Clinical Outcomes and Toxicity After Combination Stereotactic Radiosurgery and Ipilimumab in Patients With Melanoma Brain Metastases

Title Page

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Student Name: Kevin Diao, BA

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Mentor Name(s) and Affiliations: Eric L. Chang, MD, Dept of Radiation Oncology, University of Southern California; Anthony V. D'Amico, MD, PhD, Dept of Radiation Oncology, Brigham and Women's Hospital

Collaborators, with Affiliations: Shelly X. Bian, MD, Dept of Radiation Oncology, University of Southern California; David M. Routman, MD, Dept of Radiation Oncology, University of Southern California; Cheng Yu, PhD, Dept of Radiation Oncology, University of Southern California; Jason C. Ye, MD, Dept of Radiation Oncology, University of Southern California; Naveed A. Wagle, MD, Dept of Clinical Neurology, University of Southern California; Michael K. Wong, MD, PhD, Dept of Medical Oncology, University of Southern California; Gabriel Zada, MD, Dept of Neurological Surgery, University of Southern California

Abstract

Title: Clinical Outcomes and Toxicity after Combination Stereotactic Radiosurgery and Ipilimumab in Patients with Melanoma Brain Metastases

Kevin Diao, Shelly X. Bian, David M. Routman, Cheng Yu, Jason C. Ye, Naveed A. Wagle, Michael K. Wong, Gabriel Zada, Eric L. Chang

Purpose: There is evidence that the combination of ipilimumab and stereotactic radiosurgery (SRS) for brain metastases improves outcomes. We investigated clinical outcomes, radiation toxicity, and impact of ipilimumab timing in patients treated with SRS for melanoma brain metastases.

Methods: We retrospectively identified 91 patients treated with SRS at our institution for melanoma brain metastases from 2006-2015. Concurrent ipilimumab administration was defined as within +/- 4 weeks of SRS procedure. Acute and late toxicities were graded with CTCAE v4.03. Overall survival (OS), local failure, distant brain failure, and failure-free survival were analyzed with the Kaplan-Meier method. OS was analyzed with Cox regression.

Results: Twenty-three patients received ipilimumab concurrent with SRS, 28 patients non-concurrently, and 40 patients did not receive ipilimumab. The median age was 62 years and 91% had KPS ≥80. The median follow-up time was 7.4 months. Patients who received ipilimumab had a median OS of 15.1 months compared to 7.8 months in patients who did not (p=0.02). In multivariate analysis, ipilimumab (p=0.05), diagnosis-specific graded prognostic assessment (p=0.02), and number of brain metastases (p=0.05) were associated with OS. There were no differences in intracranial control by ipilimumab administration or timing. Most radiation necrosis events occurred in patients who received ipilimumab.

Conclusions: Patients who received ipilimumab had improved OS even after adjusting for prognostic factors. Ipilimumab did not appear to increase risk for acute toxicity. The majority of radiation necrosis events, however, occurred in patients who received ipilimumab. Our results support the continued use of SRS and ipilimumab as clinically appropriate.

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Glossary of Abbreviations

AJCC; American Joint Committee on Cancer

BBB; Blood brain barrier

CI; Confidence interval

CTCAE; Common Terminology Criteria for Adverse Events

CTLA-4; Cytotoxic T-lymphocyte antigen-4

DBF; Distant brain failure

DS-GPA; Diagnosis-specific graded prognostic assessment

FFS; Failure-free survival

HR; Hazard ratio

IQR; Interquartile range

KPS; Karnofsky Performance Scale

LF; Local failure

MRI; Magnetic resonance imaging

OS; Overall survival

RN; Radiation necrosis

SRS; Stereotactic radiosurgery

USC; University of Southern California

Section 1: Introduction

There are 76,000 cases of melanoma diagnosed and 9,000 deaths due to melanoma each year in the United States. The incidence of melanoma has tripled over the past 30 years and it is currently the second most common invasive malignancy in people under 39 years old.[1] In addition, brain metastases are common in melanoma, occurring in up to 50% of patients having advanced disease. Melanoma brain metastases carry a particularly poor prognosis with a historical median survival of 2-5 months.[2–4]

Recently, however, the advent of targeted therapy agents has shown promise in the treatment of patients with metastatic melanoma. Ipilimumab, a human monoclonal antibody, blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) and has been demonstrated to improve overall survival (OS) in two large randomized trials.[5,6] Although ipilimumab is not able to cross an intact blood brain barrier (BBB), there is evidence that ipilimumab is either able to penetrate tumors at leaky BBB sites or activates cytotoxic T lymphocytes which in turn infiltrate the tumor environment and induce anti-tumor acivity.[7–10] In addition, some postulate that radiotherapy can induce an abscopal effect that enhances the immunologic effectiveness of ipilimumab.[11–14] Several retrospective studies have now found an OS and/or intracranial control benefit of ipilimumab when used in combination with stereotactic radiosurgery (SRS) for treatment of melanoma brain metastases.[15–19]

Despite this, the effect of combination treatment on radiation toxicity – including acute events such as cerebral hemorrhage and late events such as radiation necrosis (RN) – remains ill-defined. The impact of the timing of administration of ipilimumab relative to SRS on toxicity, cancer control outcomes, and survival is also unclear. In the present study, we aim to describe clinical outcomes and radiation toxicity in patients treated with combination ipilimumab and SRS compared to patients treated with SRS alone. We explore the effect of ipilimumab timing relative to SRS on the above outcomes and identify associated prognostic factors.

Section 2: Student Role

I, Kevin Diao, worked with Dr. Eric Chang to conceptualize the research project idea. I performed a relevant literature search and described the methodology that would be used to execute the research project. I created the database and requested and collected data from paper charts and electronic medical records. I maintained and curated the database. I was responsible

for formal statistical analysis of the data. I created visualization for the project, including tables and figures. I wrote the original draft of the manuscript, coordinated communication between collaborators for comments, and revised the draft. I submitted an abstract, which was accepted to a nationally recognized radiation oncology conference, and submitted the manuscript as first author and corresponding author to a peer-reviewed medical journal of choice and responded to their request for revision.

Detailed Author Contributions:

Conceptualization, K. Diao, E. Chang; **Methodology**, K. Diao, S. Bian, D. Routman, E. Chang; **Investigation**, K. Diao, S. Bian; **Data Curation**, K. Diao; **Formal Analysis**, K. Diao; **Resources**, C. Yu, E. Chang; **Writing – Original Draft**, K. Diao, S. Bian, D. Routman, E. Chang; **Writing – Review & Editing**, K. Diao, S. Bian, D. Routman, C. Yu, J. Ye, N. Wagle, M. Wong, G. Zada, E. Chang; **Visualization**, K. Diao; **Supervision**, J. Ye, N. Wagle, M. Wong, G. Zada, E. Chang; **Funding Acquisition**, E. Chang

Section 3: Methods

This retrospective cohort study was approved by the University of Southern California (USC) Keck School of Medicine Institutional Review Board. We identified 107 consecutive patients who were treated with SRS at our institution for melanoma brain metastases between 2006 and 2015. Patients who did not have clinical follow-up were excluded. Ipilimumab, if administered, was at a dose of either 3 mg/kg or 10 mg/kg every 3 weeks for up to 4 cycles with the option for additional maintenance cycles. Concurrent ipilimumab administration was defined as within +/- 4 weeks of SRS procedure. Our selection of this definition was based on a combination of factors, including the 14.7 day half-life of ipilimumab, existing studies that examine timing of ipilimumab, size of treatment groups for statistical analysis, and our goal of investigating the interaction between ipilimumab and SRS administered together within a short time frame.[18,20–22]

Patient information was obtained from institutional electronic medical records. All cancer staging was performed according to the American Joint Committee on Cancer (AJCC) 7th edition guidelines.[23] The diagnosis-specific graded prognostic assessment (DS-GPA) score for melanoma, which takes into account Karnofsky performance status (KPS) and number of brain

metastases, was calculated based on the study by Sperduto et al.[24] Acute and late radiation toxicities were defined as events that occurred ≤90 days or >90 days after SRS treatment, respectively, that were either attributable to treatment or unexplained. A diagnosis of RN required pathologic confirmation. Both acute and late toxicities were graded with the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

All patients received SRS using the Gamma Knife® Perfexion™ Unit (Elekta AB, Stockholm, Sweden) given by a team consisting of a radiation oncologist, a neurosurgeon, and a medical physicist. A stereotactic head frame was attached to the skull of the patient under conscious sedation by an anesthesiologist. Contrast-enhanced magnetic resonance imaging (MRI) of the brain was performed, lesions were identified and contoured on Leksell GammaPlan treatment planning software, and radiation was delivered the same day. Radiation doses were based on factors including tumor size, shape, and location as described in RTOG 9005.[25] After SRS, our institutional practice was to follow patients clinically and with MRIs every 2 – 3 months.

Baseline patient and treatment characteristics were compared with the Kruskal-Wallis test by ranks and Pearson chi-square test. OS, local failure (LF), distant brain failure (DBF), and failure-free survival (FFS) were calculated from the date of first SRS treatment and analyzed with the Kaplan-Meier method with significance testing by the Wilcoxon procedure and log-rank test. LF was analyzed per patient as the date of first in-field tumor progression. DBF was analyzed per patient as the date of first new distant brain metastasis. FFS was defined as the first occurrence of LF, DBF, or death. Censoring occurred at the date of last clinical follow-up in the absence of any of the above events. Univariate and multivariate analysis were performed using the Cox proportional hazards model. Clinically relevant risk factors were entered into univariate analysis and significant variables were further entered into multivariate analysis. Acute toxicities were analyzed per SRS procedure and late toxicities were analyzed per patient with statistical comparison by Fisher's exact test. Significance was defined as $p \leq 0.05$. Statistical calculations were performed in JMP Pro (version 13; SAS Institute, Cary, NC).

Section 4: Results

Patient and Treatment Characteristics

A total of 91 patients were included in this analysis, 51 (56%) of whom received ipilimumab and 40 (44%) of whom did not (**Table 1**). Among all patients, the median age was 62 years (range, 27-85 years), 29 (32%) were female, and 82 (91%) had KPS ≥80. The median follow-up time was 7.4 months. Of patients who received ipilimumab, 36 (77%) were treated at a dose of 3 mg/kg and 11 (23%) were treated at 10 mg/kg. The median cycles of ipilimumab administered was 4 (range, 1-6). During initial SRS, 256 brain metastases with a median tumor volume of 0.27 cm^3 (range, 0.01-30.33 cm^3) were treated to a median marginal dose of 20 Gy (range, 12-22 Gy). A total of 155 SRS treatments were given, with 46 (51%) patients receiving 1 SRS treatment and 37 (41%) patients receiving 2 SRS treatments.

Twenty-three patients received ipilimumab concurrent with SRS and 28 did not. Of the patients who received ipilimumab non-concurrently, 23 (82%) completed therapy prior to initial SRS whereas 5 (18%) began therapy after SRS. Patients who received ipilimumab prior to SRS completed therapy at a median 4.5 months prior to SRS (range, 1.1-48.4 months). Patients who received ipilimumab following SRS started therapy at a median 2.6 months after SRS (range, 1.1-11.9 months).

Overall, patient and treatment characteristics, including age, sex, KPS, DS-GPA, extracranial metastases, neurologic status, number of brain metastases treated, and tumor volume were similar between patients who did not receive ipilimumab, received ipilimumab concurrently, and received ipilimumab non-concurrently. However, patients who received non-concurrent ipilimumab received prior chemotherapy at a higher rate (39% vs. 13%) and more often received ipilimumab at a dose of 10 mg/kg (35% vs. 10%) compared to concurrent ipilimumab patients. In addition, patients who did not receive ipilimumab were treated with SRS at an earlier median year (2009) compared to those who received concurrent ipilimumab (2011) and non-concurrent ipilimumab (2010). **Figure 1** depicts the distribution of patients in each treatment group by calendar year of SRS treatment.

Overall Survival

The median OS among all patients was 10.6 months. Patients who received ipilimumab had a median OS of 15.1 months compared to 7.8 months in patients who did not receive ipilimumab (p=0.02). The median survival of patients treated with SRS between 2006-2010 was 11.7 months compared to 10.0 months for patients treated from 2011-2015 (p=0.53). Patients

who received non-concurrent ipilimumab had the most favorable OS (median 18.7 months), followed by concurrent ipilimumab (median 11.8 months) and no ipilimumab (median 7.8 months) (p=0.05). At 1 year, OS was 63%, 50%, and 28%, respectively, in patients who received non-concurrent ipilimumab, concurrent ipilimumab, and no ipilimumab (p=0.02) (**Figure 2A**).

On univariate analysis of OS, significant protective factors included non-concurrent ipilimumab administration (HR, 0.55; 95% CI, 0.30-0.95; p=0.03) and higher DS-GPA score (HR, 0.60; 95% CI, 0.46-0.78; p<0.001) (**Table 2**). KPS ≥80 was nearly significant (HR, 0.72; 95% CI, 0.45-1.17; p=0.06). Deleterious factors included 2-4 brain metastases (HR, 2.35; 95% CI, 1.35-4.17; p=0.003) or 5+ brain metastases (HR, 2.46; 95% CI, 1.27-4.69; p=0.009) compared to 1 brain metastasis. In multivariate analysis, non-concurrent ipilimumab administration (HR, 0.50; 95% CI, 0.27-0.87; p=0.01), DS-GPA (HR, 0.67; 95% CI, 0.49-0.92; p=0.02), and 2-4 brain metastases treated (HR, 1.84; 95% CI, 1.01-3.42; p=0.05) all remained significantly associated with OS. Any ipilimumab was significant for improved OS (p=0.05).

Cancer Control Outcomes

The 1-year freedom from any LF was 45%, 58%, and 70%, respectively, in patients receiving no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab (p=0.35) (**Figure 2B**). The 1-year freedom from DBF was 23%, 23%, and 45%, respectively, in patients receiving no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab (p=0.33) (**Figure 2C**). The 1-year FFS was 10%, 9%, and 29%, respectively, in patients receiving no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab (p=0.26) (**Figure 2D**). Furthermore, there were no significant differences in pairwise testing between any of the treatment groups for LF, DBF, or FFS.

Acute and Late Toxicities

Acute toxicities were analyzed per SRS procedure performed (**Table 3**). Out of a total of 155 courses of SRS, 59 were given in patients who did not receive ipilimumab, 23 were given concurrently with ipilimumab, and 73 were given non-concurrently with ipilimumab. Overall, 25 (16%) SRS treatments resulted in an acute toxicity. The incidence of acute toxicity was 14%, 26%, and 15%, respectively, following no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab SRS procedures (p=0.36). There was no significant difference in the

distribution of acute toxicity grades among the treatment groups (p=0.51). There were 4 total grade 3-4 events and no grade 5 events. Grade 3-4 events included 2 cases of cerebral edema and 2 cases of cerebral hemorrhage. Other events included headache (10), nausea (5), seizure (4), gait disturbance (4), paresis (2), and cerebral edema (1).

Late toxicities were analyzed per patient (**Table 4**). Out of a total of 91 patients, 12 (13%) experienced a late toxicity. The incidence of late toxicity was 13%, 17%, and 11%, respectively, in patients receiving no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab (p=0.79). There were 5 total grade 3-4 events and no grade 5 events. There was no significant difference in the distribution of late toxicity grades among the treatment groups (p=0.29). However, 4 out of 5 grade 3-4 events were in patients who received ipilimumab. The grade 3-4 events were all pathologically-confirmed cases of RN. Other late events included focal neurologic deficit (10), cognitive dysfunction (5), cerebral hemorrhage (1), and cerebrovascular accident (1).

Of the RN events, median time from SRS to event was 6.6 months (range, 3.5-42 months). Notably, the single non-ipilimumab event was associated with the longest time to event of 42 months, compared to the longest time to event of 11.4 months among ipilimumab-associated events. Among the 4 patients who developed RN and received ipilimumab, 1 received ipilimumab prior to SRS (last dose 21 months prior), 2 received ipilimumab concurrent with SRS, and 1 received ipilimumab after SRS (first dose 3 months after). All patients received ipilimumab prior to their respective RN event. The individual chronologies of SRS, ipilimumab, and RN were as follows: Patient 1: Ipilimumab at -21 months, SRS at time 0, RN at +3.5 months. Patient 2: Concurrent ipilimumab and SRS at time 0, RN at +4.5 months. Patient 3: Concurrent ipilimumab and SRS at time 0, RN at +11.4 months. Patient 4: SRS at time 0, ipilimumab at +3 months, RN at +6.6 months. Patient 5: SRS at time 0, RN at +42 months.

Section 5: Discussion, Limitations, Conclusions, and Suggestions for Future Work

Discussion

The combination of ipilimumab and SRS has shown promise for improving cancer outcomes in patients with melanoma brain metastases in multiple retrospective studies.[15–19] However, owing to the small number of patients receiving this combination of treatments who have been reported on to date, additional data is needed to elucidate the effect of treatment on

clinical outcomes and radiation toxicity, as well as the impact that timing of ipilimumab administration relative to SRS has on these measures.[26] In the current study, to our knowledge, we describe results from our institutional experience with the largest cohort of patients with melanoma brain metastases treated with SRS and ipilimumab to date (n=51).

With a median follow-up of 7.4 months, we found that patients who received ipilimumab had a median OS of 15.1 months versus 7.8 months for control patients who did not receive ipilimumab. The OS of control patients observed in our cohort correlates closely with historical data presented by Sperduto et al, in which patients with melanoma brain metastases who received SRS had a median OS of 7.26 months.[24] The increased OS observed in patients receiving ipilimumab supports prior studies with similar findings.[15–19] Although patients who did not receive ipilimumab were treated with SRS in earlier years, we did not find a significant difference in survival based on SRS treatment year. In addition, the latest patient in the control group was treated with SRS in 2011, the same year as FDA approval of ipilimumab for metastatic melanoma. Prior to 2011, ipilimumab was available primarily through clinical trials, for which brain metastases were frequently an exclusion criteria. As KPS and DS-GPA did not differ significantly between treatment groups, it is most likely that patients in the control group did not receive ipilimumab due to restricted access and/or varying practice patterns at the time. Furthermore, the observed improved survival in our study persisted after controlling for DS-GPA score and number of brain metastases in multivariate analysis, suggesting that the survival differences were truly due to treatment effect as opposed to pre-treatment selection bias.

We found that patients who had ipilimumab delivered non-concurrently with SRS, i.e. either >4 weeks before or after SRS, had the most favorable survival outcomes. On the other hand, there were significant baseline differences between the non-concurrent and concurrent ipilimumab groups. Patients who received ipilimumab non-concurrently more frequently received prior chemotherapy (39% vs. 13%) and a higher dose of ipilimumab (35% versus 10% received 10 mg/kg). In addition, we hypothesize that patients who received ipilimumab non-concurrently may have had less aggressive disease, as the majority of them (82%) received ipilimumab prior to requiring SRS, 56% of non-concurrent ipilimumab patients versus only 31% of concurrent ipilimumab patients were initially diagnosed with stage I-II disease, and non-concurrent ipilimumab patients had the longest time from diagnosis of primary cancer to brain metastasis development. As ipilimumab is currently FDA-approved at a dosage of 10 mg/kg only

for adjuvant melanoma treatment, more patients who received ipilimumab non-concurrently were likely treated with the higher dose of 10 mg/kg as adjuvant therapy given their less aggressive disease and longer time to development of metastases.[27]

Although these factors may partially explain the observed differences in survival, we were not able to completely explain the differences even when controlling for these factors during analysis. Systemic disease burden among the two groups was also comparable, as evidenced by the similar rate of extracranial metastases. An additional possibility is that administering ipilimumab non-concurrently actually is associated with improved survival. Although the mechanism of interaction between ipilimumab and SRS continues to be elucidated, studies have found that CTLA4 blockade directly activates CD4+ and CD8+ T cells, while reduction of tumor burden following radiotherapy is associated with T-cell response and is greatly amplified by immunotherapy.[28,29] A study published by Twyman-Saint Victor et. al. found that anti-CTLA4 antibodies such as ipilimumab promote expansion of T cells whereas radiotherapy may help shape the T-cell receptor repertoire of these clonal expansions.[30] Based on a model of radiotherapy shaping T-cell receptors following clonal expansion with ipilimumab, it is conceivable that ipilimumab requires time to develop and "prime" the immune system for a greater response to subsequent radiotherapy. Supporting this hypothesis is a recent meta-analysis finding that the median onset of immune-related adverse events following initiation of ipilimumab was 10 weeks (IQR, 6-12 weeks), which was correlated to objective clinical response.[31] Despite this, the optimal timing of ipilimumab with radiotherapy remains to be determined.[32]

In our study, there were no significant differences in terms of LF, DBF, or FFS among the treatment groups. However, patients who received non-concurrent ipilimumab consistently had the most favorable numerical outcomes in all categories, though this was never statistically significant. The same possible explanatory factors that were discussed above relating to observed disparities in OS between treatment groups – including differences in therapy, aggressiveness of disease, and mechanism of action of combination ipilimumab and SRS – are applicable here as well. Nonetheless, our observation that tumor control was similar among treatment groups yet OS favored the ipilimumab groups suggests that the improved survival outcomes with ipilimumab were likely related to improvements in systemic disease control as opposed to

intracranial disease control. This finding is consistent with previous literature in which systemic disease, rather than intracranial disease, was typically the limiting survival factor.[33]

The relative risk of toxicity in patients treated with combination ipilimumab and SRS has not been well-defined in part because only a few existing studies with small sample sizes have compared combination treatment with a SRS-only control group (n=62 total among all studies), and none of these studies provided detailed toxicity reporting.[16,34–36] Recently, the results of a phase I study that enrolled 11 patients treated with SRS and ipilimumab were published, in which only 1 patient experienced grade ≥3 neurotoxicity, occurring prior to ipilimumab administration.[37] In the present study, we did not find statistically significant differences in the incidence of acute radiation toxicities following SRS procedures by ipilimumab or timing of ipilimumab. Although the rate of acute toxicities was 26% following concurrent ipilimumab SRS procedures compared to 15% and 14% in procedures with non-concurrent ipilimumab and without ipilimumab, respectively, there was only 1 grade ≥3 acute toxicity observed among concurrent SRS procedures. In general, grade ≥3 acute toxicities were rare, occurring after only 3% of SRS procedures overall.

There were no statistically significant differences in the incidence of late toxicities. Late radiation toxicities occurred in 14% and 13% of patients treated with and without ipilimumab, respectively, and severe grade ≥3 toxicities occurred in 5% of patients overall. All severe late toxicities were pathologically-confirmed RN, and 4 out of 5 of these events occurred in patients who received ipilimumab (concurrently or non-concurrently). Although this was not statistically significant, it raises concern that ipilimumab immunotherapy may increase the risk for symptomatic RN – a result that other studies have previously reported.[38,39] Furthermore, the relatively short time to onset of RN observed among patients who received ipilimumab in the present study compared to historical cohorts points to the possibility that ipilimumab may be associated with faster time to onset of RN as well.[40] However, the low incidence of toxicities and absence of fatal toxicity events in the ipilimumab groups, combined with the documented OS benefit supports the continued use of combination SRS and ipilimumab for the treatment of melanoma brain metastases as clinically appropriate.

Limitations and Suggestions for Future Work

The current study was performed as a retrospective review and thus there was likely some selection bias that occurred when patients elected to undergo various treatments. The relatively small sample size raises the possibility that the study was underpowered to detect differences in outcomes and toxicities within subgroups. Although we attempted to control for prognostic factors in multivariate analysis, there may have been baseline differences between groups that remained unaccounted for. Standardized symptom and/or quality of life assessments were not administered prospectively, making highly accurate toxicity detection and assessment difficult. We did not report on non-radiation related toxicities and were not able to definitively differentiate between RN and tumor progression except when surgical pathology was available. Larger prospective studies are needed to further investigate the safety, efficacy, and mechanisms of combination SRS and ipilimumab therapy.

Conclusions

In our institutional experience with the largest cohort of patients with brain metastases treated with SRS and ipilimumab to date, patients who received ipilimumab had an improved OS of 15.1 months compared to 7.8 months for patients who did not receive ipilimumab. Other prognostic factors for OS included DS-GPA score and number of brain metastases treated. Non-concurrent ipilimumab had the most favorable survival outcomes; however, this observation may in part be due to selection bias. Ipilimumab did not appear to significantly increase risk for acute toxicity. The majority of radiation necrosis events, however, occurred in patients who received ipilimumab. Our results support the continued use of SRS and ipilimumab for treatment of melanoma brain metastases as clinically appropriate. Larger prospective studies are needed to further investigate this topic.

Section 6: Acknowledgements

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Table 1. Patient and Treatment Characteristics

Characteristic	No Ipilimumab (n=40)	Concurrent Ipilimumab (n=23)	Non-Concurrent Ipilimumab (n=28)	*p*-value
Age, median (range)	62.5 (35-84)	62 (29-85)	59 (27-76)	0.38
Sex				0.59
Male	29 (73%)	16 (70%)	17 (61%)	
Female	11 (27%)	7 (30%)	11 (39%)	
KPS, median (range)	90 (60-100)	90 (70-100)	90 (60-100)	0.29
DS-GPA, median (range)	2 (0-4)	3 (1-4)	3 (1-4)	0.47
Stage at diagnosis of cancer				0.15
I-II	5 (25%)	5 (31%)	10 (56%)	
III-IV	15 (75%)	11 (69%)	8 (44%)	
Brain metastases diagnosed within 3 months of primary				0.72
Yes	5 (13%)	3 (13%)	2 (7%)	
No	35 (87%)	20 (87%)	26 (93%)	
Time from primary cancer to brain metastasis, in years, median (range)	3.38 (0-22.74)	1.6 (0-20.10)	7.14 (0.04-29.10)	**0.007**
Extracranial metastases				0.15
Yes	27 (68%)	20 (87%)	23 (82%)	
No	13 (32%)	3 (13%)	5 (18%)	
Neurologically symptomatic at baseline				0.71
Yes	7 (18%)	4 (17%)	7 (25%)	
No	33 (82%)	19 (83%)	21 (75%)	
Prior WBRT				0.69
Yes	3 (8%)	1 (4%)	3 (11%)	
No	36 (92%)	22 (96%)	25 (89%)	
Prior chemotherapy				**0.04**
Yes	16 (41%)	3 (13%)	11 (39%)	
No	23 (59%)	20 (87%)	17 (61%)	
Prior targeted therapy				0.15
Yes	15 (38%)	9 (39%)	17 (61%)	
No	24 (62%)	14 (61%)	11 (39%)	
Prior neurosurgery				0.60
Yes	17 (44%)	8 (35%)	9 (32%)	
No	22 (56%)	15 (65%)	19 (68%)	
BRAF therapy				0.65
Yes	4 (10%)	3 (13%)	5 (18%)	
No	36 (90%)	20 (87%)	23 (82%)	
Ipilimumab dose				**0.04**
3 mg/kg	-	19 (90%)	17 (65%)	
10 mg/kg	-	2 (10%)	9 (35%)	
Ipilimumab cycles, median (range)	-	4 (2-5)	4 (1-6)	0.81
Year treated with SRS, median (range)	2009 (2006-2011)	2011 (2008-2014)	2010 (2007-2015)	**<0.001**
2006-2010	34 (85%)	6 (26%)	16 (57%)	
2011-2015	6 (15%)	17 (74%)	12 (43%)	
Time from brain metastasis diagnosis to SRS, in days,	21 (0-285)	25 (6-154)	22 (3-1663)	0.63

median (range)				
Number of brain metastases treated, median (range)	2 (1-8)	3 (1-16)	2 (1-9)	0.49
Tumor volume, cm^3, median (range)	0.42 (0.01-21.80)	0.20 (0.01-30.33)	0.20 (0.01-10.60)	0.10

Abbreviations: DS-GPA, diagnosis-specific graded prognostic assessment; Gy, Gray; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy

Table 2. Univariate and Multivariate Analysis of Overall Survival

	Univariate		Multivariate	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age (per year)	1.00 (0.98-1.02)	0.98	-	-
Sex				
Male	1.35 (0.83-2.29)	0.23	-	-
Female	Ref.	Ref.	-	-
Group		Global p=0.10		**Global p=0.05**
No ipilimumab	Ref.	Ref.	Ref.	Ref.
Concurrent ipilimumab	0.77 (0.43-1.35)	0.37	0.65 (0.35-1.18)	0.16
Non-concurrent Ipilimumab	0.55 (0.30-0.95)	**0.03**	0.50 (0.27-0.87)	**0.01**
Ipilimumab dose				
3 mg/kg	Ref.	Ref.	-	-
10 mg/kg	0.72 (0.30-1.55)	0.41	-	-
Ipilimumab cycles (per cycle)	1.24 (0.91-1.73)	0.17	-	-
KPS				
≥80	0.72 (0.45-1.17)	0.06	-	-
<80	Ref.	Ref.	-	-
DS-GPA (per unit increase)	0.60 (0.46-0.78)	**<0.001**	0.67 (0.49-0.92)	**0.02**
Stage at diagnosis				
I-II	Ref.	Ref.	-	-
III-IV	0.89 (0.48-1.71)	0.50	-	-
Time from primary cancer to brain metastasis (per year)	0.97 (0.93-1.01)	0.10		
Extracranial metastases				
Yes	1.36 (0.78-2.50)	0.29	-	-
No	Ref.	Ref.	-	-
Year treated with SRS				
2006-2010	Ref.	Ref.	-	-
2011-2015	1.41 (0.87-2.28)	0.16	-	-
Number of brain metastases treated				
1	Ref.	Ref.	Ref.	Ref.
2-4	2.35 (1.35-4.17)	**0.003**	1.84 (1.01-3.42)	**0.05**
5+	2.46 (1.27-4.69)	**0.009**	1.39 (0.61-3.19)	0.43
Prior WBRT				
Yes	1.37 (0.57-2.81)	0.45	-	-
No	Ref.	Ref.	-	-
Prior chemotherapy				
Yes	0.78 (0.46-1.28)	0.33	-	-
No	Ref.	Ref.	-	-
Prior targeted therapy				
Yes	0.83 (0.52-1.33)	0.44	-	-
No	Ref.	Ref.	-	-
Prior neurosurgery				
Yes	1.00 (0.61-1.61)	0.99	-	-
No	Ref.	Ref.	-	-

Abbreviations: CI, confidence interval; DS-GPA, diagnosis-specific graded prognostic assessment; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy

Table 3. Acute Toxicity Events for Each SRS Procedure

Treatment Group	Maximum Grade of Acute Toxicity[a]				Acute Toxicity[b]		Total
	1	2	3	4	Yes	No	
No ipilimumab	3	3	1	1	8 (14%)	51 (86%)	59
Concurrent ipilimumab	4	1	1	0	6 (26%)	17 (74%)	23
Non-concurrent ipilimumab	6	4	0	1	11 (15%)	62 (85%)	73
Total	13	8	2	2	25 (16%)	130 (84%)	155

[a]p=0.51 with Fisher's Exact Test
[b]p=0.36 with Fisher's Exact Test

Table 4. Late Toxicity Events for Each Patient

Treatment Group	Maximum Grade of Late Toxicity[a]				Late Toxicity[b]		Total
	1	2	3	4	Yes	No	
No ipilimumab	0	4	1	0	5 (13%)	35 (87%)	40
Concurrent ipilimumab	0	2	1	1	4 (17%)	19 (83%)	23
Non-concurrent ipilimumab	1	0	2	0	3 (11%)	25 (89%)	28
Total	1	6	4	1	12 (13%)	79 (87%)	91

[a]p=0.29 with Fisher's Exact Test
[b]p=0.79 with Fisher's Exact Test

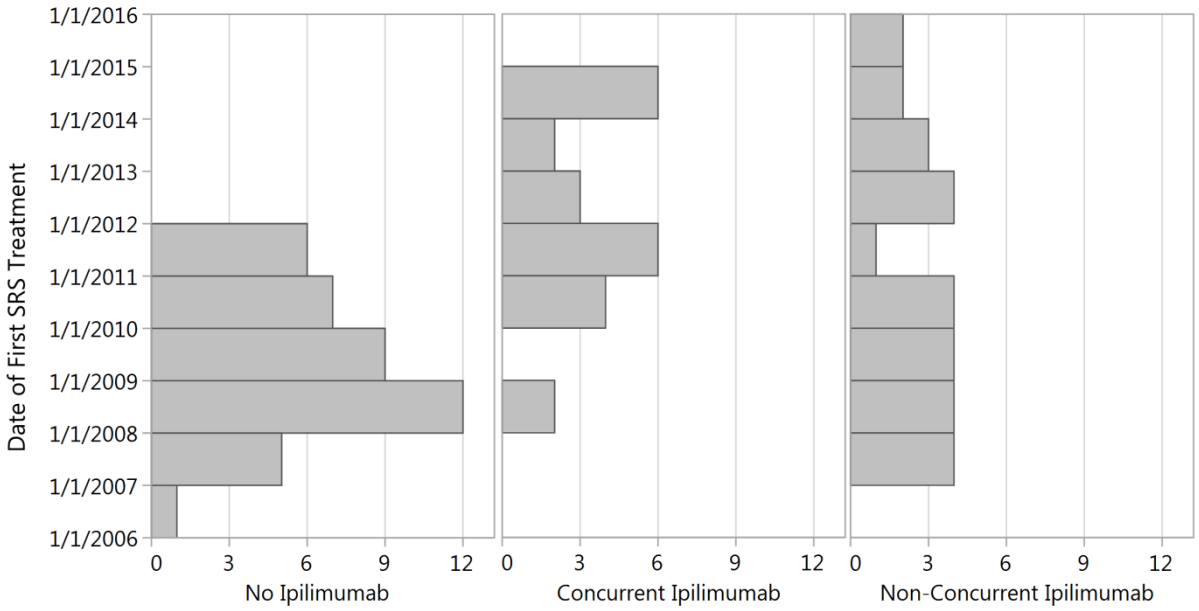

Figure 1.

Number of patients treated with first stereotactic radiosurgery (SRS) by calendar year for no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab treatment groups.

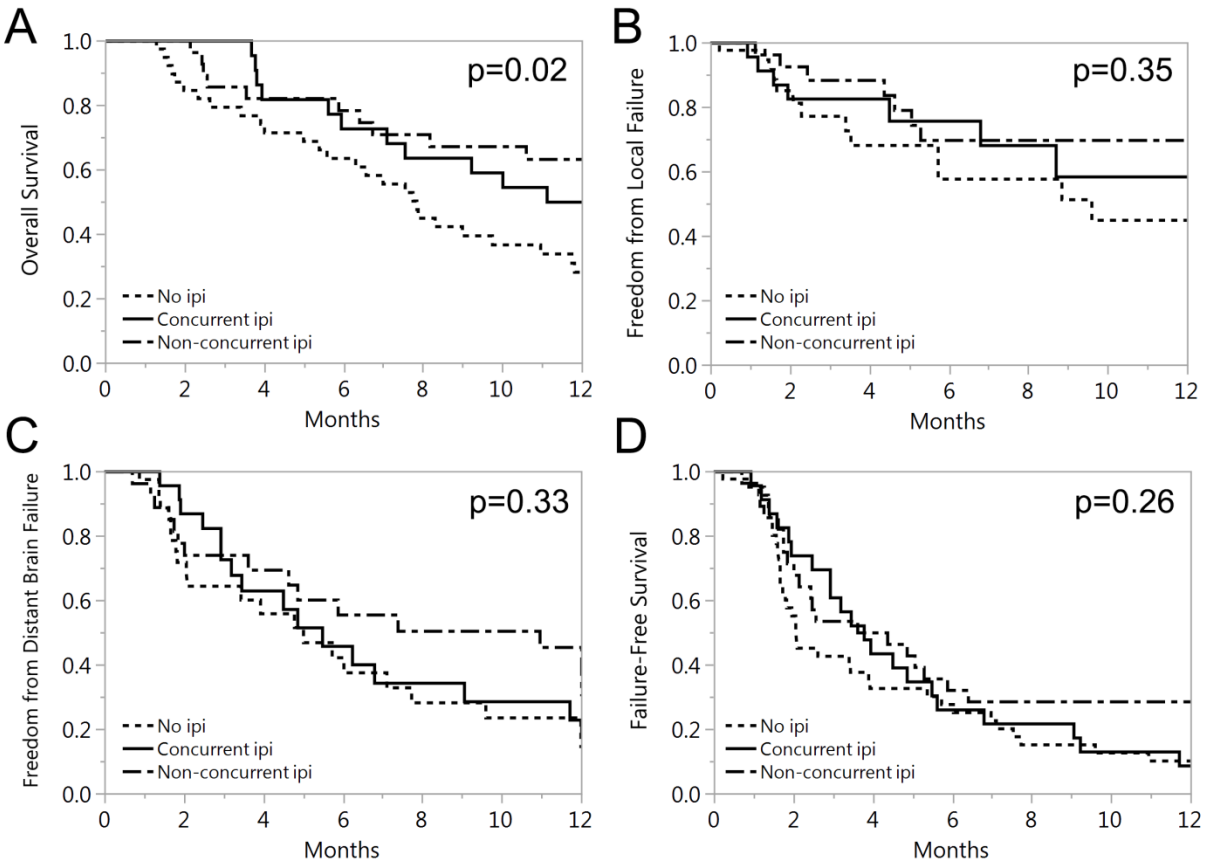

Figure 2.

Kaplan-Meier 1-year survival curves for (A) overall survival, (B) freedom from local failure, (C) freedom from distant brain failure, and (D) failure-free survival for no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab.

Appendix A: Full Manuscript Submitted for Publication

Stereotactic Radiosurgery and Ipilimumab for Patients with Melanoma Brain Metastases: Clinical Outcomes and Toxicity

Ipilimumab and Radiosurgery for Brain Metastases

Kevin Diao, BA[1,2]; Shelly X. Bian, MD[2]; David M. Routman, MD[2]; Cheng Yu, PhD[2]; Jason C. Ye, MD[2]; Naveed A. Wagle, MD[3]; Michael K. Wong, MD, PhD[4]; Gabriel Zada, MD[5]; Eric L. Chang, MD[2]

[1]Harvard Medical School, Boston, MA; [2]Department of Radiation Oncology, Keck School of Medicine of USC, Los Angeles, CA; [3]Department of Clinical Neurology, Keck School of Medicine of USC, Los Angeles, CA; [4]Division of Medical Oncology, Keck School of Medicine of USC, Los Angeles, CA; [5]Department of Neurological Surgery, Keck School of Medicine of USC, Los Angeles, CA

Corresponding Author: Kevin Diao

Mailing Address: 1441 Eastlake Ave. G356, Los Angeles, CA 90033

Phone: 323-865-3072

Fax: 323-865-3037

E-mail: kevin_diao@hms.harvard.edu

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Abstract

Background: There is evidence that the combination of ipilimumab and stereotactic radiosurgery (SRS) for brain metastases improves outcomes. We investigated clinical outcomes, radiation toxicity, and impact of ipilimumab timing in patients treated with SRS for melanoma brain metastases.

Methods: We retrospectively identified 91 patients treated with SRS at our institution for melanoma brain metastases from 2006-2015. Concurrent ipilimumab administration was defined as within +/- 4 weeks of SRS procedure. Acute and late toxicities were graded with CTCAE v4.03. Overall survival (OS), local failure, distant brain failure, and failure-free survival were analyzed with the Kaplan-Meier method. OS was analyzed with Cox regression.

Results: Twenty-three patients received ipilimumab concurrent with SRS, 28 patients non-concurrently, and 40 patients did not receive ipilimumab. The median age was 62 years and 91% had KPS ≥80. The median follow-up time was 7.4 months. Patients who received ipilimumab had a median OS of 15.1 months compared to 7.8 months in patients who did not (p=0.02). In multivariate analysis, ipilimumab (p=0.05), diagnosis-specific graded prognostic assessment (p=0.02), and number of brain metastases (p=0.05) were associated with OS. There were no differences in intracranial control by ipilimumab administration or timing. Most radiation necrosis events occurred in patients who received ipilimumab.

Conclusions: Patients who received ipilimumab had improved OS even after adjusting for prognostic factors. Ipilimumab did not appear to increase risk for acute toxicity. The majority of radiation necrosis events, however, occurred in patients who received ipilimumab. Our results support the continued use of SRS and ipilimumab as clinically appropriate.

Keywords

Melanoma brain metastases; ipilimumab immunotherapy; stereotactic radiosurgery; clinical outcomes; radiation toxicity

Importance of the Study

Despite increasing utilization in clinical practice, there is a scarcity of data on the outcome of patients receiving SRS and ipilimumab for melanoma brain metastases. In the current study, we present results from what is, to our knowledge, the largest cohort of patients with melanoma brain metastases treated with SRS and ipilimumab to date. Furthermore, only a few existing studies with small sample sizes have compared toxicity in combination treatment with a SRS-only control group and none of these studies provided substantial toxicity analysis. By including a SRS-only control group and detailed toxicity reporting, we were better able to elucidate the relative risk of radiation toxicity in patients treated with ipilimumab and SRS. We additionally analyzed ipilimumab timing, intracranial tumor control, and prognostic factors for survival, making this one of the most complete discourses on the clinical impact of this combination of treatments.

Introduction

There are 76,000 cases of melanoma diagnosed and 9,000 deaths due to melanoma each year in the United States. The incidence of melanoma has tripled over the past 30 years and it is currently the second most common invasive malignancy in people under 39 years old.[1] In addition, brain metastases are common in melanoma, occurring in up to 50% of patients having advanced disease. Melanoma brain metastases carry a particularly poor prognosis with a historical median survival of 2-5 months.[2–4]

Recently, however, the advent of targeted therapy agents has shown promise in the treatment of patients with metastatic melanoma. Ipilimumab, a human monoclonal antibody, blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4) and has been demonstrated to improve overall survival (OS) in two large randomized trials.[5,6] Although ipilimumab is not able to cross an intact blood brain barrier (BBB), there is evidence that ipilimumab is either able to penetrate tumors at leaky BBB sites or activates cytotoxic T lymphocytes which in turn infiltrate the tumor environment and induce anti-tumor acivity.[7–10] In addition, some postulate that radiotherapy can induce an abscopal effect that enhances the immunologic effectiveness of ipilimumab.[11–14] Several retrospective studies have now found an OS and/or intracranial control benefit of ipilimumab when used in combination with stereotactic radiosurgery (SRS) for treatment of melanoma brain metastases.[15–19]

Despite this, the effect of combination treatment on radiation toxicity – including acute events such as cerebral hemorrhage and late events such as radiation necrosis (RN) – remains ill-defined. The impact of the timing of administration of ipilimumab relative to SRS on toxicity, cancer control outcomes, and survival is also unclear. In the present study, we aim to describe clinical outcomes and radiation toxicity in patients treated with combination ipilimumab and

SRS compared to patients treated with SRS alone. We explore the effect of ipilimumab timing relative to SRS on the above outcomes and identify associated prognostic factors.

Methods

This retrospective cohort study was approved by the University of Southern California (USC) Keck School of Medicine Institutional Review Board. We identified 107 consecutive patients who were treated with SRS at our institution for melanoma brain metastases between 2006 and 2015. Patients who did not have clinical follow-up were excluded. Ipilimumab, if administered, was at a dose of either 3 mg/kg or 10 mg/kg every 3 weeks for up to 4 cycles with the option for additional maintenance cycles. Concurrent ipilimumab administration was defined as within +/- 4 weeks of SRS procedure. Our selection of this definition was based on a combination of factors, including the 14.7 day half-life of ipilimumab, existing studies that examine timing of ipilimumab, size of treatment groups for statistical analysis, and our goal of investigating the interaction between ipilimumab and SRS administered together within a short time frame.[18,20–22]

Patient information was obtained from institutional electronic medical records. All cancer staging was performed according to the American Joint Committee on Cancer (AJCC) 7th edition guidelines.[23] The diagnosis-specific graded prognostic assessment (DS-GPA) score for melanoma, which takes into account Karnofsky performance status (KPS) and number of brain metastases, was calculated based on the study by Sperduto et al.[24] Acute and late radiation toxicities were defined as events that occurred ≤90 days or >90 days after SRS treatment, respectively, that were either attributable to treatment or unexplained. A diagnosis of RN

required pathologic confirmation. Both acute and late toxicities were graded with the Common Terminology Criteria for Adverse Events (CTCAE), version 4.03.

All patients received SRS using the Gamma Knife® Perfexion™ Unit (Elekta AB, Stockholm, Sweden) given by a team consisting of a radiation oncologist, a neurosurgeon, and a medical physicist. A stereotactic head frame was attached to the skull of the patient under conscious sedation by an anesthesiologist. Contrast-enhanced magnetic resonance imaging (MRI) of the brain was performed, lesions were identified and contoured on Leksell GammaPlan treatment planning software, and radiation was delivered the same day. Radiation doses were based on factors including tumor size, shape, and location as described in RTOG 9005.[25] After SRS, our institutional practice was to follow patients clinically and with MRIs every 2 – 3 months.

Baseline patient and treatment characteristics were compared with the Kruskal-Wallis test by ranks and Pearson chi-square test. OS, local failure (LF), distant brain failure (DBF), and failure-free survival (FFS) were calculated from the date of first SRS treatment and analyzed with the Kaplan-Meier method with significance testing by the Wilcoxon procedure and log-rank test. LF was analyzed per patient as the date of first in-field tumor progression. DBF was analyzed per patient as the date of first new distant brain metastasis. FFS was defined as the first occurrence of LF, DBF, or death. Censoring occurred at the date of last clinical follow-up in the absence of any of the above events. Univariate and multivariate analysis were performed using the Cox proportional hazards model. Clinically relevant risk factors were entered into univariate analysis and significant variables were further entered into multivariate analysis. Acute toxicities were analyzed per SRS procedure and late toxicities were analyzed per patient with statistical

comparison by Fisher's exact test. Significance was defined as $p \leq 0.05$. Statistical calculations were performed in JMP Pro (version 13; SAS Institute, Cary, NC).

Results

Patient and Treatment Characteristics

A total of 91 patients were included in this analysis, 51 (56%) of whom received ipilimumab and 40 (44%) of whom did not (**Table 1**). Among all patients, the median age was 62 years (range, 27-85 years), 29 (32%) were female, and 82 (91%) had KPS ≥80. The median follow-up time was 7.4 months. Of patients who received ipilimumab, 36 (77%) were treated at a dose of 3 mg/kg and 11 (23%) were treated at 10 mg/kg. The median cycles of ipilimumab administered was 4 (range, 1-6). During initial SRS, 256 brain metastases with a median tumor volume of 0.27 cm^3 (range, 0.01-30.33 cm^3) were treated to a median marginal dose of 20 Gy (range, 12-22 Gy). A total of 155 SRS treatments were given, with 46 (51%) patients receiving 1 SRS treatment and 37 (41%) patients receiving 2 SRS treatments.

Twenty-three patients received ipilimumab concurrent with SRS and 28 did not. Of the patients who received ipilimumab non-concurrently, 23 (82%) completed therapy prior to initial SRS whereas 5 (18%) began therapy after SRS. Patients who received ipilimumab prior to SRS completed therapy at a median 4.5 months prior to SRS (range, 1.1-48.4 months). Patients who received ipilimumab following SRS started therapy at a median 2.6 months after SRS (range, 1.1-11.9 months).

Overall, patient and treatment characteristics, including age, sex, KPS, DS-GPA, extracranial metastases, neurologic status, number of brain metastases treated, and tumor volume were similar between patients who did not receive ipilimumab, received ipilimumab

concurrently, and received ipilimumab non-concurrently. However, patients who received non-concurrent ipilimumab received prior chemotherapy at a higher rate (39% vs. 13%) and more often received ipilimumab at a dose of 10 mg/kg (35% vs. 10%) compared to concurrent ipilimumab patients. In addition, patients who did not receive ipilimumab were treated with SRS at an earlier median year (2009) compared to those who received concurrent ipilimumab (2011) and non-concurrent ipilimumab (2010). **Figure 1** depicts the distribution of patients in each treatment group by calendar year of SRS treatment.

Overall Survival

The median OS among all patients was 10.6 months. Patients who received ipilimumab had a median OS of 15.1 months compared to 7.8 months in patients who did not receive ipilimumab (p=0.02). The median survival of patients treated with SRS between 2006-2010 was 11.7 months compared to 10.0 months for patients treated from 2011-2015 (p=0.53). Patients who received non-concurrent ipilimumab had the most favorable OS (median 18.7 months), followed by concurrent ipilimumab (median 11.8 months) and no ipilimumab (median 7.8 months) (p=0.05). At 1 year, OS was 63%, 50%, and 28%, respectively, in patients who received non-concurrent ipilimumab, concurrent ipilimumab, and no ipilimumab (p=0.02) (**Figure 2A**).

On univariate analysis of OS, significant protective factors included non-concurrent ipilimumab administration (HR, 0.55; 95% CI, 0.30-0.95; p=0.03) and higher DS-GPA score (HR, 0.60; 95% CI, 0.46-0.78; p<0.001) (**Table 2**). KPS ≥80 was nearly significant (HR, 0.72; 95% CI, 0.45-1.17; p=0.06). Deleterious factors included 2-4 brain metastases (HR, 2.35; 95% CI, 1.35-4.17; p=0.003) or 5+ brain metastases (HR, 2.46; 95% CI, 1.27-4.69; p=0.009) compared to 1 brain metastasis. In multivariate analysis, non-concurrent ipilimumab

administration (HR, 0.50; 95% CI, 0.27-0.87; p=0.01), DS-GPA (HR, 0.67; 95% CI, 0.49-0.92; p=0.02), and 2-4 brain metastases treated (HR, 1.84; 95% CI, 1.01-3.42; p=0.05) all remained significantly associated with OS. Any ipilimumab was significant for improved OS (p=0.05).

Cancer Control Outcomes

The 1-year freedom from any LF was 45%, 58%, and 70%, respectively, in patients receiving no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab (p=0.35) (**Figure 2B**). The 1-year freedom from DBF was 23%, 23%, and 45%, respectively, in patients receiving no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab (p=0.33) (**Figure 2C**). The 1-year FFS was 10%, 9%, and 29%, respectively, in patients receiving no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab (p=0.26) (**Figure 2D**). Furthermore, there were no significant differences in pairwise testing between any of the treatment groups for LF, DBF, or FFS.

Acute and Late Toxicities

Acute toxicities were analyzed per SRS procedure performed (**Table 3**). Out of a total of 155 courses of SRS, 59 were given in patients who did not receive ipilimumab, 23 were given concurrently with ipilimumab, and 73 were given non-concurrently with ipilimumab. Overall, 25 (16%) SRS treatments resulted in an acute toxicity. The incidence of acute toxicity was 14%, 26%, and 15%, respectively, following no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab SRS procedures (p=0.36). There was no significant difference in the distribution of acute toxicity grades among the treatment groups (p=0.51). There were 4 total grade 3-4 events and no grade 5 events. Grade 3-4 events included 2 cases of cerebral edema and

2 cases of cerebral hemorrhage. Other events included headache (10), nausea (5), seizure (4), gait disturbance (4), paresis (2), and cerebral edema (1).

Late toxicities were analyzed per patient (**Table 4**). Out of a total of 91 patients, 12 (13%) experienced a late toxicity. The incidence of late toxicity was 13%, 17%, and 11%, respectively, in patients receiving no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab (p=0.79). There were 5 total grade 3-4 events and no grade 5 events. There was no significant difference in the distribution of late toxicity grades among the treatment groups (p=0.29). However, 4 out of 5 grade 3-4 events were in patients who received ipilimumab. The grade 3-4 events were all pathologically-confirmed cases of RN. Other late events included focal neurologic deficit (10), cognitive dysfunction (5), cerebral hemorrhage (1), and cerebrovascular accident (1).

Of the RN events, median time from SRS to event was 6.6 months (range, 3.5-42 months). Notably, the single non-ipilimumab event was associated with the longest time to event of 42 months, compared to the longest time to event of 11.4 months among ipilimumab-associated events. Among the 4 patients who developed RN and received ipilimumab, 1 received ipilimumab prior to SRS (last dose 21 months prior), 2 received ipilimumab concurrent with SRS, and 1 received ipilimumab after SRS (first dose 3 months after). All patients received ipilimumab prior to their respective RN event. The individual chronologies of SRS, ipilimumab, and RN were as follows: Patient 1: Ipilimumab at -21 months, SRS at time 0, RN at +3.5 months. Patient 2: Concurrent ipilimumab and SRS at time 0, RN at +4.5 months. Patient 3: Concurrent ipilimumab and SRS at time 0, RN at +11.4 months. Patient 4: SRS at time 0, ipilimumab at +3 months, RN at +6.6 months. Patient 5: SRS at time 0, RN at +42 months.

Discussion

The combination of ipilimumab and SRS has shown promise for improving cancer outcomes in patients with melanoma brain metastases in multiple retrospective studies.[15–19] However, owing to the small number of patients receiving this combination of treatments who have been reported on to date, additional data is needed to elucidate the effect of treatment on clinical outcomes and radiation toxicity, as well as the impact that timing of ipilimumab administration relative to SRS has on these measures.[26] In the current study, to our knowledge, we describe results from our institutional experience with the largest cohort of patients with melanoma brain metastases treated with SRS and ipilimumab to date (n=51).

With a median follow-up of 7.4 months, we found that patients who received ipilimumab had a median OS of 15.1 months versus 7.8 months for control patients who did not receive ipilimumab. The OS of control patients observed in our cohort correlates closely with historical data presented by Sperduto et al, in which patients with melanoma brain metastases who received SRS had a median OS of 7.26 months.[24] The increased OS observed in patients receiving ipilimumab supports prior studies with similar findings.[15–19] Although patients who did not receive ipilimumab were treated with SRS in earlier years, we did not find a significant difference in survival based on SRS treatment year. In addition, the latest patient in the control group was treated with SRS in 2011, the same year as FDA approval of ipilimumab for metastatic melanoma. Prior to 2011, ipilimumab was available primarily through clinical trials, for which brain metastases were frequently an exclusion criteria. As KPS and DS-GPA did not differ significantly between treatment groups, it is most likely that patients in the control group did not receive ipilimumab due to restricted access and/or varying practice patterns at the time. Furthermore, the observed improved survival in our study persisted after controlling for DS-GPA

score and number of brain metastases in multivariate analysis, suggesting that the survival differences were truly due to treatment effect as opposed to pre-treatment selection bias.

We found that patients who had ipilimumab delivered non-concurrently with SRS, i.e. either >4 weeks before or after SRS, had the most favorable survival outcomes. On the other hand, there were significant baseline differences between the non-concurrent and concurrent ipilimumab groups. Patients who received ipilimumab non-concurrently more frequently received prior chemotherapy (39% vs. 13%) and a higher dose of ipilimumab (35% versus 10% received 10 mg/kg). In addition, we hypothesize that patients who received ipilimumab non-concurrently may have had less aggressive disease, as the majority of them (82%) received ipilimumab prior to requiring SRS, 56% of non-concurrent ipilimumab patients versus only 31% of concurrent ipilimumab patients were initially diagnosed with stage I-II disease, and non-concurrent ipilimumab patients had the longest time from diagnosis of primary cancer to brain metastasis development. As ipilimumab is currently FDA-approved at a dosage of 10 mg/kg only for adjuvant melanoma treatment, more patients who received ipilimumab non-concurrently were likely treated with the higher dose of 10 mg/kg as adjuvant therapy given their less aggressive disease and longer time to development of metastases.[27]

Although these factors may partially explain the observed differences in survival, we were not able to completely explain the differences even when controlling for these factors during analysis. Systemic disease burden among the two groups was also comparable, as evidenced by the similar rate of extracranial metastases. An additional possibility is that administering ipilimumab non-concurrently actually is associated with improved survival. Although the mechanism of interaction between ipilimumab and SRS continues to be elucidated, studies have found that CTLA4 blockade directly activates CD4+ and CD8+ T cells, while

reduction of tumor burden following radiotherapy is associated with T-cell response and is greatly amplified by immunotherapy.[28,29] A study published by Twyman-Saint Victor et. al. found that anti-CTLA4 antibodies such as ipilimumab promote expansion of T cells whereas radiotherapy may help shape the T-cell receptor repertoire of these clonal expansions.[30] Based on a model of radiotherapy shaping T-cell receptors following clonal expansion with ipilimumab, it is conceivable that ipilimumab requires time to develop and "prime" the immune system for a greater response to subsequent radiotherapy. Supporting this hypothesis is a recent meta-analysis finding that the median onset of immune-related adverse events following initiation of ipilimumab was 10 weeks (IQR, 6-12 weeks), which was correlated to objective clinical response.[31] Despite this, the optimal timing of ipilimumab with radiotherapy remains to be determined.[32]

In our study, there were no significant differences in terms of LF, DBF, or FFS among the treatment groups. However, patients who received non-concurrent ipilimumab consistently had the most favorable numerical outcomes in all categories, though this was never statistically significant. The same possible explanatory factors that were discussed above relating to observed disparities in OS between treatment groups – including differences in therapy, aggressiveness of disease, and mechanism of action of combination ipilimumab and SRS – are applicable here as well. Nonetheless, our observation that tumor control was similar among treatment groups yet OS favored the ipilimumab groups suggests that the improved survival outcomes with ipilimumab were likely related to improvements in systemic disease control as opposed to intracranial disease control. This finding is consistent with previous literature in which systemic disease, rather than intracranial disease, was typically the limiting survival factor.[33]

The relative risk of toxicity in patients treated with combination ipilimumab and SRS has not been well-defined in part because only a few existing studies with small sample sizes have compared combination treatment with a SRS-only control group (n=62 total among all studies), and none of these studies provided detailed toxicity reporting.[16,34–36] Recently, the results of a phase I study that enrolled 11 patients treated with SRS and ipilimumab were published, in which only 1 patient experienced grade ≥3 neurotoxicity, occurring prior to ipilimumab administration.[37] In the present study, we did not find statistically significant differences in the incidence of acute radiation toxicities following SRS procedures by ipilimumab or timing of ipilimumab. Although the rate of acute toxicities was 26% following concurrent ipilimumab SRS procedures compared to 15% and 14% in procedures with non-concurrent ipilimumab and without ipilimumab, respectively, there was only 1 grade ≥3 acute toxicity observed among concurrent SRS procedures. In general, grade ≥3 acute toxicities were rare, occurring after only 3% of SRS procedures overall.

There were no statistically significant differences in the incidence of late toxicities. Late radiation toxicities occurred in 14% and 13% of patients treated with and without ipilimumab, respectively, and severe grade ≥3 toxicities occurred in 5% of patients overall. All severe late toxicities were pathologically-confirmed RN, and 4 out of 5 of these events occurred in patients who received ipilimumab (concurrently or non-concurrently). Although this was not statistically significant, it raises concern that ipilimumab immunotherapy may increase the risk for symptomatic RN – a result that other studies have previously reported.[38,39] Furthermore, the relatively short time to onset of RN observed among patients who received ipilimumab in the present study compared to historical cohorts points to the possibility that ipilimumab may be associated with faster time to onset of RN as well.[40] However, the low incidence of toxicities and

absence of fatal toxicity events in the ipilimumab groups, combined with the documented OS benefit supports the continued use of combination SRS and ipilimumab for the treatment of melanoma brain metastases as clinically appropriate. Larger prospective studies are needed to further investigate the safety, efficacy, and mechanisms of combination SRS and ipilimumab therapy.

Limitations

The current study was performed as a retrospective review and thus there was likely some selection bias that occurred when patients elected to undergo various treatments. The relatively small sample size raises the possibility that the study was underpowered to detect differences in outcomes and toxicities within subgroups. Although we attempted to control for prognostic factors in multivariate analysis, there may have been baseline differences between groups that remained unaccounted for. Standardized symptom and/or quality of life assessments were not administered prospectively, making highly accurate toxicity detection and assessment difficult. We did not report on non-radiation related toxicities and were not able to definitively differentiate between RN and tumor progression except when surgical pathology was available.

Conclusion

In our institutional experience with the largest cohort of patients with brain metastases treated with SRS and ipilimumab to date, patients who received ipilimumab had an improved OS of 15.1 months compared to 7.8 months for patients who did not receive ipilimumab. Other prognostic factors for OS included DS-GPA score and number of brain metastases treated. Non-concurrent ipilimumab had the most favorable survival outcomes; however, this observation may

in part be due to selection bias. Ipilimumab did not appear to significantly increase risk for acute toxicity. The majority of radiation necrosis events, however, occurred in patients who received ipilimumab. Our results support the continued use of SRS and ipilimumab for treatment of melanoma brain metastases as clinically appropriate. Larger prospective studies are needed to further investigate this topic.

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Table 1. Patient and Treatment Characteristics

Characteristic	No Ipilimumab (n=40)	Concurrent Ipilimumab (n=23)	Non-Concurrent Ipilimumab (n=28)	*p*-value
Age, median (range)	62.5 (35-84)	62 (29-85)	59 (27-76)	0.38
Sex				0.59
Male	29 (73%)	16 (70%)	17 (61%)	
Female	11 (27%)	7 (30%)	11 (39%)	
KPS, median (range)	90 (60-100)	90 (70-100)	90 (60-100)	0.29
DS-GPA, median (range)	2 (0-4)	3 (1-4)	3 (1-4)	0.47
Stage at diagnosis of cancer				0.15
I-II	5 (25%)	5 (31%)	10 (56%)	
III-IV	15 (75%)	11 (69%)	8 (44%)	
Brain metastases diagnosed within 3 months of primary				0.72
Yes	5 (13%)	3 (13%)	2 (7%)	
No	35 (87%)	20 (87%)	26 (93%)	
Time from primary cancer to brain metastasis, in years, median (range)	3.38 (0-22.74)	1.6 (0-20.10)	7.14 (0.04-29.10)	**0.007**
Extracranial metastases				0.15
Yes	27 (68%)	20 (87%)	23 (82%)	
No	13 (32%)	3 (13%)	5 (18%)	
Neurologically symptomatic at baseline				0.71
Yes	7 (18%)	4 (17%)	7 (25%)	
No	33 (82%)	19 (83%)	21 (75%)	
Prior WBRT				0.69
Yes	3 (8%)	1 (4%)	3 (11%)	
No	36 (92%)	22 (96%)	25 (89%)	
Prior chemotherapy				**0.04**
Yes	16 (41%)	3 (13%)	11 (39%)	
No	23 (59%)	20 (87%)	17 (61%)	
Prior targeted therapy				0.15
Yes	15 (38%)	9 (39%)	17 (61%)	
No	24 (62%)	14 (61%)	11 (39%)	
Prior neurosurgery				0.60
Yes	17 (44%)	8 (35%)	9 (32%)	
No	22 (56%)	15 (65%)	19 (68%)	
BRAF therapy				0.65
Yes	4 (10%)	3 (13%)	5 (18%)	
No	36 (90%)	20 (87%)	23 (82%)	
Ipilimumab dose				**0.04**
3 mg/kg	-	19 (90%)	17 (65%)	
10 mg/kg	-	2 (10%)	9 (35%)	
Ipilimumab cycles, median (range)	-	4 (2-5)	4 (1-6)	0.81
Year treated with SRS, median (range)	2009 (2006-2011)	2011 (2008-2014)	2010 (2007-2015)	**<0.001**
2006-2010	34 (85%)	6 (26%)	16 (57%)	
2011-2015	6 (15%)	17 (74%)	12 (43%)	
Time from brain metastasis diagnosis to SRS, in days, median (range)	21 (0-285)	25 (6-154)	22 (3-1663)	0.63

Number of brain metastases treated, median (range)	2 (1-8)	3 (1-16)	2 (1-9)	0.49
Tumor volume, cm^3, median (range)	0.42 (0.01-21.80)	0.20 (0.01-30.33)	0.20 (0.01-10.60)	0.10

Abbreviations: DS-GPA, diagnosis-specific graded prognostic assessment; Gy, Gray; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy

Table 2. Univariate and Multivariate Analysis of Overall Survival

	Univariate		Multivariate	
Variable	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
Age (per year)	1.00 (0.98-1.02)	0.98	-	-
Sex				
Male	1.35 (0.83-2.29)	0.23	-	-
Female	Ref.	Ref.	-	-
Group		Global p=0.10		**Global p=0.05**
No ipilimumab	Ref.	Ref.	Ref.	Ref.
Concurrent ipilimumab	0.77 (0.43-1.35)	0.37	0.65 (0.35-1.18)	0.16
Non-concurrent Ipilimumab	0.55 (0.30-0.95)	**0.03**	0.50 (0.27-0.87)	**0.01**
Ipilimumab dose				
3 mg/kg	Ref.	Ref.	-	-
10 mg/kg	0.72 (0.30-1.55)	0.41	-	-
Ipilimumab cycles (per cycle)	1.24 (0.91-1.73)	0.17	-	-
KPS				
≥80	0.72 (0.45-1.17)	0.06	-	-
<80	Ref.	Ref.	-	-
DS-GPA (per unit increase)	0.60 (0.46-0.78)	**<0.001**	0.67 (0.49-0.92)	**0.02**
Stage at diagnosis				
I-II	Ref.	Ref.	-	-
III-IV	0.89 (0.48-1.71)	0.50	-	-
Time from primary cancer to brain metastasis (per year)	0.97 (0.93-1.01)	0.10		
Extracranial metastases				
Yes	1.36 (0.78-2.50)	0.29	-	-
No	Ref.	Ref.	-	-
Year treated with SRS				
2006-2010	Ref.	Ref.	-	-
2011-2015	1.41 (0.87-2.28)	0.16	-	-
Number of brain metastases treated				
1	Ref.	Ref.	Ref.	Ref.
2-4	2.35 (1.35-4.17)	**0.003**	1.84 (1.01-3.42)	**0.05**
5+	2.46 (1.27-4.69)	**0.009**	1.39 (0.61-3.19)	0.43
Prior WBRT				
Yes	1.37 (0.57-2.81)	0.45	-	-
No	Ref.	Ref.	-	-
Prior chemotherapy				
Yes	0.78 (0.46-1.28)	0.33	-	-
No	Ref.	Ref.	-	-
Prior targeted therapy				
Yes	0.83 (0.52-1.33)	0.44	-	-
No	Ref.	Ref.	-	-
Prior neurosurgery				
Yes	1.00 (0.61-1.61)	0.99	-	-
No	Ref.	Ref.	-	-

Abbreviations: CI, confidence interval; DS-GPA, diagnosis-specific graded prognostic assessment; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy

Table 3. Acute Toxicity Events for Each SRS Procedure

Treatment Group	Maximum Grade of Acute Toxicity[a]				Acute Toxicity[b]		Total
	1	2	3	4	Yes	No	
No ipilimumab	3	3	1	1	8 (14%)	51 (86%)	59
Concurrent ipilimumab	4	1	1	0	6 (26%)	17 (74%)	23
Non-concurrent ipilimumab	6	4	0	1	11 (15%)	62 (85%)	73
Total	13	8	2	2	25 (16%)	130 (84%)	155

[a]p=0.51 with Fisher's Exact Test
[b]p=0.36 with Fisher's Exact Test

Table 4. Late Toxicity Events for Each Patient

Treatment Group	Maximum Grade of Late Toxicity[a]				Late Toxicity[b]		Total
	1	2	3	4	Yes	No	
No ipilimumab	0	4	1	0	5 (13%)	35 (87%)	40
Concurrent ipilimumab	0	2	1	1	4 (17%)	19 (83%)	23
Non-concurrent ipilimumab	1	0	2	0	3 (11%)	25 (89%)	28
Total	1	6	4	1	12 (13%)	79 (87%)	91

[a]p=0.29 with Fisher's Exact Test
[b]p=0.79 with Fisher's Exact Test

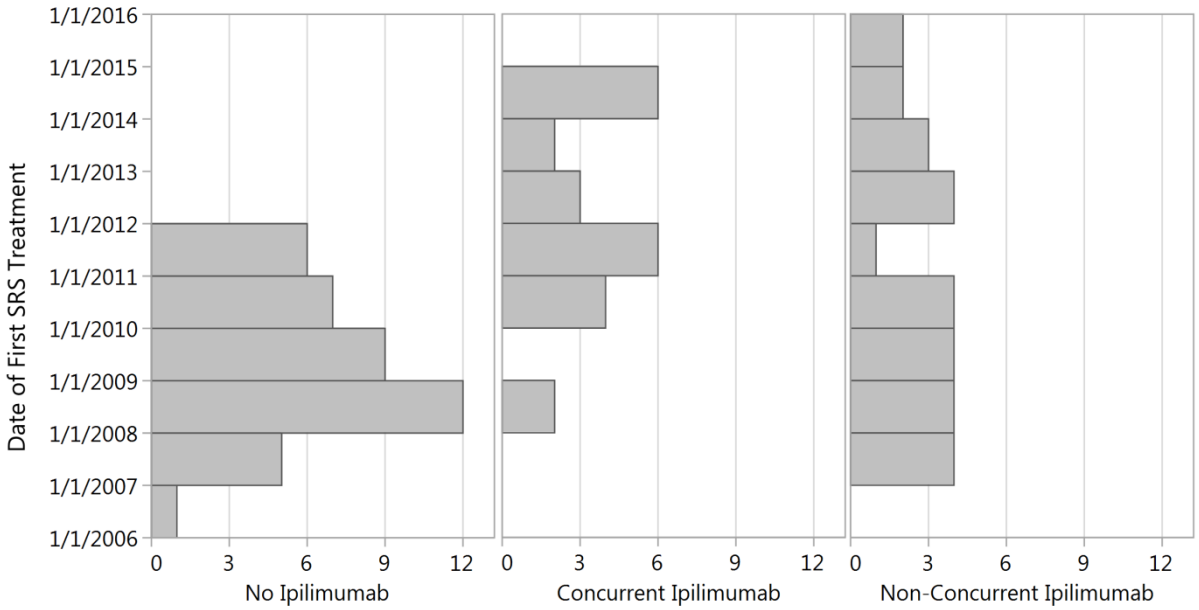

Figure 1.

Number of patients treated with first stereotactic radiosurgery (SRS) by calendar year for no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab treatment groups.

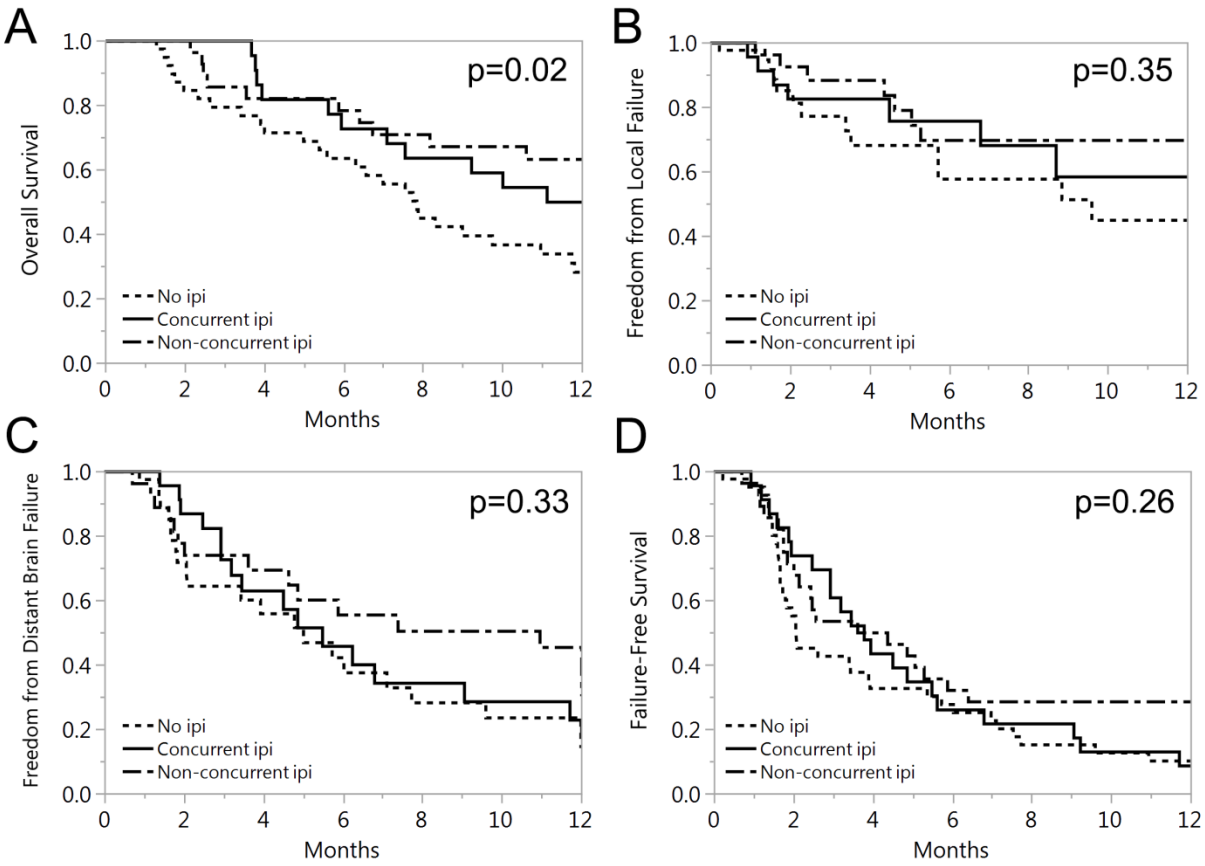

Figure 2.

Kaplan-Meier 1-year survival curves for (A) overall survival, (B) freedom from local failure, (C) freedom from distant brain failure, and (D) failure-free survival for no ipilimumab, concurrent ipilimumab, and non-concurrent ipilimumab.