BRIEF REPORT

PD-L1, Tumor Mutational Burden, and Outcomes in NSCLC With Brain Metastases: A Brief Report

Elio Adib, MD,[a,*] Amin H. Nassar, MD,[b] Elias Bou Farhat, MD,[c] Shyam K. Tanguturi, MD,[a] Rifaquat M. Rahman, MD,[a] Daphne A. Haas-Kogan, MD, MBA,[a] Wenya Linda Bi, MD, PhD,[d] Omar Arnaout, MD,[d] Patrick Y. Wen, MD,[e] David J. Kwiatkowski, MD, PhD,[c] Mark M. Awad, MD, PhD,[c] Ayal A. Aizer, MD[a]

[a]*Department of Radiation Oncology, Brigham and Women's Hospital, Boston, Massachusetts*
[b]*Department of Medical Oncology, Yale New-Haven Cancer Center, New Haven, Connecticut*
[c]*Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*
[d]*Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts*
[e]*Center For Neuro-Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*

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ABSTRACT

Introduction: Patients with NSCLC and brain metastases have a poor prognosis. Combining brain-directed radiation therapy (RT) with immune checkpoint inhibitors (ICIs) may be synergistic. Nevertheless, predictors of response and toxicity are lacking.

Methods: This retrospective study conducted at Dana-Farber Brigham Cancer Center from 2015 to 2023 included patients with non-*EGFR* and non-*ALK*-altered NSCLC and newly diagnosed brain metastases starting ICI within 90 days of brain-directed RT. We assessed all-cause mortality, systemic and neurologic death, systemic and intracranial progression at the patient level, and local recurrence and radiation necrosis at the metastasis level.

Results: Among the 178 patients with 536 brain metastases, the median age was 64 years, and 53% were female individuals. The median number of brain metastases detected at diagnosis was three. Most patients received pembrolizumab (93%) and were treated with stereotactic radiation (81%). Higher programmed death-ligand 1 (PD-L1) expression was associated with improved all-cause mortality (median survival: PD-L1 less than 1%: 10.7 mo, 1%–49%: 14.3 mo, more or equal to 50%: 29.5 mo), driven by longer time to systemic death. Higher PD-L1 was also associated with improved systemic progression-free survival ($p_{\geq 50\% \text{ versus } <1\%} = 0.02$) and distant intracranial disease-free survival ($p_{\geq 50\% \text{ versus } <1\%} = 0.02$). The rate of local recurrence was low across all groups (1%–4% at 2 y). Patients with higher PD-L1 had numerically higher radiographic radiation necrosis rates (2.3%, 5.5%, 9.3% at 2 y for PD-L1 <1%, 1%–49%, and ≥50%, respectively, $p_{\geq 50\% \text{ versus } <1\%} = 0.08$) and significantly higher symptomatic radiation necrosis rates ($p_{\geq 50\% \text{ versus } <1\%} = 0.04$).

Conclusions: The combination of brain-directed RT and ICI is effective in treating patients with NSCLC and brain metastases. Although high PD-L1 levels are associated with longer survival and improved intracranial control, radiation necrosis occurs more frequently in patients with high PD-L1 expression. Clinicians should be aware of long-term treatment-related toxicities in this population.

Keywords: Non–small cell lung cancer; Brain metastasis; Stereotactic radiation; Immunotherapy; Biomarkers; Radiation necrosis

***Corresponding author.**

Address for correspondence: Elio Adib, MD, Department of Radiation Oncology, Brigham and Women's Hospital, 75 Francis Street, Boston, Massachusetts 02115. E-mail: elio_adib@dfci.harvard.edu

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Introduction

Brain metastases occur in approximately 50% of patients with NSCLC, significantly affecting patient prognosis and quality of life.[1] Radiation forms the mainstay of intracranial management in patients with nontargetable disease and is increasingly administered in a targeted manner using stereotactic radiosurgery or radiotherapy (SRS or SRT).

Immune checkpoint inhibitors (ICIs) represent a component of the standard of care systemic therapy for eligible patients with advanced NSCLC and brain metastases without targetable driver mutations, as they have reported efficacy both intracranially and extracranially.[2–4] Tumor programmed death-ligand 1 (PD-L1) expression and tumor mutational burden (TMB) may predict extracranial response to ICI in NSCLC.[5–7]

Combining brain-directed radiation with ICI has shown synergistic effects in patients with NSCLC and brain metastases.[6] Nevertheless, predictors of intracranial outcomes remain lacking in this population. We aimed to explore the outcomes of patients treated with a combination of brain-directed radiation and immunotherapy, focusing on the impact of PD-L1 and TMB.

Materials and Methods

We identified patients managed at the Dana-Farber Brigham Cancer Center between 2015 and 2023 with *EGFR* and *ALK* wild-type NSCLC who started ICI (with or without concurrent chemotherapy) within 90 days of brain-directed radiation therapy (RT) and underwent immunohistochemical PD-L1 testing. Next-generation sequencing was performed using an institutional platform, Oncopanel.[8] When available, resected brain tumor tissue was used for PD-L1 and next-generation sequencing testing. The study was approved by the institutional review board of our center, and the need for individual patient consent was waived.

We included patients who received either whole brain RT (WBRT), SRS or SRT with or without neurosurgical resection. Patients who did not undergo a follow-up brain magnetic resonance imaging after brain-directed RT were excluded. WBRT was performed using a traditional or hippocampal-sparing approach, most frequently at 30 Gy in 10 fractions. SRS typically entailed 20 Gy in one fraction, with lower doses (15–19 Gy) utilized for tumors greater than 2 cm. Targets greater than 2 cm in size were typically managed with SRT, using 24 to 27 Gy in three fractions or 25 to 30 Gy in five fractions. All patients who underwent resection received stereotactic treatment for the surgical cavity (25 Gy in five fractions if gross totally resected and 30 Gy in five fractions if subtotally resected). Patients undergoing neurosurgical resection can also undergo radiation treatment for intact lesions.

Patient-level end points included all-cause mortality, systemic death, neurologic death, distant intracranial disease-free survival, systemic progression-free survival, time to seizures, and time to leptomeningeal disease. Metastasis-level end points included rates of local recurrence and radiation necrosis (RN). Radiographic RN was defined as changes consistent with RN on magnetic resonance imaging. Symptomatic RN is an RN that causes focal neurologic symptomatology with or without the need for steroids, bevacizumab, or neurosurgical intervention.

RN versus local recurrence was determined through a standardized approach incorporating pathologic confirmation when surgical specimens were available, characteristic imaging findings on dual-phase positron emission tomography–computed tomography or serial magnetic resonance imaging showing classic radionecrotic changes, and final assessment by an attending radiation oncologist specializing in brain metastases, with our previously validated approach for nonsurgical cases demonstrating 90% accuracy in this differentiation.[9]

The outcomes were calculated from the time of brain metastasis diagnosis. Descriptive statistics were used to summarize the patient characteristics. Multivariate Cox regression analysis was used to assess all-cause mortality, systemic progression-free survival, and distant intracranial disease-free survival, adjusting for the following variables at the time of diagnosis selected a priori: age at diagnosis, sex, Karnofsky Performance Scale score, Charlson Comorbidity Index score, number of brain metastases at diagnosis, extracranial disease at diagnosis, and number of prior systemic treatments. PD-L1 categories were based on joint guidelines (less than 1%, 1%–49%, or more or equal to 50%) and TMB was derived from Oncopanel.[8,10] Fine-Gray models were used to assess time to systemic death, time to neurologic death, and per-metastasis outcomes such as local recurrence and RN, with a sandwich estimator used to account for intrapatient correlations in per-metastasis models. All p values were two-sided. Statistical analyses were performed using R version 4.3.2.

Results

A total of 178 patients with 536 newly diagnosed brain metastases secondary to NSCLC were included (Table 1). The median patient age was 64 years. Most patients (147 of 178, 83%) had adenocarcinoma, 11% had squamous cell carcinoma, and 6% had other histologic types. Only eight patients were never smokers. The median number of brain metastases was three

Table 1. Baseline Demographic and Clinical Characteristics for 178 Patients With NSCLC and Brain Metastases Treated With ICI and Brain-Directed Radiation Therapy

Baseline Characteristics	Total (N = 178)
Age, y (median [IQR])	64 (57-70)
Sex, n (%)	
Female	94 (53)
Male	84 (47)
Histologic subtype, n (%)	
Adenocarcinoma	147 (83)
Squamous cell carcinoma	19 (11)
Adenosquamous	4 (2)
Other[a]	8 (4)
Smoking status, n (%)	
Former or current	170 (96)
Never	8 (4)
Brain metastases at cancer diagnosis, n (%)	
Yes	66 (37)
No	112 (63)
Number of brain metastases at time of initial intracranial involvement (median [IQR])	3 (1-7)
Karnofsky performance status score, n (%)	
≤70%	16 (9)
80%	55 (31)
90%	102 (57)
100%	5 (3)
Charlson Comorbidity Index, n (%)	
0	99 (56)
1	44 (25)
2	25 (14)
≥3	10 (5)
Neurosurgical resection, n (%)	
Yes	55 (31)
No	123 (69)
Radiation type, n (%)	
Stereotactic radiosurgery or radiotherapy	145 (81)
HA-whole brain radiation therapy	14 (8)
Non-HA-whole brain radiation therapy	19 (11)
ICI start time, n (%)	
31-90 d before RT start	12 (7)
1-30 d before RT start	20 (11)
0-30 d after RT start	99 (56)
31-90 d after RT start	47 (26)
PD-L1 TPS, n (%)	
<1%	51 (29)
1%-49%	55 (31)
≥50%	72 (40)
Tumor mutational burden, mut per MB (Median [IQR])	11 (7- 15)

[a]Includes large cell neuroendocrine, bronchoalveolar, or NSCLC NOS.
HA, hippocampal avoidance; ICI, immune checkpoint inhibitor; IQR, interquartile range; mut per MB, mutations per megabase; NOS, otherwise specified; PD-L1, programmed death-ligand 1; RT, radiation therapy; TPS, tumor proportion score.

(interquartile range: 1–7). Most (145 of 178, 81%) of the patients received SRS or SRT. Fifty-five patients (31%) underwent neurosurgical resection of at least one brain metastasis before brain-directed RT as a component of the initial brain-directed management. Regarding ICI, most patients received pembrolizumab (167 of 178, 94%), followed by atezolizumab (5 of 178, 3%), and 94 patients (53%) received concurrent chemotherapy, most frequently carboplatin and pemetrexed, in combination with pembrolizumab (79 of 94, 84%). PD-L1 levels were less than 1%, 1% to 49%, and 50% or higher in 51 (29%), 55 (31%), and 72 patients (40%), respectively. The median TMB was 11 mutations per megabase (mut per MB; interquartile range: 7–15). The median follow-up period for the entire cohort was 30.1 months (range: 1.2–78.6 mo).

Higher PD-L1 expression was associated with improved all-cause mortality, with a median survival in patients with PD-L1 levels less than 1%, 1% to 49%, and 50% or higher of 10.7, 14.3, and 29.5 months, respectively ($p_{1\text{ to }49\%\text{ versus less than }1\%} = 0.09$, $p_{\geq 50\%\text{ versus }<1\%} = 0.02$; Fig. 1*A*, Supplementary Table 1). Similarly, higher PD-L1 level was associated with a longer time to systemic death (hazard ratio $[HR]_{1\%-49\%\text{ versus }<1\%} = 0.72$, 95% confidence interval [CI]: 0.38–1.34, $p = 0.30$; $HR_{\geq 50\%\text{ versus }<1\%} = 0.48$, 95% CI: 0.24–0.93, $p = 0.03$; Fig. 1*B*, Supplementary Table 2), but not longer time to neurologic death (all $p > 0.05$; Fig. 1*C*; Supplementary Table 3).

Of the 178 patients, 152 died or experienced intracranial or extracranial progression. The median time to progression or death was 5.6 months (95% CI: 5.8–6.8 mo). Higher PD-L1 was associated with improved distant intracranial failure-free survival ($HR_{1\%-49\%\text{ versus }<1\%} = 0.85$, 95% CI: 0.50–1.45, $p = 0.54$; $HR_{\geq 50\%\text{ versus }<1\%} = 0.52$, 95% CI: 0.30–0.88, $p = 0.02$; Fig. 1*D*, Supplementary Table 4) and systemic progression-free survival ($HR_{1\%-49\%\text{ versus }<1\%} = 0.72$, 95% CI: 0.43–1.23, $p = 0.23$; $HR_{\geq 50\%\text{ versus }<1\%} = 0.54$, 95% CI: 0.33–0.89, $p = 0.02$; Fig. 1*E*, Supplementary Table 5). A higher TMB was not significantly associated with improved outcomes (all $p > 0.05$; Supplementary Tables 1–5). There were only six leptomeningeal disease events and 24 seizure events post-initial management in the entire cohort, precluding meaningful comparisons.

Local recurrence rates were low across all PD-L1 expression categories (all $p > 0.05$; Fig. 2*A*). Cumulative incidence of local recurrence at two years was 4.2% (95% CI: 1.8%–8.0%) in the less than 1% PD-L1, 1% (95% CI: 0.2%–3.4%) in 1% to 49% PD-L1, and 1.5% (95% CI: 0.3%–5%) in the 50% or higher PD-L1 categories. Local recurrence rates at six, 12, 18, and 24 months are shown in Supplementary Table 6. Cumulative incidence of radiographic RN at two years was numerically higher in patients with higher PD-L1 (2.3% versus 5.5% versus 9.3% for PD-L1 < 1%, 1%–49%, and ≥50%, respectively; Supplementary Table 6), but did not reach statistical significance ($p_{1\%-49\%\text{ versus }<1\%} = 0.15$, $p_{\geq 50\%\text{ versus }<1\%} = 0.08$; Fig. 2*B*). The rate of symptomatic RN was significantly higher in patients with higher

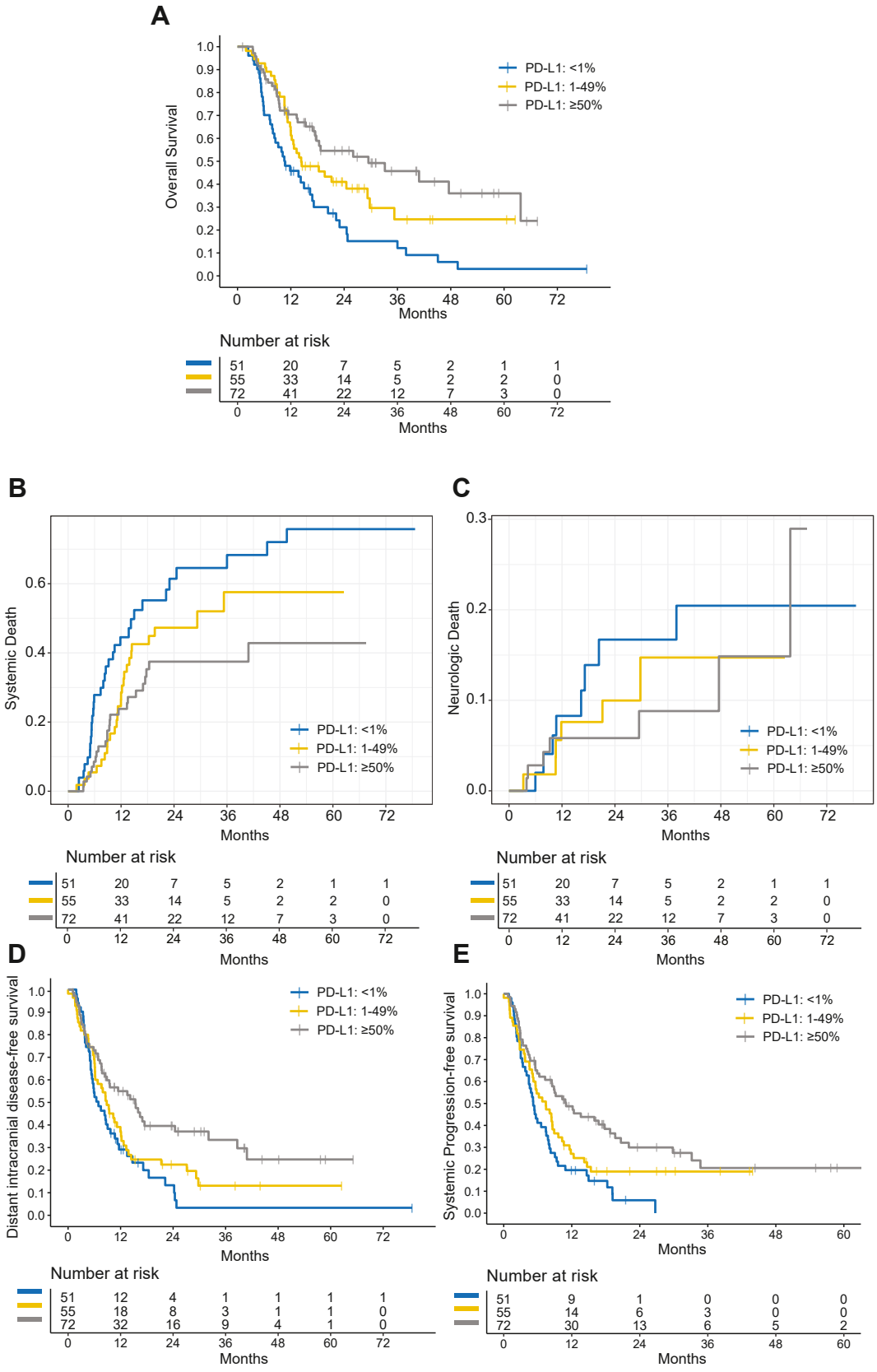

Figure 1. All-cause mortality *(A)*, time to systemic death *(B)*, time to neurologic death *(C)*, distant intracranial disease-free survival *(D)*, and systemic progression-free survival *(E)* for 178 patients treated with ICI and brain-directed radiation by PD-L1 level. ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1.

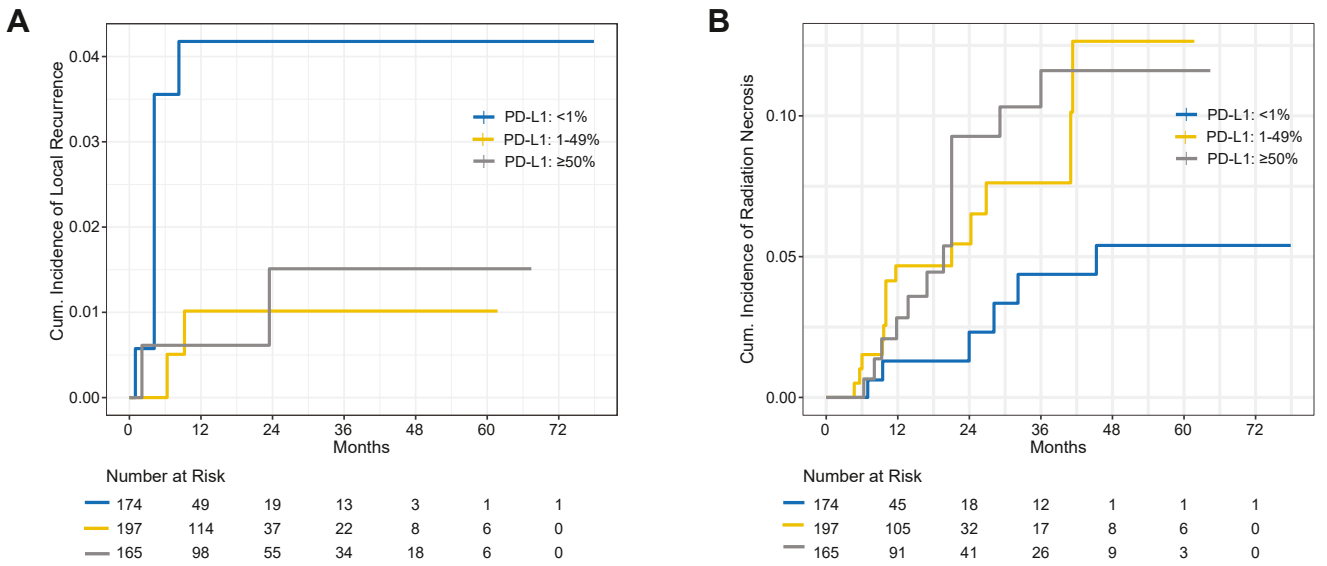

Figure 2. Local recurrence *(A)* and radiation necrosis *(B)* rates for 536 metastatic lesions treated with ICI and brain-directed radiation by PD-L1 level. ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1.

PD-L1 expression after adjusting for prior neurosurgical resection (Supplementary Table 7; $p_{\geq 50\% \text{ versus } <1\%} = 0.04$). A higher TMB was not associated with significantly higher local control or RN. Of 12 patients who survived for more than years without intracranial failure, 11 (92%) had positive PD-L1, and eight (67%) had PD-L1 levels of 50% or higher. In this subset, RN was reported in 4 of 44 (9%) lesions (Supplementary Fig. 1). Sixty-four patients received subsequent cranial RT: 58 received SRS and six received WBRT.

Analyses were also performed on a subset of patients receiving SRS alone (96 of 178 patients), which reported similar excellent local control rates and HR trends that did not reach statistical significance, likely owing to reduced statistical power (Supplementary Table 8).

Discussion

To the best of our knowledge, this is the largest retrospective study assessing the efficacy and safety of concurrent ICI and brain-directed RT in patients with NSCLC and brain metastases, whereas also incorporating biomarkers such as PD-L1 levels and TMB. These results highlight the promising outcomes achieved through the integration of RT and immunotherapy for nontargetable NSCLC and brain metastasis. Across all subsets, two-year local control rates surpassed 95%, suggesting synergism between radiation and ICI, especially relative to ICI monotherapy, where intracranial response rates in favorable subsets remain at approximately 30%.[3]

The primary concern with SRS and SRT is RN, which can affect 5% to 30% of patients.[11] In our study, RN occurred in 33 of 536 lesions, and the two-year rates were numerically increased with higher PD-L1 expression levels, with the 50% or higher PD-L1 category showing the highest rates of RN (9.3%). Although high PD-L1 expression was associated with an increased risk of RN, this finding should be interpreted considering that these patients also reported longer survival times, potentially allowing more opportunity for RN development, although our competing risk regression analysis attempted to account for this time-dependent effect.

PD-L1 is an established predictive biomarker for NSCLC and is used to guide systemic management.[12] More recently, TMB was found to correlate with survival, particularly in subsets in the ninetieth and higher percentile.[7] In our study, higher PD-L1 tumor expression was associated with improved all-cause mortality, largely driven by a reduction in systemic, rather than neurologic death. A higher TMB was also correlated with a longer time to systemic progression or systemic death. The excellent local control and extended survival, but higher rates of RN seen in PD-L1 high tumors might engender trials evaluating de-intensification (e.g., dose or margin reduction) in this population.

The limitations of our study include its retrospective design. Therefore, variations exist in the concomitant delivery of chemotherapy. In addition, our analysis did not account for the effect of neurosurgical resection or concurrent chemotherapy on the studied outcomes. Finally, although the patients were treated at a single institution, some differences in follow-up imaging schedules existed, which could have impacted the estimation of time-to-event outcomes. Moving forward, continued research efforts aimed at refining patient selection criteria, optimizing the sequencing of treatments,

and developing strategies to mitigate radiation-related toxicities will be essential for further improving outcomes in this challenging patient population.

CRediT Authorship Contribution Statement

Elio Adib: Conceptualization, Methodology, Data curation, Data analysis, Visualization, Writing - original draft.

Amin H. Nassar: Data analysis, Visualization, Writing - reviewing & editing.

Elias Bou Farhat: Visualization, Writing - reviewing & editing.

Shyam K. Tanguturi: Data curation, Writing - reviewing & editing.

Rifaquat M. Rahman: Writing - reviewing & editing.

Daphne Haas-Kogan: Writing - reviewing & editing.

Wenya Linda Bi: Writing - reviewing & editing.

Omar Arnaout: Writing - reviewing & editing.

Patrick Y. Wen: Writing - reviewing & editing.

David J. Kwiatkowski: Writing - reviewing & editing.

Mark M. Awad: Methodology, Writing - reviewing & editing.

Ayal A. Aizer: Conceptualization, Methodology, Data curation, Writing - original draft.

Disclosure

Dr. Nassar receives honoraria from OncLive, TEMPUS, and Korean Society for Medical Oncology; and consulting fees from Guidepoint Global. Dr. Rahman reports consulting fees from Servier Pharmaceuticals, Telix Pharmaceuticals. Dr. Wen reports research support from AstraZeneca, Black Diamond, Bristol Meyers Squibb, Chimerix, Eli Lily, Erasca, Global Coalition For Adaptive Research, Kazia, MediciNova, Merck, Novartis, Quadriga, Servier, VBI Vaccine and honoraria for participation on advisory boards or consultation from Anheart, AstraZeneca, Black Diamond, Celularity, Chimerix, Day One Bio, Genenta, Glaxo Smith Kline, Kintara, Merck, Mundipharma, Novartis, Novocure, Prelude Therapeutics, Sagimet, Sapience, Servier, Symbio, Tango, Telix, VBI Vaccines. Dr. Kwiatkowski reports research contracts with Genentech, AADI, and Revolution Medicines; and has been a consultant to Genentech, AADI, Expertconnect, Guidepoint, Bridgebio, Slingshot Insights, William Blair, MEDACorp, and Radyus Research. Dr. Aizer reports research funding from Varian and NH TherAguix and consulting for Novartis and Seagen. The remaining authors declare no conflict of interest.

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.2025.100797.

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