases. We investigated the outcomes of PD-1 pathway inhibitors and stereotactic radiosurgery (SRS) for the treatment of patients with lung cancer brain metastases.

Methods: We retrospectively reviewed records of non-small cell lung cancer (NSCLC) patients with brain metastases consecutively treated with PD-1 pathway inhibitors and SRS at our institution between 2012 and 2017. Local control (LC), distant brain failure (DBF), and overall survival (OS) were assessed using Kaplan-Meier estimates and Cox regression models. Toxicity was graded according to the Common Criteria for Adverse Events v 4.0.

Results: We identified 37 patients treated with SRS to 85 lesions (90.6% intact, 9.4% resected) and a median total of 7 doses of PD-1 pathway inhibitors (83.8% nivolumab, 10.8% atezolizumab, 5.4% pembrolizumab). Most lesions were treated with 18 Gy in a single fraction (n=61, 71.8%). Patients treated with concurrent SRS and PD-1 pathway inhibitors had longer OS and reduced rates of DBF as compared with patients treated with SRS prior to or after PD-1 pathway inhibitors (1-year OS 87.3% vs. 70.0% vs. 0%, p=0.008; 1-year DBF 38.5% vs. 65.8% vs.100%, p=0.042). LC was favorable among lesions treated with SRS concurrent or after PD-1 pathway inhibitors compared to prior to PD-1 pathway inhibitors (1-year LC 100% vs. 72.3%, p=0.016). Three lesions transiently enlarged after SRS and then partially or completely resolved on follow-up imaging. Four patients required steroids for SRS-associated toxicity. No patient had ≥ grade 4 toxicity.

Conclusion: Concurrent treatment with SRS and PD-1 pathway inhibitors is associated with favorable overall survival and locoregional disease control for NSCLC patients with brain metastases. This combination of therapy was well tolerated and merits further evaluation in larger cohorts in a prospective setting.

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Glossary of Abbreviations

ALK: Anaplastic lymphoma kinase

BBB: Blood brain barrier

CI: Confidence interval

CPI: Checkpoint inhibitor

EGFR: Epidermal growth factor receptor

DBF: Distant brain failure

FDA: Food and Drug Administration

Gy: Gray

GTV: Gross tumor volume

HR: Hazard ratio

LC: Local control

KPS: Karnofosky performance status

SRS: Stereotactic radiosurgery

PD-1: Programmed death receptor 1

PD-L1: Programmed death receptor ligand 1

MHC: Major histocompatibility complex

Mo: Months

NSCLC: Non-small cell lung cancer

OS: Overall survival

PFS: Progression free survival

MRI: Magnetic resonance imaging

RN/TRIC: Radiation necrosis/treatment related imaging changes

RT: Radiation therapy

WBRT: Whole brain radiation therapy

Introduction

Checkpoint Inhibitors for Non-Small Cell Lung Cancer

Lung cancer remains a significant cause of morbidity and mortality, with over 200,000 new diagnoses and 150,000 deaths annually in the United States alone.[1] Non-small cell lung cancer (NSCLC) accounts for 85% of new diagnoses.[2] Checkpoint inhibitors (CPIs) have transformed the management of advanced non-small cell lung cancer (NSCLC), offering potential for improved disease control and survival. Nivolumab, a PD-1 inhibitor, was the first CPI granted Food and Drug Administration (FDA) approval for NSCLC cancer as second-line therapy in 2015.[3] An additional PD-1 inhibitor (pembrolizumab) as well as two PD-L1 inhibitors (atezolizumab and durvalumab) have since been granted FDA approval for an increasing number of indications for NSCLC patients, including as a first-line therapy for subsets of NSCLC patients.

CPIs specific for PD-1 and PD-L1 inhibit the PD-1:PD-L1 signaling pathway, facilitating immune-mediated tumor eradication. PD-1 is an inhibitory transmembrane protein expressed on T and B cells that binds to PD-L1, a cell surface protein expressed on tumor cells. The PD-1:PD-L1 signaling restricts T-cell proliferation, migration, secretion of cytotoxins and tumor cell killing. These immune checkpoints mechanisms normally function protect against damaging inflammation and autoimmune disease. However, in the setting of malignancy such as NSCLC, these mechanisms are utilized by the tumor cells to promote immune tolerance.[4,5]

A significant challenge is the selection of NSCLC patients most likely to respond to PD-1 pathway inhibitors. Tumoral PD-L1 expression has been explored as a predictive biomarker, with the hypothesis that CPIs targeting PD-1:PD-L1 interaction are most effective in patients with immune suppression mediated by this pathway.[6] However, utilizing PD-L1 as a predictive biomarker has had limited success owing to the dynamic nature of PD-L1 expression and heterogeneous PD-L1 expression in the same patient between sites of primary and metastatic disease.[7] Somatic mutation burden has been found to positively correlate with responsiveness to PD-1 pathway inhibitors. Increased nonsynonymous mutational burden (a mutation that alters the amino acid sequence), the

molecular smoking signature, and DNA repair pathway mutations including mismatch repair deficiency are associated with increased clinical efficacy of pembrolizumab. These genetic alterations increase the number of neoantigens, or tumor specific-antigens, which are critical in immune system recognition and eradication of malignancy.[8,9]

Management Strategies for Patients with NSCLC Brain Metastases

Patients diagnosed with metastatic NSCLC frequently develop brain metastases. Approximately 10% of patients with NSCLC have brain metastases at the time of diagnosis, and another 30% develop brain metastases during the course of their disease.[10] The proportion of patients diagnosed with brain metastases is increasing, likely due to improved imaging technology and prolonged survival.[11] The prognosis for patients with NSCLC brain metastases ranges from 7 months to 47 months from the time of brain metastasis diagnosis. Prognosis depends on performance status, age, extracranial disease status, number of brain metastases, and presence of the *EGFR* or *ALK* alterations.[11]

Data on the efficacy of PD-1 pathway inhibitors for management of brain metastases is lacking. Randomized trials establishing the clinical benefit of PD-1 and PD-L1 inhibitors excluded all patients with brain metastases or excluded patients with untreated or symptomatic brain metastases.[12-17] A Phase II prospective trial of 18 patients with asymptomatic, untreated NSCLC brain metastases demonstrated that pembrolizumab has intracranial activity. Six patients (33%) had durable responses (four complete responses and two partial responses) lasting between 3.2 and 7.0 months with all but one patient continuing to respond at the time of analysis. Another six patients (33%) experienced intracranial disease progression. Four patients (22%) could not be evaluated for intracranial response due to rapid systemic disease progression. There was high concordance between systemic and intracranial response.[18] A retrospective analysis of five patients new NSCLC brain metastases treated with nivolumab observed intracranial response among two patients. One patient experienced a partial response, and another patient experienced a complete response. Both responses were durable for over 6 months.[19] There are several ongoing clinical trials investigating the role of CPIs for management of patients with NSCLC brain metastases, including pembrolizumab with

bevacizumab (NCT02681549) and pembrolizumab with stereotactic radiosurgery (NCT02858869).

There are several hypotheses to explain the immunomodulatory effects of CPI in the brain. A significant challenge in treated central nervous system disease with systemic therapy is penetrance of the blood brain barrier (BBB). Most large molecules, likely including antibodies such as PD-1 and PD-L1 inhibitors, are unable to penetrate the BBB.[20] Radiation therapy diminishes the integrity of the BBB, which may improve penetrance of CPI into the central nervous system.[21] However, it is also possible that activated T cells are able to penetrate BBB and exert effects directly on BM.[22]

RT and CPI Synergy and Toxicity

Radiation therapy (RT) may act synergistically with immune CPIs. RT kills malignant cells through two distinct mechanisms. The delivery of ionizing radiation to the tumor cells results in DNA damage that can cause cell death. In addition, RT can induce an immunogenic cell death. Immunogenic cell death occurs via enhanced expression of MHC Class I, release of damage-associated molecular patterns, increase FAS surface expression, activation of antigen-presenting dendritic cells, and T cell recruitment. RT may induce tumor cell death at sites distant from the irradiated field, a phenomenon termed the abscopal effect. The abscopal effect is an immune-mediated phenomenon that is rarely observed clinically for reasons that are not well-uderstood.[23-29] Given the ability of RT to generate immunogenic cell death, it is possible that RT may potentiate the clinical efficacy of CPIs.

Given the paucity of data on the intracranial activity of PD-1 pathway inhibitors, clinicians are increasingly faced with questions regarding the relative roles of PD-1 and PD-L1 inhibitors and cranial irradiation including SRS. At our own institution, we have observed an increase in the use of SRS among patients actively receiving PD-1 or PD-L1 inhibitors. To investigate outcomes of combined SRS and PD-1 pathway inhibition in advanced NSCLC, we performed a retrospective analysis of patients treated with a

combination of therapies with a focus on the timing of PD-1 pathway inhibitors relative to SRS treatment.

Materials and methods

Patient Selection

With institutional review board approval, we retrospectively reviewed the medical records of patients with NSCLC brain metastases treated at our institution between 2012 and 2017 and identified patients who received combination SRS and PD-1 pathway inhibitors. Clinical variables collected include age, sex, performance status, smoking history, histology, prior chemotherapy, number of brain metastases, relationship of brain metastasis diagnosis and therapies, type and number of total PD-1 pathway inhibitor doses, and toxicities. Toxicities were graded according to National Cancer Institute Common Criteria for Adverse Events v4.0. The lung molecular graded prognostic assessment (Lung-molGPA) from the time of brain metastasis diagnosis was calculated using age, performance status, extracranial metastases, number of brain metastases, and *EGFR* and *ALK* alteration status.[11]

Radiation therapy

Patients were treated with either photon or proton SRS based upon logistical availability or by patient preference. Photon SRS was delivered with a linear accelerator. Proton SRS was administered using passive single scattering technique. For both forms of SRS delivery, patients were immobilized using a noninvasive modified Gill-Thomas-Cosman stereotactic frame. The patient's most recent MRI was fused with the planning CT to delineate target structures. Treatment was typically delivered in one fraction but ranged up to 5 fractions with any fractionation incorporated to increase safety, most commonly for larger lesions or eloquent location in the brain.

Treatment assessment

MR imaging was typically obtained per institutional standard of care, commonly at two or three month intervals following SRS. Post-treatment radiographic effects were assessed with input from radiation oncology, neuro-oncology, and neuroradiology. Pathology-confirmed radiation necrosis (RN) and its imaging equivalent treatment related imaging changes (RN/TRIC) were grouped together. TRIC was defined as post-RT MRI findings consistent with inflammation with subsequent histologic confirmation or at least

partial resolution on serial imaging without intervention. Distant brain failure (DBF) was defined as the appearance of new brain metastases or the development of new leptomeningeal disease. Local control (LC) was defined as a stable or decreasing lesion size on post-SRS imaging or pathological confirmation of RN/TRIC. Treated lesions without at least one month of imaging follow-up were excluded from analysis.

Statistical analysis

The Kaplan-Meier method was used to estimate rates of LC, DBF, and overall survival (OS). Event time was calculated from date of first SRS fraction. Patients were categorized based on the relative timing of therapies: SRS at least one month prior to PD-1 pathway inhibitors ("SRS prior"), SRS within 1 month of PD-1 pathway inhibitors ("SRS concurrent"), and SRS more than 1 month after PD-1 pathway inhibitors ("SRS after"). Cox regression models were used to assess the association of SRS timing with LC, DBF and OS. A marginal approach was used to account for intra-patient correlation in analyzing LC and DBF.[30] Multivariate analysis was used to adjust for potential confounders individually, in particular, Lung-molGPA (3-4 vs. 1.0-2.5), age ($\leq$ 65 vs. >65), KPS (90-100 vs. 60-80) and SRS dose (<18 vs. $\geq$18 Gy) were analyzed as binary covariates. All p-values were based on the score test for a two-sided hypothesis, adjusted by the robust sandwich estimator for clustered data analysis. Statistical computation was performed using SAS 9.4 (SAS Inst Inc, Cary, NC).

Results

Patient characteristics

We identified 37 NSCLC patients treated with PD-1 or PD-L1 inhibitors and SRS for brain metastases between 2012 and 2017. Baseline patient and treatment characteristics are listed in Table 1. The median age at diagnosis of brain metastases was 63 years (range: 42 – 84). At the time of brain metastasis diagnosis, a majority had a KPS of 90 or 100 (n=24, 64.9%). Two patients had *EGFR* mutations; no patient had an *ALK* rearrangement. The median Lung-molGPA was 2.0 (range: 1.0 – 4.0). All patients received prior chemotherapy. Only one patient had PD-L1 levels available (PD-L1 membranous staining on 50% of tumoral cells on a resected small bowel metastasis).

Patients received a median of 7 total doses of PD-1 pathway inhibitors (range: 1 - 91 doses). Thirty-one patients (83.8%) received nivolumab, four patients received atezolizumab (10.4%), and two patients received pembrolizumab (5.4%). Twenty-four patients (64.9%) were treated with SRS prior to PD-1 or PD-L1 inhibitors, 8 patients (21.6%) were treated with concurrent SRS and PD-1 or PD-L1 inhibitors, and 5 (23.5%) patients were treated with SRS after PD-1 or PD-L1 inhibitors.

Treatment characteristics

Lesion characteristics are summarized in Table 2. Among 37 patients in this cohort, a total of 85 lesions were treated with SRS. Twenty-three (62.2%) patients received SRS to two or more brain metastases. Most lesions were treated with photon radiation (n=70, 82.4%). The median radiation dose was 18 Gy in a single fraction (range: 15 – 25). Eight lesions were treated following surgical resection. The remaining non-resected lesions (n=77) had a median axial diameter of 6 mm (range: 2 – 26). SRS was concurrent with PD-1 pathway inhibitor administration in 21 lesions (24.7%). Fifty-one (60%) lesions were treated with SRS at a median of 7.0 months (range: 1.2 – 33.4 months) prior to PD-1 pathway administration. Thirteen lesions (15.3%) lesions were treated with SRS a median of 5.5 months (range: 2.8 – 16.3 months) after PD-1 pathway inhibitor administration.

Overall survival

At the time of analysis, 20 patients (54.1%) had died and 17 patients were alive. The median follow-up from initial SRS was 14.3 months (range: 5.1 – 53.1) among the patients still alive. The median OS from initial SRS was 17.6 months. OS was significantly improved among patients treated with concurrent SRS and PD-1 pathway inhibitors compared to SRS prior or after PD-1 pathway inhibitors, respectively (1-year OS 87.3% vs. 70.0% vs. 0%, p=0.008). The OS difference remains significant after controlling for Lung-molGPA, age, KPS or systemic AE $\geq$ grade 2 in multivariate analysis (Figure 1). OS was significantly longer among patients treated with SRS concurrent with or prior to PD-1 pathway inhibitors compared to those treated with SRS afterwards (p = 0.002). Lung-molGPA of 3-4 was associated with significantly improved OS compared to lower Lung-molGPA of 1.0-2.5 (p= 0.041). Younger age ($\leq$ 65 years old) at the time of brain metastasis diagnosis showed a trend towards improved OS, although the associations of age (p=0.107) was not strictly significant.

Local control

LC was favorable among lesions treated with SRS concurrent or after PD-1 pathway inhibitors compared to prior to PD-1 inhibitors (1-year LC 100% vs. 72.3%, p=0.016). All lesions treated with SRS after PD-1 pathway inhibitors had limited local control follow-up of 2-8 months. LC was significantly longer when lesions were treated with SRS concurrent with or prior to PD-1 pathway inhibitors compared to those treated with SRS afterwards (p= 0.016). The LC difference was confined to intact lesions with axial diameter at least 5mm (1-year LC 100% vs. 64.9%, p=0.012), while all smaller lesions had local control. LC was not associated with SRS dose (p=0.636).

Distant brain failure

The one-year rate of DBF among all courses of SRS was 65.8%. The one-year rate of DBF was 38.5% among lesions treated with concurrent SRS and PD-1 pathway inhibitors compared to 65.8% among lesions treated with SRS prior to PD-1 pathway inhibitors and 100% among lesions treated with SRS after PD-1 pathway inhibitors. The timing of PD-1

pathway inhibitors relative to SRS was significantly associated with DBF (p=0.042). DBF was not associated with prior WBRT (p=0.813).

Treatment-related toxicity

Table 3 summarizes SRS-associated toxicity among patients treated with SRS and PD-1 pathway inhibitors with toxicity categorized according to timing of SRS relative to PD-1 pathway inhibitors. There were too few events to analyze statistically. No patient experienced greater than grade 3 toxicity.

Eleven patients (29.7%) received steroid prophylaxis prior to SRS. Among the four patients (10.8%) requiring steroids for SRS-associated toxicity, two patients were treated with SRS concurrent to PD-1 pathway inhibitors: one patient developed grade 1 headache and another patient developed grade 3 headache, grade 3 ataxia, and grade 2 vision impairment. Two patients were treated with SRS prior to PD-1 pathway inhibitors: one patient developed grade 2 motor impairment and grade 1 headache and a second patient developed grade 1 seizure secondary to RN/TRIC.

A total of three lesions had RN/TRIC at a median of 4.8 months (range: 2.3 – 23.4) following SRS: two lesions treated with SRS prior to PD-1 pathway inhibition and one lesion treated with SRS concurrent to PD-1 pathway inhibition. All lesions met RN/TRIC criteria on imaging. No patient underwent surgical resection for RN/TRIC, and there were no pathologically confirmed cases of RN/TRIC.

Figure 2 shows RN/TRIC in a 72-year old male treated with SRS (18 Gy in one fraction) 23 days prior to starting nivolumab. Follow-up scans showed increase in lesion size, T1 contrast enhancement, and T2 FLAIR detected seven weeks post-SRS and reaching a peak in approximately six months post-SRS before gradually resolving without intervention. The patient was asymptomatic. He remained on nivolumab for 40 cycles until disease progression 19 months from drug initiation.

Discussion

To our knowledge, this is the first analysis demonstrating favorable rates of locoregional disease control and overall survival among patients treated with concurrent SRS and PD-1 pathway inhibitors. Strategies for local control of NSCLC brain metastases have historically included surgical resection or radiation therapy, including whole brain radiation therapy (WBRT) and SRS. WBRT causes neurocognitive toxicity including memory impairment that may reduce quality of life after treatment. SRS delivers a large dose of radiation to a precisely defined target, limiting the radiation dose to normal tissue. SRS is generally preferred for patients presenting with a limited number of brain metastases though patients have an elevated risk of developing new brain metastases and increased need for salvage treatment.[31-33] Reduced risk of DBF with concurrent PD-1 or PD-L1 inhibition offers a way to minimize the risk of DBF that is a primary disadvantage of treatment with SRS relative to WBRT. Decreased DBF may be due to improved control of micrometastatic disease already in the brain parenchyma at the time of SRS but too small to be observed on imaging. Alternatively, improved systemic disease control with PD-1 or PD-L1 inhibitors may reduce reseeding of the brain parenchyma.

Clinical evidence supports the hypothesis that radiation therapy may potentiate the clinical activity of CPIs. A secondary analysis of a phase I study (KEYNOTE-001) of pembrolizumab included 98 NSCLC patients of whom 42 received prior radiation. Patients who received prior radiation had improved progression free survival (4.4 months versus 2.1 months) and overall survival (10.7 months versus 5.3 months).[34] Radiation of tumors can prime the immune system through several mechanisms. Irradiated tumor cells release damage associated molecular patterns that are recognized by immune cells. Radiation increases the number of tumor-associated markers, providing unique antigens that support immune recognition of the tumor.[23,28]

The significant association between locoregional disease control and overall survival with timing of SRS relative to PD-1 pathway inhibition is consistent with pre-clinical evidence that the timing of radiation relative to CPIs is important.[25] Dovedi et al demonstrated that concurrent rather than sequential radiation and CPI maximized clinical efficacy.[35] Delay

of PD-1 pathway inhibitors until after the completion of radiation resulted in diminished clinical efficacy.[36]

We observed excellent rates of local control in our study, particularly for smaller lesions. All lesions less than 5 mm demonstrated local control one year following SRS (100% vs. 64.9%, p=0.012). This finding is consistent with other recent reviews of SRS for NSCLC brain metastases which have reported a 1-year local control rate between 77% and 83.[37,38] Size of irradiated lesion is a known risk factor for recurrence after SRS, with larger lesions more likely to recur and smaller lesions more likely to demonstrate local control.[39]

The dose-limiting toxicity of SRS is radiation necrosis or treatment related imaging changes (RN/TRIC), inflammation or injury of the brain tissue adjacent to the tumor.[40] Radiation necrosis can negatively impact quality of life. Patients may experience headache, nausea, seizures or focal neurologic deficits. Steroids are often required for management of RN/TRIC which may reduce the efficacy of CPIs.[41] There are a number of known risk factor for radiation necrosis, including volume irradiated, dose, select systemic therapies, and receipt of previous radiation such as WBRT.[42-44] A full understanding of the impact of PD-1 pathway inhibition on radiation-associated toxicity will become increasingly important, as more patients are treated with PD-1 pathway inhibitors in the first-line setting.

We found low rates of radiation-associated toxicity among patients in our cohort, regardless of the timing of SRS relative to PD-1 pathway inhibitors. We observed three cases of RN/TRIC, including one patient treated with concurrent SRS and PD-1 pathway inhibition. Consistent with our findings, an analysis of 163 NSCLC patients found no increased risk of adverse events (including radiation necrosis) among the 50 patients treated with PD-1 pathway inhibitors and cranial irradiation, including SRS, partial brain irradiation, and WBRT. This was the case regardless of the timing of PD-1 pathway inhibitors relative to SRS.[45]

However, several analyses have observed an increased risk of RN/TRIC among patients treated with SRS and CPIs.[46,47] A retrospective of analysis of 480 patients treated with SRS and CPIs found an increased risk of symptomatic radiation necrosis among patients treated with CPIs. The analysis included lung, melanoma, and renal cell carcinoma patients and both PD-1, PD-L1, and CTLA-4 inhibitors. The association was particularly strong in melanoma patients who received the CTLA-4 inhibitor ipilimumab (HR, 4.70; 95% CI, 1.36-16.19; P = .01). Case reports have also examined instances of RN/TRIC among patients treated with CPIs and SRS. Notably, this enlargement was sometimes temporally related to PD-1 pathway inhibition (such as regression after SRS with transient enlargement after initiation of PD-1 pathway inhibitors). This finding is suggestive of an immune therapy-driven inflammatory reaction.[22,48,49]

Analogous concerns that CPIs may increase radiation-associated toxicity for other disease sites have not come to fruition. In particular, there was concern that the addition of CPIs may increase the risk of pneumonitis among patients treated with thoracic radiotherapy. A retrospective study by Hwang et al found no increase risk of immune-related adverse events, all grade pneumonitis, or grade 2 or greater pneumonitis among patients treated with thoracic radiotherapy and PD-1 pathway inhibitors compared to patients treated with thoracic radiotherapy alone.[50] These findings are consistent with the results of the PACIFIC trial, which randomized 713 NSCLC patients to receive durvalumab or placebo after definitive chemoradiation. The was no significant difference in toxicity between the two groups.[51] KEYNOTE-001, a Phase I trial which included 98 patients treated with pembrolizumab, found no increased risk of pneumonitis among the 24 patients who received prior thoracic radiotherapy compared with the 73 patients who had not previously received prior thoracic radiotherapy.[34] Despite these findings, the risk for increased toxicity among patients treated with a combination of CPIs and radiation therapy remains a significant concern. CPIs have long half-lives that make consideration of a wash-out period between CPI administration and RT infeasible. The half-lives of pembrolizumab, atezolizumab, nivolumab, and durvalumab range from 17 days (durvalumab) to 27 days (atezolizumab).

There are several limitations to this study. Although this is the largest series to date investigating of the outcomes of NSCLC brain metastases treated with PD-1 pathway inhibitors and SRS, the analysis was retrospective, single-institution, and still limited by patient numbers. Given the non-randomized assignment of SRS with respect to timing of PD-1 pathway inhibitors, this data is subjecting to confounding. For example, patients treated with SRS after PD-1 pathway inhibitors may have naturally evolved more aggressive disease that is no longer responsive to PD-1 pathway inhibitors and inherently with limited survival regardless of further local intracranial intervention. Follow-up for the group treated with SRS after PD-1 pathway inhibitors was also shorter than other groups. Patients received PD-1 pathway inhibitors in different lines of therapy, although no patients received PD-1 pathway inhibitors in the first-line setting. Most patients in the series were treated with PD-1 inhibitors, while only four patients received PD-L1 inhibitors, thus limiting our ability to report results separately for the PD-L1 inhibitor treated cohort. The findings in this study generate hypotheses that require evaluation in larger cohorts in a prospective setting.

In summary, our findings suggest improved locoregional control and overall survival among patients treated with concurrent SRS and PD-1 pathway inhibitors, consistent with preclinical evidence suggesting that concurrent irradiation may potentiate the activity of CPIs. The combination of SRS and PD-1 pathway inhibitors is well tolerated with an acceptable safety profile.

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Table 1. Patient characteristics (n=37)

	Number	%
Female sex	24	64.9
Male sex	13	35.1
Age at BM diagnosis, median (range)	63 years (42 – 84)	
No. of BM treated per patient, median (range)	2 (1 - 7)	
Type of PD-1 pathway inhibitor		
Nivolumab	31	83.8
Pembrolizumab	2	5.4
Atezolizumab	4	10.8
No. of doses, median (range)	7 (1 – 43)	
SRS timing		
SRS prior	24	64.9
SRS concurrent	8	21.6
SRS after	5	13.5
No. with prior chemotherapy	37	100
[1]Lung-molGPA, median (range)	2.0 (1.0 – 4.0)	
Karnofsky performance status at BM diagnosis		
90 – 100	24	64.9
70 – 80	12	32.4
60	1	2.7
Receipt of WBRT	14	37.8

BM, brain metastasis; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy

1. Lung-molGPA is the updated graded prognostic assessment by Sperduto et al. for patients with newly diagnosed non-small cell lung cancer brain metastases. It incorporates EGFR and ALK status in addition to performance status, age, extracranial disease status, and number of brain metastases at the time of initial brain metastasis diagnosis.[11]

Table 2. Brain metastases and radiation therapy characteristics (n=85)

	Number	%
[1]Axial diameter, median (range)	6 mm (2 - 26)	
[2]GTV, median (range)	0.2 cm^3 (0.01 – 5.9)	
Intact lesions	77	90.6
Resected lesions	8	9.4
Timing of SRS		
SRS prior	51	60.0
SRS concurrent	21	24.7
SRS after	13	15.3
PD-1 pathway inhibitor-SRS interval		
SRS prior, median (range)	7.0 mos (1.2 – 33.4)	
SRS after, median (range)	5.5 mos (2.8 – 16.3)	
Dose (Gy)/number of fractions		
25/5	1	1.2
22/2	2	2.4
21/3	3	3.5
20/2	1	1.2
18/1	61	71.8
17/1	14	16.5
16/1	1	1.2
15/1	2	2.4
Location		
Cerebellum	14	16.5
Frontal lobe	32	37.6
Occipital lobe	14	16.5
Parietal lobe	17	20.0
Temporal lobe	6	7.1
Thalamus	1	1.2
Brainstem	1	1.2

SRS, stereotactic radiosurgery; GTV, gross tumor volume; Mos: months; Gy, Gray

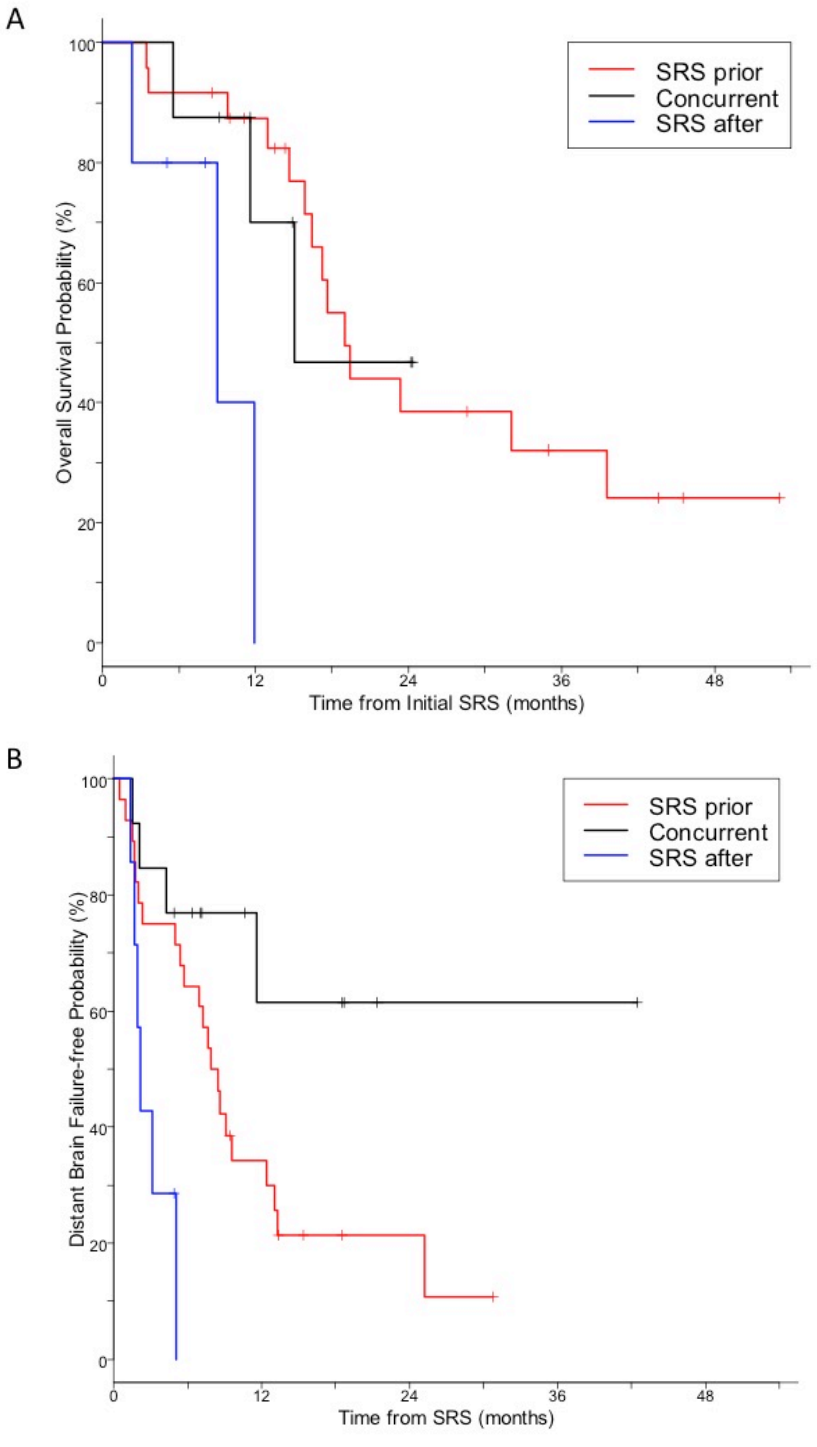
1. Axial diameter of the 77 lesions not resected prior to SRS
2. GTV available for 83/85 lesions

Table 3. Radiation-associated toxicities*

	Grade 1			Grade 2			Grade 3		
	SRS prior	SRS concurrent	SRS after	SRS prior	SRS concurrent	SRS after	SRS prior	SRS concurrent	SRS after
Aphasia	1 (4.2%)	0	0	0	0	0	0	0	0
Anorexia	0	0	0	0	1 (12.5%)	0	0	0	0
Ataxia	0	0	0	0	0	0	1 (4.2%)	0	0
Concentration impairment	2 (8.3%)	1 (12.5%)	1 (20%)	0	0	0	0	0	0
Fatigue	3 (12.5%)	0	0	2 (8.3%)	1 (12.5%)	1 (20%)	0	0	0
Fever	0	0	0	1 (4.2%)	0	0	0	0	0
Headache	4 (16.7%)	2 (25%)	0	0	0	0	1 (4.2%)	0	0
Motor impairment	0	0	0	1 (4.2%)	0	0	0	0	0
Nausea	1 (4.2%)	0	0	1 (4.2%)	0	0	0	0	0
Paresthesia	2 (8.3%)	0	0	0	0	0	0	0	0
Seizure	2 (8.3%)	1 (12.5%)	0	0	0	0	0	0	0
Vision impairment	1 (4.2%)	0	0	1 (4.2%)	0	0	0	0	0

*No grade 4 or grade 5 toxicities were observed

Figure 1. **Overall survival, local control, and distant brain failure based on timing of SRS relative to PD-1 pathway inhibitors.** A/B/C. Timing was significantly associated with rates overall survival (p=0.008), distant brain failure (p=0.042), and local control (p=0.016).



C

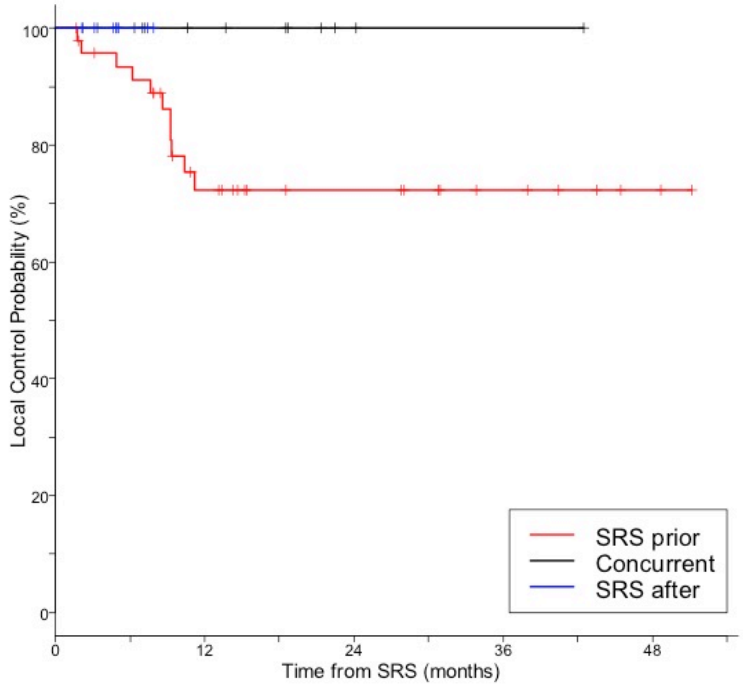

100
80
60
40
20
0
Local Control Probability (%)
0
12
24
36
48
Time from SRS (months)
SRS prior
Concurrent
SRS after

Figure 2. **Asymptomatic radiation necrosis/treatment related imaging changes in a patient treated with SRS and nivolumab.** The patient was treated with SRS 23 days prior to initiation of nivolumab. The lesion increased in size, T1 contrast enhancement, and T2 FLAIR hyperintensity, peaking six months after SRS and resolving without intervention. The patient remained on nivolumab for 40 cycles until disease progression.