ORIGINAL ARTICLE

Incidence and Outcomes of Brain Metastasis in Pleural Mesothelioma in the Era of Immunotherapy

Margaret Stalker, MD,[a,*] Suzanne L. Walker, PhD, CRNP, AOCN, BC,[b] Emily Lebow, MD,[c] Emily Ling-Lin Pai, MD, PhD,[d] Alex Watts, MS,[e] Wei-Ting Hwang, PhD,[e] Amir Banihashemi, MD,[d] Evan Anderson, MSN,[b] Leonid Roshkovan, MD,[c] Sharyn I. Katz, MD,[c] Leslie Litzky, MD,[d] Andrew R. Haas, MD, PhD,[f] Sunil Singhal, MD,[g] Corey J. Langer, MD,[b] Keith Cengel, MD, PhD,[c] Melina E. Marmarelis, MD, MSCE[b]

[a]*Department of Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania*
[b]*Division of Hematology & Oncology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania*
[c]*Department of Radiation Oncology, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania*
[d]*Department of Pathology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania*
[e]*Department of Biostatistics, Epidemiology, and Informatics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania*
[f]*Department of Pulmonary, Allergy, and Critical Care, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania*
[g]*Division of Thoracic Surgery, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania*

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ABSTRACT

Introduction: Immunotherapy (IO) has reported efficacy in pleural mesothelioma (PM). Brain metastases (BMs) in PM are rare; thus, surveillance brain imaging is not included in the guidelines. We evaluated the incidence of BM by treatment type.

Methods: In this retrospective analysis, patients with PM treated at the University of Pennsylvania between January 1, 2015, and August 31, 2023, were included. Demographic and clinical data were extracted from the medical records. The treatment categories included chemotherapy, single-agent IO, and dual-agent IO. A two-tailed Z score was used to determine a difference in the proportion of BM. Overall survival (OS) was analyzed using the Kaplan-Meier method. Of those with BM, available brain tissue was further analyzed.

Results: In total, 251 patients were included; the median age of the participants was 73 years (range: 35–92 y), 79% were male individuals, 91% were white, and 73% had epithelioid histology. In the study, 102 (40.6%) were treated with chemotherapy, 100 (39.8%) with single-agent IO, and 49 (19.5%) with dual-agent IO. The median OS (mOS) was 21.6 months (95% confidence interval: 17.7–25.5) and did not differ between treatment groups ($p = 0.774$). A higher proportion of patients treated with IO developed BM than those treated with chemotherapy (6/149 [4%] versus 0/102 [0%]; Z score $p = 0.04$). The mOS from BM diagnosis was 95 days (range: 16–1025 d). The histomorphology of three patients with available brain tissue were similar to the primary site and reported substantial edema and hemorrhage.

Conclusions: In this retrospective study, clinically significant BM was most prevalent in those exposed to IO and not seen in those receiving chemotherapy despite similar mOS between the groups. Brain imaging should be considered before starting IO in patients with PM.

Keywords: Mesothelioma; Immunotherapy; Brain metastasis; Survival; Pleural mesothelioma

***Corresponding author.**

Address for correspondence: Margaret Stalker, MD, Internal Medicine, Hospital of the University of Pennsylvania, 3400 Spruce St, Philadelphia, Pennsylvania 19104. E-mail: margaret.stalker@pennmedicine.upenn.edu

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Introduction

Mesothelioma is a highly aggressive cancer of the mesothelial tissue lining the pleura or peritoneum. Mesothelioma is rare, with about 3000 new cases diagnosed annually in the United States.[1] Global incidence has been increasing, and the five-year survival remains dismal at 12% for all stages combined.[2,3]

Immunotherapy (IO) has emerged as a treatment option for patients with mesothelioma. In October 2020, the Food and Drug Administration approved ipilimumab and nivolumab (ipi/nivo) as first-line (1L) therapy for unresectable pleural mesothelioma (PM) after the CheckMate-743 trial reported improved overall survival (OS) compared with standard chemotherapy (CT), with the greatest benefit in non-epithelioid histology.[4,5] The improvement in survival for non-epithelioid PM shown in CheckMate-743 for ipi/nivo was prominent, with a doubled median OS (mOS).[6]

Despite these new therapy options, disease progression is common, and distant metastatic disease has been reported to be prevalent in as many as two-thirds of patients, predominantly with bone, visceral, lung, and peritoneal metastases.[7] Despite the high occurrence of metastases elsewhere, clinically significant brain metastases (BMs) in PM are rare ($\sim$3%).[8,9] Given the historically low incidence of BM, routine brain imaging has not been included in the National Comprehensive Cancer Network guidelines for patients who are asymptomatic.

To our knowledge, there have been no studies to date focused on BM incidence in mesothelioma as it pertains to therapy received. In this retrospective study, we aim to analyze the incidence of BM in PM, categorized by the type of treatment received.

Materials and Methods

Patient Characteristics

In this retrospective cohort study, adult patients (age $\geq$18 y) diagnosed with PM and treated within the University of Pennsylvania Health System between January 1, 2015, and August 31, 2023, were included. The data cutoff was June 28, 2024. Patients were excluded if they had primary peritoneal mesothelioma, did not receive treatment, records were missing regarding treatment, or if they had another concurrent active metastatic malignancy. Local institutional review board approval was obtained with a waiver of consent due to the retrospective nature of this study.

Study Measures

Patients were divided into three categories based on treatment history at any line: single agent IO, dual agent IO (ipi/nivo), and computed tomography (CT) without ever receiving IO. Patients were categorized into dual agent IO if they received ipi/nivo at any point regardless of receiving earlier single agent IO. Chart review for computed tomography of the head or magnetic resonance imaging was performed to identify patients with BM from mesothelioma, although all patients were included in the analysis regardless of the presence of brain imaging. Therapy during or immediately before BM was recorded. Patient demographic data, treatment history, brain imaging, and clinical history were extracted from the electronic medical record. Demographic data collected included age and diagnosis year (before or after 2020), sex (male or female), race (white, black, Asian/Pacific islander, other), smoking status (former, never, or current), Eastern Cooperative Oncology Group performance status (0–1, $\geq$2, or missing), diagnosis year (before or after 2020). Lines of therapy were noted in treatment history and type of treatment received. Clinical history collected included histology from pathologic reports, absence or presence of brain imaging and timing of brain imaging, patient's presence or absence of symptoms during brain imaging, and presence of BMs. In the total cohort, OS was defined as the time of diagnosis to date of death or censored at last contact. Follow-up time was defined as time from diagnosis to last time of contact.

If BMs were found, further analysis was performed to determine time from IO to BM, time from BM to death or last contact, treatment for the BM (surgery or radiation), type of radiation received (whole brain radiation therapy [WBRT] or stereotactic radiosurgery [SRS]), and clinical status at the time of the analysis (alive or deceased).

Intracranial progression was defined as local recurrence of treated BM or development of new BM not present at the time of irradiation. Time from IO to BM was defined as the start date when the patient first received IO to date of the brain imaging scan with the BM. Time from DM to death was defined as date of brain imaging scan of BM diagnosis to date of death.

Of those with BM, surgical resection samples that were available were analyzed for tumor histomorphology based on hematoxylin and eosin stain on formalin-fixed paraffin embedded tissue sections (5 μm in thickness), and the intratumoral inflammatory component was evaluated through an immunohistochemistry study using antibodies against the following antigens: CD3 (Pan T-cell marker), CD4 (helper T-cell), CD8 (cytotoxic T-cell), granzyme B (T-cell subpopulation), CD20 (B-cell marker), and CD163 (macrophage marker). Supplementary Table 1 reports the clones of the antibodies used for the immunohistochemistry. The immunohistochemistry was performed on the Leica XL autostainer.

Statistical Analysis

Descriptive statistics were used such as mean and median for continuous variables and proportions for categorical variables. A two-tailed Z score with an alpha

of 0.05 was used to determine a difference in proportion of patients with BM by treatment group.

Overall survival was analyzed using the Kaplan-Meier methodology.

A sensitivity analysis was performed on those with brain imaging available for mOS, median follow-up time, and a two-tailed Z score of proportions by treatment group.

Results

In total, 251 patients were included in the study (Supplementary Fig. 1). Of these patients, 102 (40.6%) were treated with CT, 100 (39.8%) were treated with single agent IO, and 49 (19.5%) were treated with dual agent IO. In the total cohort (Table 1), the median age was 73 (range: 35–92), 79% were male individuals, 91% were of white race, 49% were never smokers, 86% had Eastern Cooperative Oncology Group performance status of 0 to 1, 76% were diagnosed before year 2020, 73% were epithelioid histology, and 121 patients (48%) had available brain imaging at some point during their disease course. A higher proportion of subjects were female individuals, treated after 2020, and had brain imaging in the dual-agent IO group. Of the 121 patients with brain imaging, most (99 of 121 [81.8%]) had magnetic resonance imaging brain scans. Of these patients with brain imaging, 55 patients (45.5%) had the brain imaging performed owing to symptoms, 26 patients (21.5%) had brain imaging at time of diagnosis and during their

Table 1. Demographic and Clinical Data by Treatment Type

Characteristic	Total cohort N = 251[a]	Chemotherapy N = 102[a]	Single-Agent Immunotherapy N = 100[a]	Dual-Agent Immunotherapy N = 49[a]	p-value[b]
Age (years)	73 (35-92)	73 (35-91)	73 (52-91)	71 (47-92)	0.4
Sex					0.014
Female	54 (22%)	17 (17%)	19 (19%)	18 (37%)	
Male	197 (78%)	85 (83%)	81 (81%)	31 (63%)	
Race					0.4
Asian	3 (1.2%)	0 (0%)	2 (2.0%)	1 (2.0%)	
Black/AA	8 (3.2%)	2 (2.0%)	4 (4.0%)	2 (4.1%)	
Multiple	3 (1.2%)	2 (2.0%)	0 (0%)	1 (2.0%)	
Other/unknown	8 (3.2%)	2 (2.0%)	3 (3.0%)	3 (6.1%)	
White	229 (91%)	96 (94%)	91 (91%)	42 (86%)	
Smoking status					0.9
Never	123 (49%)	47 (46%)	50 (50%)	26 (53%)	
Former	119 (47%)	52 (51%)	46 (46%)	21 (43%)	
Current	9 (3.6%)	3 (2.9%)	4 (4.0%)	2 (4.1%)	
ECOG					>0.9
0-1	216 (86%)	88 (86%)	86 (86%)	42 (86%)	
≥ 2	14 (5.6%)	5 (4.9%)	6 (6.0%)	3 (6.1%)	
missing	21 (8.4%)	9 (8.8%)	8 (8.0%)	4 (8.2%)	
Year Diagnosed					<0.001
2020 and after	59 (24%)	19 (19%)	10 (10%)	30 (61%)	
Before 2020	192 (76%)	83 (81%)	90 (90%)	19 (39%)	
Histology					0.11
Biphasic	37 (15%)	16 (16%)	12 (12%)	9 (18%)	
Epithelioid	183 (73%)	77 (75%)	77 (77%)	29 (59%)	
Sarcomatoid	30 (12%)	9 (8.8%)	10 (10%)	11 (22%)	
Unknown	1 (0.4%)	0 (0%)	1 (1.0%)	0 (0%)	
Brain Imaging	121 (48%)	42 (41%)	46 (46%)	33 (67%)	0.009
Type of IO received					<0.001
Durvalumab	1 (0.7%)	0 (NA%)	1 (1.0%)	0 (0%)	
Ipilimumab/Nivolumab	49 (33%)	0 (NA%)	0 (0%)	49 (100%)	
Nivolumab	4 (2.7%)	0 (NA%)	4 (4.0%)	0 (0%)	
Pembrolizumab	95 (64%)	0 (NA%)	95 (95%)	0 (0%)	
Unknown	102	102	0	0	
Line of Therapy (IO)	2.00 (1.00-8.00)	NA (Inf-Inf)	2.00 (1.00-7.00)	2.00 (1.00-8.00)	0.027
Unknown	102	102	0	0	

[a]Median (Min-Max); n (%).
[b]Kruskal-Wallis rank sum test; Pearson's Chi-squared test; Fisher's exact test.
ECOG, Eastern Cooperative Oncology Group; IO, immunotherapy.

disease course, 34 patients (28.1%) only had brain imaging at diagnosis, and 61 patients (50.4%) only had brain imaging during their disease course and not at diagnosis. In the single agent IO cohort, 96 (96%) received pembrolizumab. The median line of therapy for any type of IO given was second-line (2L) (range: 1–8).

Median survival from time of diagnosis to death or censored at last contact for the total cohort was 21.6 months (95% confidence interval [CI]: 17.7–25.5) (Fig. 1*A*). The mOS for patients who received Chemo, single-agent IO, and dual-agent IO was 16.4 months (95% CI: 13.8–22.5), 24.0 months (95% CI: 21.8–28.8), and 20.6 months (95% CI: 16.0–41.7), respectively (Fig. 1*B*). A log-rank test determined there was no evidence of a difference in mOS times between groups ($p = 0.774$). The median follow-up time was 105 months (86–not reached [NR]) for the overall cohort and 105 (45–NR), 105 (93–NR), and 78 months (44–NR) for the CT, single-agent IO, and dual-agent IO subgroups, respectively.

A higher proportion of patients treated with IO developed BM compared with those treated with CT (six of 149 [4%] versus zero of 102 [0%]; Z score $p = 0.04$). Numerically a higher proportion of patients in the ipi/nivo treatment group developed a BM compared with those treated with single-agent IO, but this was not statistically significant (four of 49 [8.2%] versus two of 100 [2%], Z score $p = 0.072$).

A total of 121 patients with brain imaging were included in the sensitivity analysis (Supplementary Table 2). Among these, a higher proportion of patients who were treated with dual-agent IO developed BM compared with those treated with CT (four of 33 [12%] versus zero of 42 [0%]; Z score $p = 0.020$). There was a trend toward significance in proportion of patients treated with any IO developing BM compared with those treated with CT (six of 79 [7%] versus zero of 42 [0%]; Z score $p = 0.067$). The mOS from diagnosis was 25.9 months (95% CI: 20.6–32.3), and by treatment group was 25.8 (95% CI: 17.7–41.9), 27.2 (95% CI: 21.9–36.9), and 20.6 (95% CI: 16.0–43.5) for CT, single-agent IO, and dual-agent IO, respectively (Supplementary Fig. 2*A* and *B*). There was no statistically significant difference in OS between cohorts ($p = 0.527$). The median follow-up time for those with brain imaging was 105 months (86–NR) for the overall cohort, and was 105 (45–NR), 105 (93–NR), and 78 (44–NR) for the CT, single-agent IO, and dual-agent cohorts, respectively. The mOS for those with brain imaging was 25.9 months (95% CI: 20.6–32.3) compared with 17.7 months (95% CI: 15.1–22.5) without brain imaging ($p = 0.01$).

Of the six patients that developed BM (Supplementary Table 3), the median age was 72.5 (range: 47–80), 83% were male individuals, and 67% were white. There was an even distribution of histology for the primary tumor with two cases each of epithelioid, biphasic, and sarcomatoid (33% each of epithelioid, biphasic, and sarcomatoid). Meanwhile, 50% received IO as 2L and 33% as 1L, and one patient received it as third-line. All patients had received IO most recently or were currently on it when BM developed. All six patients (100%) were symptomatic from their BM prompting the brain imaging. Three

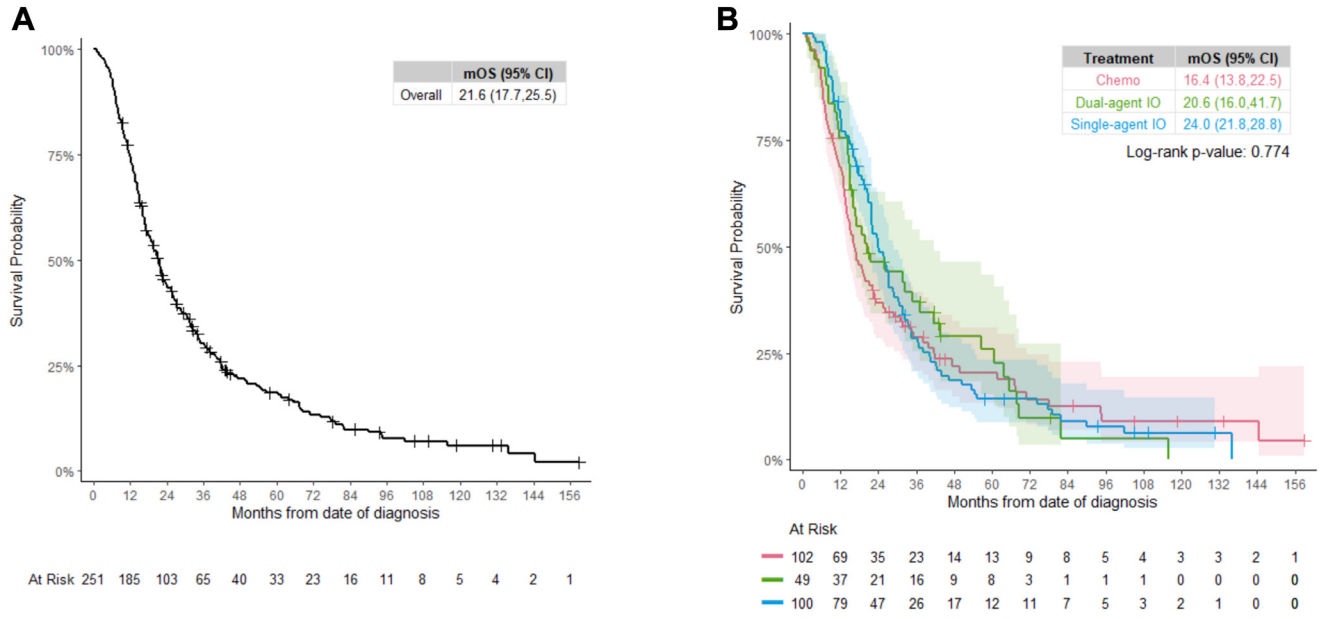

Figure 1. Overall survival. *(A)* Full cohort and *(B)* stratified by treatment type. Chemo, chemotherapy; CI, confidence interval; IO, immunotherapy; mOS, median overall survival.

patients had new metastases elsewhere at the time of BM diagnosis (liver/spleen/kidneys, pleura/lung, bone/peritoneum, soft tissue/pericardium), whereas three (50%) had oligometastatic progression only in the brain without metastases elsewhere at the time of BM diagnosis (Fig. 2).

Median time to BM from the start of IO was 144.5 days (range: 2–913 d) (Table 2). Four patients received IO in 2L or third-line and had a median BM free time from IO start to BM of 234 days (range: 2–913 d) compared with 144.5 days (range: 105–184 d) for the two patients who received IO in 1L. The median time from mesothelioma diagnosis to BM was 312.5 days (range: 97–1314 d). The median survival from diagnosis of BM was 95 days (range: 16–1025 d). Four patients (67%) underwent surgery for the BM followed by radiation, whereas two patients received only radiation. Two patients received WBRT, whereas four patients received SRS to a median of four BM (range: 1–7). A timeline by patient case is shown in Figure 2. The two patients who received WBRT and one patient who received SRS had no post-treatment brain imaging. Five patients (83.3%) completed their radiation course. Of the five patients that completed radiation therapy, two developed new lesions outside of the radiation field including one patient with rapid progression 20 days after radiation therapy (Fig. 3*A* and *B*). An additional patient developed imaging findings concerning for progression, but was ultimately attributed to treatment-related change.

Three out of the six patients' brain metastatic tumor tissue was available for analysis (Fig. 4*A*–*F*). The histomorphology of the brain metastatic lesions from the three patients are overall similar in histology to the primary site with two showing sarcomatoid and one showing epithelioid histologies. Immunohistochemistry demonstrates that CD163+ macrophages are the dominant intratumoral inflammatory cells. In addition, variable amounts of CD3 positive T-lymphocytes are also present, a subset of which is noted to be CD8 positive and granzyme-positive T-lymphocytes. CD20 positive B lymphocytes are minimal. Of note, one tumor shows abundant intratumoral neutrophils.

Discussion

In this retrospective analysis of BMs in PM, we found a higher incidence of BM in those treated with IO compared with those treated with CT, which was irrespective of OS. Rates of intracranial disease with both ipi/nivo and single-agent IO were higher compared with the CT cohort, where none of the patients developed BM. The 8% incidence of BM in the ipi/nivo cohort was higher than previously reported data that suggested an incidence of about 3% for all patients with PM.[8,9] Most patients (83%) in this analysis developed BM within a year of starting checkpoint blockade. Time to death after BM development was quick and in 80% patients occurred within approximately three months. This increased

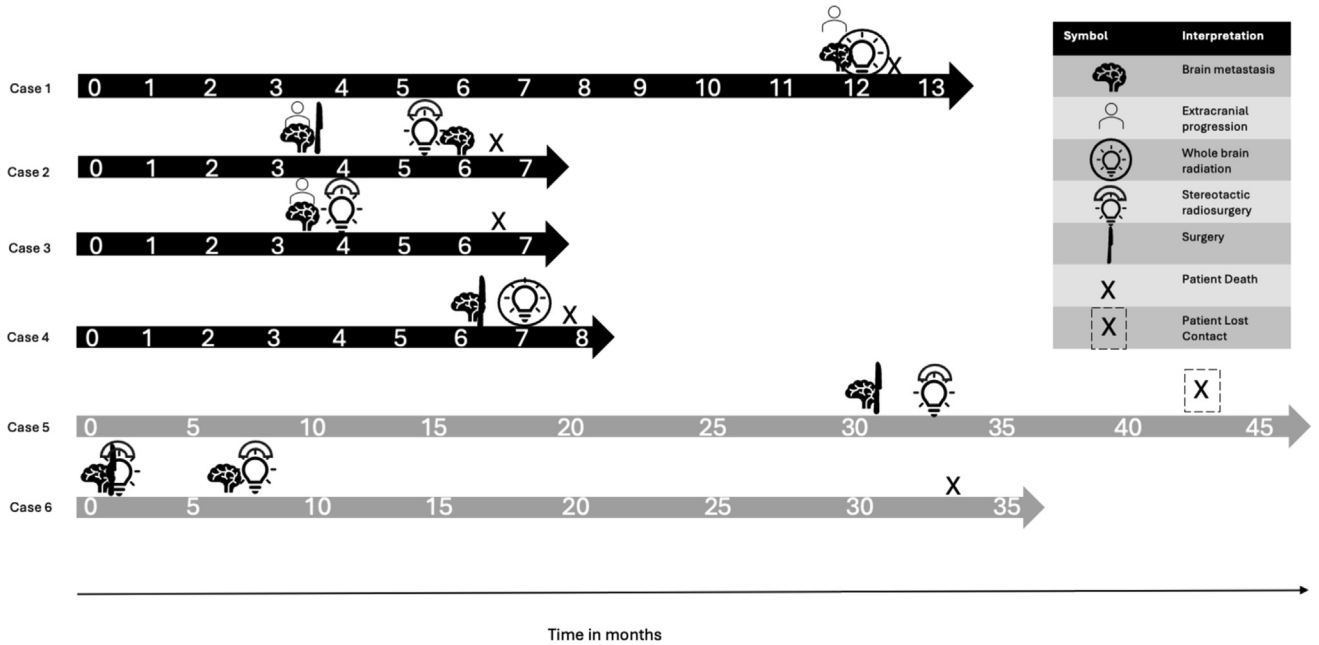

Figure 2. Timeline by patient with brain metastases from immunotherapy start to brain metastasis, to treatment, to death or last contact.

Table 2. Patients with Brain Metastases, Time to Incidence of BM, Time to Death from BM, Treatment for BM

Patient	Time from IO to BM (Days)	Treatment Immediately Before or During BM (Line of Therapy)	Surgery for Brain Metastasis (Y/N)	Type of Radiation	Time from BM to Death or Last Contact (Days)
1	364	Ipi/Nivo, (3L)	N	WBRT	16
2	104	Ipi/Nivo, (2L)	Y	SRS	95
3	105	Ipi/Nivo, (1L)	N	SRS	95
4	184	Ipi/Nivo, (1L)	Y	WBRT	51
5	913	Pembro, (2L)	Y	SRS	416
6	2	Pembro, (2L)	Y	SRS	1025

BM, brain metastasis; IO, immunotherapy.

incidence of BM in patients who received IO may warrant consideration of surveillance brain imaging in patients with PM receiving IO.

BMs developed in patients with all three histologies and was not correlated with prolonged survival. The mOS was similar across all three treatment groups in the overall population, including all histologies, but rates of BM development were significantly different. This highlights that the increased incidence of BM development compared with historical reports is likely due to more than just improved survival of patients overall, allowing time for metastasis to the brain. In agreement with our results, all histologic subtypes have been shown to metastasize to the brain, and dedifferentiation to more aggressive subtypes has also been reported.[9] In the cases presented, although small in number, the available brain tissue from metastatic brain disease (two sarcomatoid and one epithelioid) reported similar histology to their corresponding primary tumors with no overt evidence of dedifferentiation.

There are several possible explanations for why BMs were more prevalent in those that received checkpoint blockade. Immune checkpoint inhibition, and especially dual checkpoint blockade, is potentially causing more edema around existing BMs leading to symptoms that prompt brain imaging in this population, as has been shown in other cancer types.[10–12] This immune reaction can be from immune cells that cross the blood brain barrier from extra-cranial immune cell activation or from activation of immune cells within the brain tumor microenvironment from ICIs that cross the blood brain barrier.[13–16] Cytokines released by tumor cells or the tumor microenvironment, which is inflammatory and composed of microglia and macrophages, promotes T-cell homing and an immune response from the IO.[15] Our pathologic results reported ample T-cells and macrophages within the tumor and in the periphery in addition to hemorrhage, suggesting that these tumors are highly inflamed. Future studies will need to clarify the role of these immune cells in the tumor microenvironment of BMs in mesothelioma.

Our study is limited by its retrospective nature and the rarity of PM. In addition, this is a real-world cohort, so certain data points were not available for all patients,

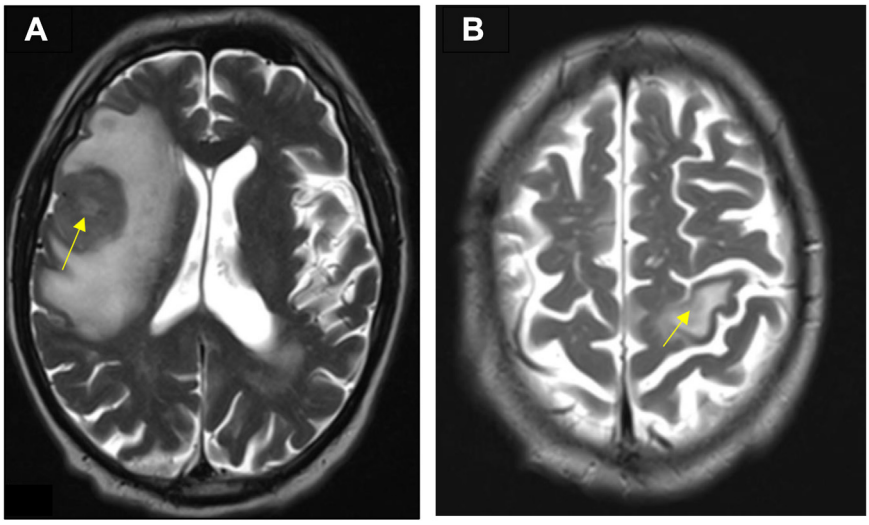

Figure 3. Example of patient with initial brain metastasis *(A)* and subsequent out-of-field progression with new brain met *(B)*. Yellow arrow pointing to brain metastasis.

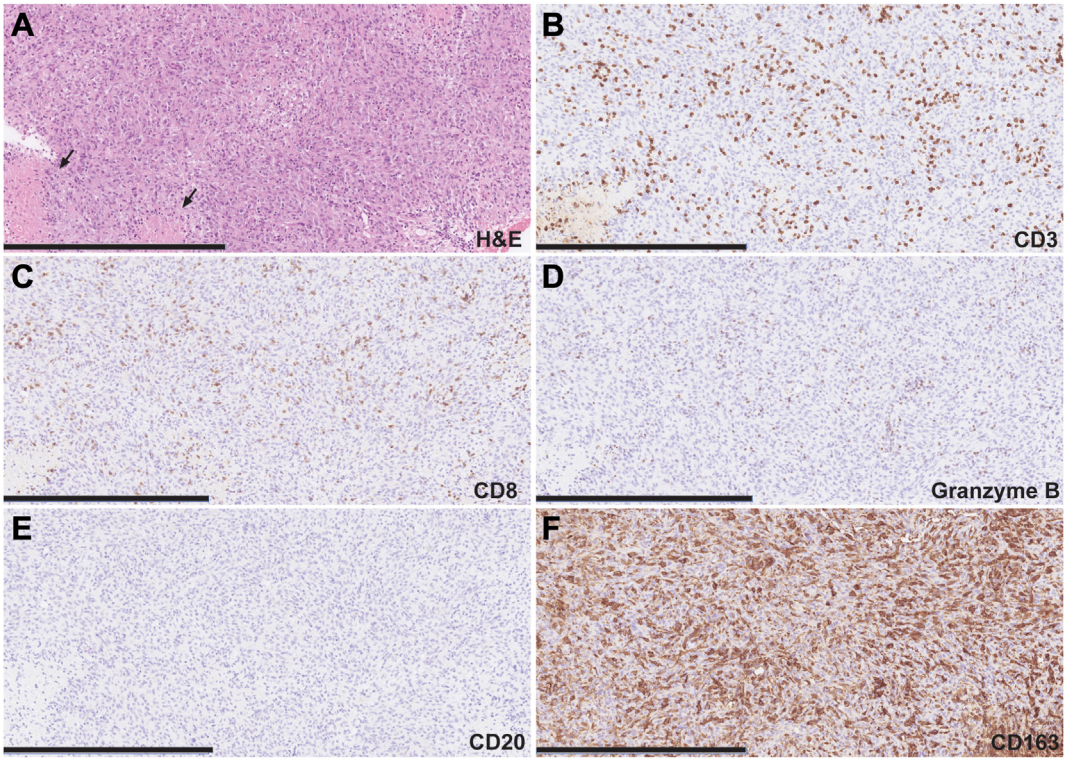

Figure 4. Brain tissue pathologic analysis from one patient. *(A)* H&E-stained section demonstrates metastatic mesothelioma with an epithelioid histology and areas of necrosis (black arrows). *(B-D)* CD3 staining highlights numerous intratumoral T-lymphocytes *(B)*, with a subset of these cells identified as CD8+ cytotoxic T-cells *(C)*, which are also positive for granzyme B *(D)*. *(E)* CD20 staining shows an absence of intratumoral B cells. *(F)* CD163 staining highlights the presence of numerous intratumoral macrophages. Scale bars in 500 μm *(A-F)*. H&E, hematoxylin and eosin.

and brain imaging was not performed on the entire cohort. In particular, brain imaging was not available for all patients because it is not routinely recommended for patients who are asymptomatic. Although we saw a longer mOS in patients who received brain imaging compared with those that did not, our sensitivity analysis, including only patients who received brain imaging, still reported a higher proportion of patients in the IO-exposed group developed BMs. Ultimately, to determine the true incidence this would need to be evaluated in a cohort of patients with routine surveillance brain imaging.

In conclusion, our study shows that diagnosed BMs are more prevalent in patients that have received IO for PM and that patients who develop BM have a poor prognosis. More research is needed for better therapeutic options for patients with PM that develop metastases to the brain and more brain surveillance is warranted in particular for those receiving checkpoint blockade.

CRediT Authorship Contribution Statement

Margaret Stalker: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing - original draft.

Suzanne L. Walker: Conceptualization, Writing - review & editing.

Emily Lebow: Data curation, Writing - review & editing.

Emily Ling-Lin Pai: Data curation, Writing - review & editing.

Alex Watts: Formal analysis.

Wei-Ting Hwang: Formal analysis.

Amir Banihashemi: Writing - review & editing.

Evan Anderson: Writing - review & editing.

Leonid Roshkovan: Writing - review & editing.

Sharyn I. Katz: Writing - review & editing.

Leslie Litzky: Writing - review & editing.

Andrew R. Haas: Conceptualization, Writing - review & editing.

Sunil Singhal: Writing - review & editing.

Corey J. Langer: Writing - review & editing.

Keith Cengel: Writing - review & editing.

Melina E. Marmarelis: Conceptualization, Formal analysis, Methodology, Supervision, Writing - review & editing.

Disclosure

The authors declare no conflict of interest.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2025.100823.

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