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Nivolumab and ipilimumab with concurrent stereotactic radiosurgery for intracranial metastases from non-small cell lung cancer: analysis of the safety cohort for non-randomized, open-label, phase I/II trial

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ABSTRACT

Background Up to 20% of patients with non-small cell lung cancer (NSCLC) develop brain metastasis (BM), for which the current standard of care is radiation therapy with or without surgery. There are no prospective data on the safety of stereotactic radiosurgery (SRS) concurrent with immune checkpoint inhibitor therapy for BM. This is the safety cohort of the phase I/II investigator-initiated trial of SRS with nivolumab and ipilimumab for patients with BM from NSCLC.

Patients and methods This single-institution study included patients with NSCLC with active BM amenable to SRS. Brain SRS and systemic therapy with nivolumab and ipilimumab were delivered concurrently (within 7 days). The endpoints were safety and 4-month intracranial progression-free survival (PFS).

Results Thirteen patients were enrolled in the safety cohort, 10 of whom were evaluable for dose-limiting toxicities (DLTs). Median follow-up was 23 months (range 9.7–24.3 months). The median interval between systemic therapy and radiation therapy was 3 days. Only one patient had a DLT; hence, predefined stopping criteria were not met. In addition to the patient with DLT, three patients had treatment-related grade ≥3 adverse events, including elevated liver function tests, fatigue, nausea, adrenal insufficiency, and myocarditis. One patient had a confirmed influenza infection 7 months after initiation of protocol treatment (outside the DLT assessment window), leading to pneumonia and subsequent death from hemophagocytic lymphohistiocytosis. The estimated 4-month intracranial PFS rate was 70.7%.

Conclusion Concurrent brain SRS with nivolumab/ipilimumab was safe for patients with active NSCLC BM. Preliminary analyses of treatment efficacy were encouraging for intracranial treatment response.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Surgical resection and radiotherapy are central to the treatment of brain metastasis. There are limited retrospective data on the safety of immunotherapy with intracranial radiation therapy. As a result, in current practice, many patients with newly diagnosed brain metastasis receive upfront local therapy with radiation, which delays systemic therapy.

WHAT THIS STUDY ADDS

⇒ This is the analysis of the safety cohort for non-randomized, open-label, phase I/II trial, which combines immune checkpoint inhibitors (nivolumab and ipilimumab) in concurrent use with stereotactic radiosurgery (SRS) for intracranial metastases.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings from the safety cohort of this study suggest that concurrent SRS with ipilimumab and nivolumab for brain metastasis from non-small cell lung cancer is safe, and the expansion cohort is under evaluation for added safety and antitumor activity assessment.

INTRODUCTION

Lung cancer is the leading cause of cancer incidence and mortality worldwide. In 2018, 2.1 million new lung cancer cases and 1.8 million deaths were predicted, representing nearly one in five cancer deaths.[1] Non-small cell lung cancer (NSCLC) accounts for over 80% of all lung cancers, and

approximately 15%–20% of patients with NSCLC develop brain metastasis (BM).[2 3] BM presents a major challenge to the treatment of lung cancer, and its appearance typically confers poor prognosis.

Surgical resection and radiotherapy are central to the multidisciplinary therapy of BM because the bioavailability of chemotherapy has generally been poor owing to the blood–brain barrier. Emerging data from several clinical trials have led to the approval of single or combination immune checkpoint inhibitors (ICIs), with or without chemotherapy, for metastatic NSCLC. The safety and feasibility of systemic therapy in patients with treated or untreated asymptomatic BM have been investigated in several prior studies for patients with metastatic NSCLC. The safety of ICI monotherapy, combination ICI therapy, and ICI therapy with chemotherapy in patients with BM has been reported.[4–9 10 11] Furthermore, the sequential use of ICI therapy and stereotactic radiosurgery (SRS) has also been reported in retrospective studies.[12–15] However, there are no prospective studies to date that assess the safety of concurrent use of ICIs with SRS in treatment of BM. As a result, in current practice, many patients with newly diagnosed BM continue to receive upfront local therapy with radiation (as either SRS or whole-brain radiotherapy (WBRT)/hippocampal-avoidance WBRT (HA-WBRT)), and the corresponding delays in systemic therapy may increase the risk of morbidity and mortality.

Out of the same concerns for safety related to receiving brain radiation and immunotherapy concurrently, some patients may receive immunotherapy only without upfront radiation, a practice that may put patients at risk of missing the best window of opportunity to achieve a durable intracranial response. This may potentially lead to intracranial progression, neurologic deficits, poor quality of life, and even death. This concern was reflected in a large German retrospective study with 380 patients with melanoma, in whom upfront local therapy with SRS or surgery led to better overall survival compared with those who did not receive upfront local therapy.[16] Additionally, our own retrospective study showed that patients with melanoma who received concurrent brain SRS and immunotherapy (within 11 days of each other) had better overall survival than those who did not receive concurrent SRS and immunotherapy.[17]

There are existing strong rationale and studies to support the combination of radiation and immunotherapy to enhance treatment efficacy. Radiation promotes tumor antigen release and other aspects of T cell-mediated immune response, effectively converting irradiated tumor into an in situ vaccine.[18 19] Radiation can also alter the immune-suppressive tumor stromal microenvironment and facilitate the action of immunotherapeutic agents.[20] At the same time, immunotherapy can potentially enhance the radiation-induced abscopal effect, reverse the immunosuppressive effects of radiation, and potentially turn radiation from a local therapy to systemic therapy.[21] Emerging preclinical and clinical data suggest a synergistic effect of radiation and immunotherapy in disease control and survival benefit.[22–26] With the increasing use of immunotherapy in NSCLC, there is an urgent need to assess the safety and efficacy of combining these two treatment modalities.

This study was designed to evaluate the safety and efficacy of concurrent use of ipilimumab and nivolumab with radiation (delivered within 7 days of each other) in patients with BM from NSCLC. Either SRS or WBRT/HA-WBRT were allowed (in separate cohorts) at the discretion of the treating physicians and recommendations from the multidisciplinary BM tumor board. Here we report the results of the safety cohort for the SRS cohort treated with concurrent ipilimumab and nivolumab.

PATIENTS AND METHODS

Study design and participants

The safety cohort (phase I part) of this non-randomized, open-label, phase I/II study (ClinicalTrials.gov NCT02696993) was designed to assess the dose-limiting toxicities (DLTs) of concurrent radiation and ICI therapy. Although the trial was originally designed with four cohorts (nivolumab+SRS, nivolumab+WBRT, ipilimumab+nivolumab+SRS, and ipilimumab+nivolumab+WBRT), findings from the CheckMate 026 and 227 trials[27 28] published during the trial led to closure of the first two arms (nivolumab with SRS or WBRT), and the arms with concurrent central nervous system (CNS) radiation (SRS or WBRT/HA-WBRT) and combined ipilimumab plus nivolumab continued to enroll patients. We report here findings from the analysis of safety cohort, treated with concurrent ipilimumab+nivolumab and SRS. The primary endpoints were safety and feasibility of concurrent therapy (phase I) and 4-month intracranial progression-free survival (PFS) (phase I/II). The phase I part was preplanned to enroll 10 patients with at least 8 weeks of prospective follow-up to assess both intracranial and extracranial DLTs.

Inclusion criteria were age 18 years or older, histologically or cytologically confirmed stage IV NSCLC with untreated or progressive BM, Eastern Cooperative Oncology Group performance status score of 0 or 1, adequate organ function, and at least one BM ≥0.3 cm in the longest axis that was amenable to radiotherapy, as assessed by brain MRI; no standard was set for the maximum number of BMs, and this will be up to the treating physician after multidisciplinary BM tumor board discussion. Tumors with activating epidermal growth factor receptor (EGFR) mutations or ALK or ROS1 translocation were allowed if the tumors were progressive, or if the patient had progression or intolerance to standard-of-care molecular targeted therapies. Prior focal CNS radiation was also allowed if the cumulative radiation doses did not exceed tolerance in critical structures, as judged by the treating radiation oncologist. Therapeutic decisions were made in all cases by a multidisciplinary tumor board. Measurement of PD-L1 protein expression in the tumor

was not required, but available data were collected for descriptive analysis.

Exclusion criteria were having leptomeningeal disease, having significant autoimmune disease, or requiring >4 mg/day dexamethasone or its equivalent, either at the start of immunotherapy or for 3 consecutive days within 1 week of starting treatment. Other inclusion and exclusion criteria are described in the protocol (online supplemental file 1). Any number of previous systemic therapies was allowed. A 2-week delay ('washout' period) was required after CNS surgery, and a 4-week washout period was required after systemic therapy, before the study treatment was to begin.

A window of 7 days was allowed for the concurrent delivery of SRS and the initiation of the ICIs, and a shorter interval was encouraged. SRS was delivered by Gamma Knife radiosurgery or linear accelerator-based approaches according to standard practice at The University of Texas MD Anderson Cancer Center (based on findings from RTOG 9005[29]). Treatment could be given in single or multiple (three to five) fractions, with the choice made by the treating physicians per standard practice. Patients were given nivolumab initially at 3 mg/kg every 2 weeks and ipilimumab at 1 mg/kg every 6 weeks for four doses, followed by 480 mg of nivolumab every 4 weeks. These doses were based on data available when the protocol was written. Treatment was continued until either intracranial or extracranial progression was documented according to the Immunotherapy Response Assessment for Neuro-Oncology (iRANO),[7] RANO BM,[8] or Response Evaluation Criteria in Solid Tumors (RECIST) V.1.1[9] systems. Patients in clinically stable condition who were experiencing clinical benefit (as judged by the investigator) could continue therapy after disease progression.

All adverse events (AEs) were evaluated by the study investigator according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE) V.4.0. Toxicity was considered dose limiting if it was attributable to the combination of nivolumab plus ipilimumab and SRS and was refractory to maximum medical management (including steroids) for >1 week. Toxicity was considered not dose limiting if it could be resolved to grade 2 or less with maximum medical management within 1 week. Intracranial DLTs were defined as grade ≥3 hypophysitis or grade ≥3 neurologic toxicity within the 8 weeks of the toxicity assessment window. Extracranial DLTs were defined as grade ≥3 non-dermatologic, non-laboratory toxicity; grade ≥4 dermatologic toxicity; or any grade ≥4 laboratory test abnormality within the 8 weeks of the toxicity assessment window. DLT stopping criteria are shown in table 1.

All patients underwent brain MRI and systemic imaging (eg, CT) scans of the chest, abdomen, and pelvis or positron emission tomography (PET)/CT scans at baseline, at 8 (±4) weeks after completion of SRS, and every 12 (±6) weeks thereafter. Response and progression were evaluated by a radiologist using the modified iRANO[30] criteria for intracranial disease and the RECIST 1.1[31] for extracranial disease. Tumor measurements were assessed by a designated neuroradiologist for intracranial disease response. Lesions present at the time of WBRT or those included in the SRS field were not considered assessable unless they were documented to be progressing (defined as unequivocal growth of a metastatic lesion after radiotherapy as assessed by brain MRI).

Table 1 Trial stopping criteria for intracranial and extracranial dose-limiting toxicities (DLTs)

Patients enrolled	Stopping condition: no of patients experiencing a DLT
Intracranial DLTs	
5	≥3
10	≥4
15	≥6
20	Always stops
Extracranial DLTs	
5	≥4
10	≥6
15	≥8
20	Always stops

Statistical analysis

General descriptive statistics were computed to assess toxicity and preliminary signs of efficacy among all patients. Overall survival was defined as the interval from initiation of study treatment until death. Patients who were alive at the last follow-up date were censored at that time.

Intracranial PFS was defined as time from initiation of study treatment to intracranial disease progression or death from any cause. Intracranial event-free survival was defined as time from initiation of study treatment to the intracranial disease progression or the last day of follow-up. Patients without intracranial progression were censored at the date of the last follow-up MRI, and patients without extracranial progression were censored at the time of last follow-up chest/pelvic CT or PET/CT scans. For patients with partial response (PR) or complete response (CR) according to the iRANO criteria (for intracranial disease) or RECIST 1.1 criteria (for extracranial disease), the interval from the date of the first imaging that showed PR or CR until the date of the first imaging that showed progressive disease was recorded. The duration of intracranial objective response (OR; includes CR and PR) and duration of extracranial OR were calculated for patients who achieved disease control as the interval from achieving response to disease progression. Patients without progression were censored at the time of last follow-up MRI or last follow-up chest/pelvic CT or PET/CT scans. If no additional images were obtained after discontinuation of the study drug, the duration of response was censored at the time the study drug was stopped. Time-to-event variables were analyzed using the

Kaplan-Meier method. Swimmer plots were generated over the period starting from initiation of study treatment to death or last follow-up, and events such as intracranial OR, extracranial OR, intracranial progression, extracranial progression, and death were marked on the plots.

All data were listed individually by patient. Continuous data were summarized with number of observations, mean, SD, minimum, median, and maximum values. Categorical data were summarized by frequency and percentage.

RESULTS

Patient characteristics

From June 15, 2018 to November 6, 2019, 13 patients were enrolled and received protocol treatment. Baseline patient characteristics are listed in table 2. The median follow-up time from initiation of study treatment was 9.7 months (range 1.2–25.8 months). Most patients were female (n=8, 62%), and the median age was 63 years (range 47–81 years). All patients had a history of smoking, and three (23%) were current smokers. Ten patients (77%) had excellent performance status (Eastern Cooperative Oncology Group performance status score of 0). All 13 patients had progressive extracranial disease: 7 patients had adenocarcinoma and 6 had squamous cell carcinoma. No patients had activating EGFR mutations or ALK, ROS1 translocations. Six patients (46%) had tumors with no (<1%) PD-L1 expression, two (15%) had 1%–49% PD-L1 expression, four (31%) had ≥50% PD-L1 expression, and one patient had unknown tumor PD-L1 status (inadequate tissue for testing; online supplemental table 2). One patient had SRS to the surgical cavity of one brain lesion at about 2 months before initiation of the study treatment, and five patients (38%) had received prior systemic therapy (four received anti-PD-1 immunotherapy and one received chemotherapy only).

The median number of BMs treated with SRS was 3 (range 1–10). The size of lesions treated ranged from 3 mm to 22 mm. Five patients had peritumoral edema, and one patient had lesions located in the eloquent brain (brainstem) (eloquent brain is defined as motor strip, brainstem and visual pathway/visual cortex). The median interval between SRS and immunotherapy was 3 days (range 1–7 days) for all 13 patients and 4 days (range 1–6 days) in the 10 patients who could be evaluated for DLTs. The median duration of study drug treatment was 10.9 weeks (range 2.3–26 weeks) for all 13 patients and 14 weeks (range 2.4–26 weeks) for the 10 evaluable patients. Characteristics of brain metastasis and radiation therapy details are provided in table 3.

Table 2 Baseline characteristics for all 13 patients

Variable	No (%)
Median age at enrollment (range), years	63 (47–81)
Sex	
Men	5 (38)
Women	8 (62)
Eastern Cooperative Oncology Group performance status	
1 (Karnofsky Performance Status 70–80 %)	3 (23)
0 (Karnofsky Performance Status 90–100%)	10 (77)
Histologic characteristics	
Adenocarcinoma	7 (54)
Squamous cell carcinoma	6 (46)
Poorly differentiated	
No	1 (8)
Yes	3 (23)
Unknown	9 (69)
EGFR mutation status	
Mutant	0 (0)
Wild type	10 (77)
Unknown*	3 (23)
PD-L1 expression level	
<1%	6 (46)
1%–50%	2 (15)
>50%	4 (31)
Unknown†	1 (8)
Smoking status	
Current	3 (23)
Former only	10 (77)
Previous systemic therapy	
Chemotherapy‡	1 (8)
Chemotherapy‡+immunotherapy§	4 (31)
None	8 (62)
Baseline extracranial disease status	
Progressive	13 (100)
Stable	0 (0)

*Tumor EGFR mutation status was unknown in two patients with squamous cell carcinoma (not required per protocol) and one patient with adenocarcinoma owing to an inadequate amount of tissue.
†Tumor PD-L1 expression was not quantifiable in one patient owing to an inadequate amount of tissue.
‡Includes carboplatin, paclitaxel, and pemetrexed.
§Two patients received prior pembrolizumab and two patients received prior nivolumab.
EGFR, epidermal growth factor receptor.

Clinical outcomes

Of the 13 patients enrolled for phase I, 3 discontinued the trial prior to completion of the 8-week DLT assessment window (1 patient had intracranial progression requiring WBRT, 1 had extracranial disease progression, and 1 died from sepsis unrelated to study treatment). Among the 10 evaluable patients, none developed an extracranial DLT and one had an intracranial DLT within the 8-week DLT assessment window. This patient, who had an episode of seizure 1 month prior to study enrollment, was found to have asymptomatic cerebral edema on the baseline imaging. One day after treatment with SRS, the patient developed grade 3 seizure, manifested

Table 3 Characteristics of brain metastasis and details of radiation therapy

Patient ID	Number of brain metastases	Size (mm)	Location within eloquent (E)* vs non-eloquent (N-E) brain	Evidence of baseline edema	Radiation dose (Gy)	Radiation fraction
Patient 1	1	4	N-E	No	20	1
Patient 2	1	21	N-E†	Yes	18	1
Patient 3	1	18	N-E	Yes	20	1
Patient 4	1	7	N-E	No	20	1
Patient 5	6	Ranging 3–5	N-E	No	20	1
Patient 6	2	4 and 14	N-E	Yes	20	1
Patient 7	3	Ranging 3–11	N-E	Yes	20	1
Patient 8	4	Ranging 5–13	N-E	No	20	1
Patient 9	10	Ranging 4–9	E†	No	16 and 20‡	1
Patient 10	3	Ranging 3–4	N-E	No	20	1
Patient 11	7	Ranging 4–14	N-E	No	20	1
Patient 12	3	Ranging 4–22	N-E	Yes	20	1
Patient 13	9	Ranging 3–11	N-E	No	20	1

*Eloquent brain is defined as motor strip, brainstem, and visual pathway/visual cortex.
†Edema was involving motor strip, but the brain metastasis was not involving motor strip.
‡Two lesions in the brainstem measuring 5 and 9 mm, both of which treated with 16 Gy.

by involuntary tongue movement, which resolved by the time the patient was admitted. The patient started receiving levetiracetam and was discharged 2 days later. The study drugs ipilimumab and nivolumab were initiated 6 days after SRS (5 days after the seizure episode). At 1-month follow-up, the patient had increased but asymptomatic cerebral edema, which was attributed to SRS and/or nivolumab plus ipilimumab and SRS. Any brain edema was considered grade 4 per CTCAE 4.0; therefore, this was considered an intracranial DLT. The patient was treated with steroids due to increased edema, and the study drugs were discontinued at that time at the physician's discretion.

Summary of AEs

Among all 13 patients, 12 (92%) experienced an AE related to the protocol treatment (table 4) (some patients experienced more than one AE). Most of these AEs were grade 1 (25 out of 44 AEs, 56.8%) or grade 2 (8 out of 44 AEs, 18.2%). Grade 3 protocol treatment-related AEs occurred in four patients (31%) and grade 4 in three patients (23%). The most common grade 3 AE was elevated alanine aminotransferase (reported in two patients; 15%). Other grade 3 AEs were fatigue, nausea, elevated aspartate aminotransferase, adrenal insufficiency, myocarditis, and seizure, each of which was observed in one patient (8%; table 5). The most common grade 4 AE was cerebral edema (grade 4 per CTCAE 4.0 and grade 3 per CTCAE 5.0), which was reported in two patients (15%; table 5), including the one with intracranial DLT described above. The other patient who developed grade 4 cerebral edema received surgical resection and SRS to the cavity 2 months prior to study enrollment and then developed new BM and was subsequently enrolled into our trial. Three months after the study treatment, cerebral edema was discovered at the margin of the prior resection cavity; this was determined to be possibly related to immunotherapy but not to SRS to the protocol target lesion. Therefore, it was not considered a DLT. No urgent intervention was indicated per treating physician owing to the non-life-threatening nature of the presentation, and the patient was successfully treated with medical management. A grade 5 protocol treatment-related AE (hemophagocytic lymphohistiocytosis syndrome) was reported in one patient (8%), described below. AEs leading to discontinuation of study drug were grade 3 adrenal insufficiency (n=1, 8%), grade 4 cerebral edema (n=1, 8%), and grade 2 lower limb muscle weakness (n=1, 8%; online supplemental table 3).

Most treatment-related AEs (36 of 44, 82%) were attributed to the ICIs only. The most common of these were grade 1 maculopapular rash (n=4, 31%), pruritus (n=4, 31%), and elevated alkaline phosphatase (n=3, 23%; online supplemental table 4). Some other AEs (16%) were attributed to SRS only, such as grade 1 facial edema (n=5, 38%) and grade 3 seizure (n=1, 8%; online supplemental table 5). Grade 1 dry mouth (n=1, 8%), grade 1–2 fatigue (n=2, 15%), and grade 4 cerebral edema (n=1, 8%) were considered to be related to concurrent SRS and ICIs (online supplemental table 6). High-grade toxicities and tumor PD-L1 status did not show any correlation (online supplemental table 7).

Two patients died while receiving active study treatment. One patient died 1 month after the initiation of study treatment due to sepsis secondary to pneumonia that

Table 4 Adverse events possibly, probably, or definitely related to the protocol treatment (nivolumab/ipilimumab or stereotactic radiosurgery)

	No (%)			
Adverse event	**Grades 1–2**	**Grade 3**	**Grade 4**	**Grade 5**
Any event	12 (92)	4 (31)	3 (23)	1 (8)
Fatigue	5 (38)	1 (8)	0	0
Facial edema	5 (38)	0	0	0
Nausea	4 (31)	1 (8)	0	0
Pruritus	4 (31)	0	0	0
Maculopapular rash	4 (31)	0	0	0
Elevated alanine aminotransferase	1 (8)	2 (15)	0	0
Elevated alkaline phosphatase	3 (23)	0	0	0
Anorexia	3 (23)	0	0	0
Elevated aspartate aminotransferase	1 (8)	1 (8)	0	0
Diarrhea	2 (15)	0	0	0
Cerebral edema	0	0	2 (15)	0
Edema in the limbs	2 (15)	0	0	0
Headache	2 (15)	0	0	0
Peripheral sensory neuropathy	2 (15)	0	0	0
Vomiting	2 (15)	0	0	0
Weight loss	2 (15)	0	0	0
Abdominal pain	1 (8)	0	0	0
Adrenal insufficiency	0	1 (8)	0	0
Adult respiratory distress syndrome	0	0	1 (8)	0
Arthralgia	1 (8)	0	0	0
Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis syndrome	1 (8)	0	0	1 (8)
Elevated blood bilirubin	1 (8)	0	0	0
Dehydration	1 (8)	0	0	0
Dry mouth	1 (8)	0	0	0
Generalized muscle weakness	1 (8)	0	0	0
Hypothyroidism	1 (8)	0	0	0
Joint range of motion decreased	1 (8)	0	0	0
Lower limb muscle weakness	1 (8)	0	0	0
Myocarditis	0	1 (8)	0	0
Neck pain	1 (8)	0	0	0
Pain	1 (8)	0	0	0
Pneumonitis	0	0	1 (8)	0
Seizure	0	1 (8)	0	0

If more than one of the same adverse events occurred in the same patient, the highest grade was counted.

was not related to the study treatment. The other patient was admitted for confirmed influenza infection 7 months after the initiation of therapy in South America, and the patient subsequently developed pneumonia/pneumonitis with acute respiratory distress syndrome with a clinical picture consistent with hemophagocytic lymphohistiocytosis per the oncologist at MD Anderson. After extensive discussion based on the information provided by the local hospital, it could not be ruled out that her condition and death were not related to immunotherapy.

Intracranial disease control

With a median follow-up time of 23 months (range 9.7–24.3 months) as of August 31, 2020, 2 of 13 patients

Table 5 Severe adverse events possibly, probably, or definitely related to the protocol treatment (nivolumab/ipilimumab or stereotactic radiosurgery)

	No (%)		
Adverse event	**Grade 3**	**Grade 4**	**Grade 5**
Elevated alanine aminotransferase	2 (15)	0	0
Cerebral edema	0	2 (15)	0
Adrenal insufficiency	1 (8)	0	0
Adult respiratory distress syndrome	0	1 (8)	0
Elevated aspartate aminotransferase	1 (8)	0	0
Blood and lymphatic system disorders: hemophagocytic lymphohistiocytosis syndrome	0	0	1 (8)
Fatigue	1 (8)	0	0
Myocarditis	1 (8)	0	0
Nausea	1 (8)	0	0
Pneumonitis	0	1 (8)	0
Seizure	1 (8)	0	0

If more than one of the same adverse events occurred in the same patient, the highest grade was counted.

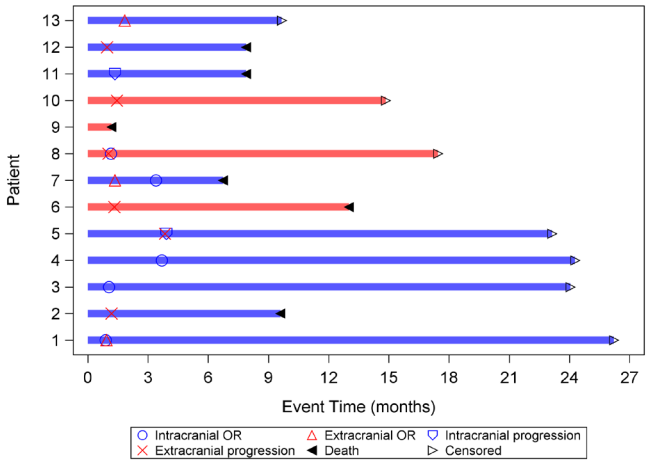

Figure 1 Swimmer plot of responses over time for the 13 patients undergoing stereotactic radiosurgery with concurrent nivolumab and ipilimumab for brain metastasis from non-small cell lung cancer. OR indicates objective response, defined as a complete response or partial response according to the Immunotherapy Response Assessment for Neuro-Oncology system (for intracranial disease) or the Response Evaluation Criteria in Solid Tumors V.1.1 system (for extracranial disease). Blue lines indicate no prior anti-PD-L1 therapy; red lines indicate prior anti-PD-L1 therapy. Event times were calculated starting from the start of study treatment (stereotactic radiosurgery or study drugs, whichever came first).

(15%) had CNS disease progression with development of new BM. No patient had experienced local failure of treated BM per iRANO. The estimated 4-month intracranial PFS rate was 70.7% in all 13 patients and was 35.4% in 12 months. The intracranial event-free survival in 4 and 12 months was the same at 65.5% (two patients had intracranial progression). The intracranial OR rate was 38% (5 of 13 patients) and duration of intracranial OR was censored for all five patients (censored at 1.4, 1.4, 2.3, 14.1, and 24.5 months).

Extracranial disease control

Twelve of the 13 patients were evaluable for extracranial disease response (one patient died prior to 1-month follow-up due to sepsis secondary to pneumonia unrelated to protocol treatment). The OR rate for extracranial disease was 25% (3 of 12 patients), and stable disease was observed in 4 of 12 patients (33%) per RECIST 1.1, leading to an overall extracranial control rate of 58%. Among the patients with an OR, the median time to OR was 7 weeks (range 4–8 weeks) and duration of OR was censored for all three patients (censored at 0, 2.0, and 24.8 months). Five patients (42%) had extracranial progression, and the median time to extracranial progression was 3.8 months (95% CI 1.0 to not reached). Of note, two patients continued to have persistent good response after discontinuation of protocol therapy. One patient (tumor PD-L1 status unknown) discontinued the study drug 6 months after initiation of the treatment owing to toxicity, and that patient's extracranial disease continued to be stable for an additional 9 months without other systemic therapy. A second patient (tumor PD-L1 0%) had extracranial PR 1 month after initiation of the protocol treatments but discontinued study drugs at 4 months owing to grade 3 adrenal insufficiency. That patient's extracranial PR persisted for an additional 22 months without any further antineoplastic therapy (total duration of OR: 26 months).

Overall survival

Six of 13 patients had died as of August 31, 2020. The median overall survival was not reached. A swimmer plot, including the events of intracranial OR, extracranial OR, intracranial progression, extracranial progression, death, and censoring, is presented in figure 1.

DISCUSSION

Although the safety of concurrent ICI therapies with stereotactic body radiotherapy has been investigated for several types of solid tumors, the current study is the first, to the best of our knowledge, to assess prospectively the safety of combining two ICIs with concurrent SRS to the brain. Our key finding from this report of the safety cohort of concurrent use of ipilimumab and nivolumab with SRS for BM from NSCLC is that concurrent use of ipilimumab and nivolumab with SRS to the brain is feasible and met the endpoint for safety, thereby justifying expansion of the therapy to studies of efficacy. This conclusion was reached on the basis of the facts that only one patient experienced

an event defined as an intracranial DLT (the patient with grade 4 cerebral edema), the predetermined stopping criteria were not met and the study thus proceeded to phase II, the rate of severe (grade ≥3) AEs related to the study therapy was 31% (4 of 13 patients), and only two patients (15%) experienced cerebral edema, rated grade 4 by CTCAE 4.0 or grade 3 by CTCAE 5.0.

In our study cohort, the only intracranial DLT observed was medically managed with therapy discontinuation and steroids. Systemic AEs observed that were considered related to combination ICI therapy were similar to those reported in prior clinical experience with ipilimumab and nivolumab combinations (CheckMate 012, CheckMate 227).[28 32]

Over the past decade, data from randomized trials assessing the safety of SRS plus WBRT have raised concerns about the cognitive deficits associated with WBRT. This has led to SRS becoming the standard of care for BM from certain solid tumors, when only a few BMs are present.[33–35] Subsequent efforts to avoid the toxicities of brain irradiation in patients led to phase II studies of single-agent anti-PD-1, anti-PD-L1, or anti-CTLA4 therapy, which showed some activity against BM from melanoma or NSCLC.[10] However, the current standard-of-care approach for CNS metastases is brain irradiation followed by systemic therapy. The clinical trials of single-agent immunotherapy for BM from metastatic NSCLC required a washout period of 14–28 days after radiation, which may have increased morbidity and mortality owing to delays in beginning the systemic therapy. The corresponding need for studies to evaluate safety of a concurrent approach led to the design of the current study. Our findings indicate that this concurrent approach is safe; indeed, descriptive findings from the two arms of the original trial that had been stopped (nivolumab with either WBRT (n=6) or SRS (n=2)) indicated that none of these eight patients developed intracranial or extracranial DLTs.

In summary, our findings from the safety cohort suggest that concurrent SRS with ipilimumab and nivolumab for BM from NSCLC is safe. However, these findings should be interpreted cautiously owing to the increased use of SRS in patients with multiple BMs; in the current study, the maximum number of BMs treated with concurrent therapy was 10. Further work is needed to assess the intracranial activity of this approach as well as the safety of concurrent use of WBRT.

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