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Review Article

The Role of Immune Checkpoint Inhibitors in Brain Metastasis: A Comprehensive Review

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Abstract

Brain metastasis (BM) is a common form of cancer that affects the central nervous system and has a significant impact on the life expectancy and quality of patients. Despite conventional treatments like surgery, chemotherapy, and radiotherapy, managing BM is challenging, and success rates are low. Immune checkpoint inhibitors (ICIs) have emerged as promising new therapies for advanced cancers and work by reversing the immune-evasive characteristics of tumor cells. ICIs have shown efficacy in various malignancies, prompting researchers to evaluate their efficacy in BM. Previously, the exclusion of BM patients from clinical trials was common due to the brain's immune-privileged nature. However, recent studies have demonstrated immune cell trafficking in and out of the brain, leading to several studies investigating the ICIs' application in BM patients. This study aimed to provide further evidence supporting the beneficial effects of ICIs in treating BM, as evidenced by improved response duration and survival time.

Keywords: Anti-PD-1/Anti-PD-L1; Anti-CTLA-4; Anti-LAG-3; Brain Metastasis; Immune Checkpoint Inhibitors (ICIs)

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Introduction

Brain metastases (BM) are the most common form of malignant tumor in the central nervous system (CNS), occurring in approximately 20–40% of patients with cancer (1). Although nearly all types of malignancies can metastasize to the brain, BMs mainly originate from the lungs (≥ 50%), breasts (15–25%), skin (melanoma)(5–20%), and less frequently, kidneys, testes, colon, rectum, and thyroid (1). Various treatments are used in different stages of primary and metastatic brain tumors, including oral or intravenous steroids for reducing intracranial edema, surgical resection, stereotactic radiosurgery (SRS), whole brain radiotherapy (WBRT), and chemotherapy (CT)(2-10). However, these treatments are not without their drawbacks. For instance, surgical resection can be mainly performed in patients with a single BM in surgically accessible locations and is also associated with a high rate of local recurrence (8). Steroid therapy is also associated with intracranial and systemic adverse events (AEs), including immunosuppression, glucose intolerance, cushingoid appearance, and myopathies (11). Hence, current therapies for BM seem relatively inadequate, emphasizing the need for modifying the present treatment paradigm.

A strong correlation has been found between the immune system and the CNS, as the immune system plays substantial roles in various brain pathophysiological processes, including cerebral edema, neurodegeneration, and neurogenesis (12-16). In this context, different therapeutic options targeting various immune system components have been applied to a wide variety of CNS abnormalities, including multiple sclerosis, neurodegenerative diseases, traumatic brain injury, stroke, and primary and metastatic brain tumors (4, 9, 17-21). A primary group of immune system components that can be used as therapeutic targets in different cancers, such as CNS tumors, are immune checkpoint (IC) proteins. ICs induce inhibitory pathways, resulting in the immune system's self-tolerance and minimizing autoimmunity (22). However, these immune inhibitory features of ICs can be exploited by tumor cells to escape the immune response, leading to their growth and invasiveness. Therefore, the blockade of the ICs might serve as a rational approach to reverse the tumor's survival mechanisms (23). In this regard, immune checkpoint inhibitors (ICIs) have been developed. They exert their anti-tumor effects by blocking the interaction between ICs and their ligands, thereby facilitating the recognition and neutralization of tumor cells by the immune system (24, 25). To date, the most frequently utilized ICIs are programmed cell death protein 1 (PD-1) inhibitors, PD ligand 1 (PD-L1) inhibitors, and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors (24).

The discovery of ICIs has led to significant progress in the treatment of a broad spectrum of cancers, like classical Hodgkin's lymphoma, metastatic melanoma, colorectal cancers, renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck (SCCHN), metastatic urothelial carcinoma, and hepatocellular carcinoma (26). Additionally, ICIs have shown acceptable efficacies in managing BM from various origins, including melanomas, RCC, and non-small cell lung cancers (NSCLCs)(27). In addition, ICIs and other cancer therapies, including radiotherapy (RT), surgery, and other systemic therapies (i.e., mitogen-activated protein kinase (MAPK) inhibitors in melanoma and epidermal growth factor receptor (EGFR) and anaplastic large-cell lymphoma kinase (ALK) inhibitors in NSCLC), have shown synergistic impacts on improving the course of BM (27-30).

Given the exclusion of many patients with active BM in most clinical trials assessing ICIs effects, the data on the role of ICIs in BM is relatively underdeveloped compared to extra-cranial metastases. Hence, this study aims to comprehensively overview the existing clinical data regarding the efficacy of ICI treatment in patients with BM. First, we provided an overview of ICI types and their role in cancers. Second, we discussed their roles in BM. Then four major ICI categories used in BM and the most important medications in each category were discussed separately, including PD-1 inhibitors (pembrolizumab, nivolumab, cemiplimab), PD-L1 inhibitors (atezolizumab, durvalumab, avelumab), CTLA-4 inhibitors (ipilimumab, tremelimumab), and lymphocyte-activation gene 3 (LAG-3) inhibitors (relatlimab). The role of combination therapies for treating BM, including dual immunotherapy or the combination of immunotherapy with conventional approaches, was also reviewed.

ICs and ICIs in Cancers

ICs are regulatory proteins of the immune system that maintain self-tolerance and prevent autoimmune tissue damage (22). However, since cancer cell growth is associated with immune suppression, the inhibitory effects of ICs on the immune system could potentiate cancer cells to grow and spread, resulting in the development of tumors and metastases (31). Tumor cells can activate different IC pathways that establish immunosuppression, facilitating their escape from the immune system (31). Therefore, the blockade of IC pathways by designing ICIs can potentially prevent the invasion and survival of tumor cells (31). To date, various types of IC proteins and their associated inhibitors have been recognized and developed.

PD-1, a transmembrane protein belonging to the cluster of differentiation (CD) 28 family, is present on the surface of T cells, B cells, natural killer (NK) cells, and NK-T cells (32). PD-1 can attach to two types of ligands, including PD-L1 (B7-H1, CD274), mainly expressed on T cells, tumor cells, antigen-presenting cells (APCs), fibroblasts, and endothelial cells, and PD-L2 (B7-DC, CD273), which is mainly expressed on the surface of B-cells, dendritic cells, macrophages, and monocytes (33, 34). The binding of PD-1 to PD-L1 results in the apoptosis of antigen-specific T cells and prevents autoimmunity. However, this process can also allow the evasion of tumor cells from the immune system (34). Summarily, PD-1 or PD-L1 inhibitors exert their anti-tumor effects by blocking the PD-1 and PD-L1 interactions and thereby activating tumor-suppressing T cells (34).

CTLA-4, a cell surface receptor of the CD28 family, is another IC expressed on various immune cells, like T cells, B cells, NK cells, and NK-T cells (32). CTLA-4 residing on inactivated T cells competes with the T cells' CD28 receptors to bind to CD80/86 on APCs, causing T cells to remain in their inactive conditions (34). In this regard, CTLA-4 inhibitors facilitate the attachment of CD28 to CD80/86 by blocking the binding of CTLA-4 and CD80/86, resulting in T-cell activation and consequently tumor cell detection and destruction (34).

LAG-3 (CD223) is another IC, located on activated T cells, B cells, and NK cells (32). This protein competes with CD4 receptors for binding to major histocompatibility complex (MHC)-II, interfering with CD4 function (32). For instance, the expression of MHC-II molecules on human melanoma cancer cells is considered a poor prognostic factor (35), as the binding of MHC-II and LAG-3 (expressed on melanoma-infiltrating T cells) can suppress the immune response, resulting in the immune evasion of the tumor cells (32, 35). Hence, blocking the interaction of MHC-II and LAG-3, through designed anti-LAG-3 agents, can facilitate the detection of tumor cells by the immune system (36). **Figure 1** presents different interactions between ICs (PD-1, PD-L1, CTLA-4, and LAG-3) and their ligands, and also the inhibitory effects of ICIs on these interactions.

ICs and ICIs in Brain Metastasis

Despite advancements in multimodality strategies, including surgery, CT, and RT, BMs are still challenging to treat (37-39). Following the discovery of immune cell trafficking in and out of the CNS, immunotherapy (treatment with ICIs, such as anti-PD-1, anti-PD-L1, anti-CTLA-4, and anti-LAG-3 antibodies) has brought new hopes for patients with BM, particularly those without druggable mutations (40-46). Accordingly, a large study by Amin *et al.* among patients who received definitive surgery for the primary cancer site, showed that the overall survival (OS) of those who received immunotherapy plus any treatment was better than that of those who received no immunotherapy (47). Moreover, a study on a huge number of patients with BM revealed improved survival with ICIs in those with melanoma brain metastasis (MBMs), NSCLC-BMs, and triple-negative breast cancer (TNBC)-BMs (46). **Table 1** and **Table 2** provide comprehensive information on studies investigating the effects of ICIs in patients with BM. The following information was extracted for each study: study-related characteristics (author, year, study type), primary tumor type, ICI or other utilized treatment approaches, outcome measures and main findings (including complete response [CR], partial response [PR], objective response [OR], best overall response rate [BORR], progression-free survival [PFS], overall survival [OS], etc.), and treatment-related AEs (tr-AEs).

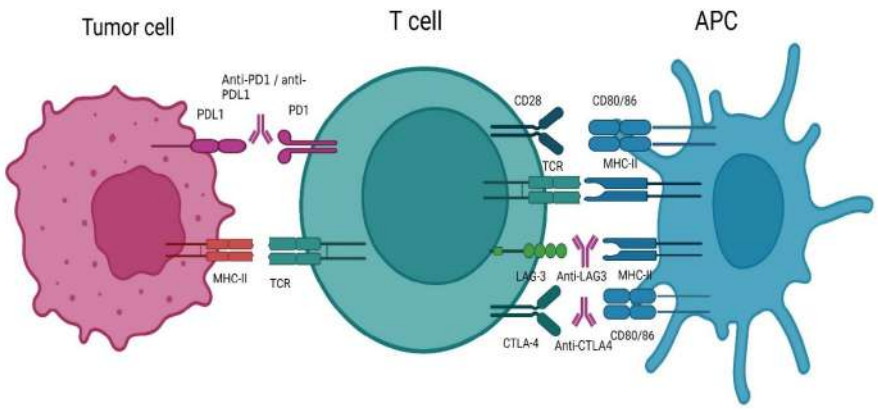

Figure 1. The Interactions between ICs and ICIs on the surface of T Cells, APCs, and Tumor Cells. ICIs block the interaction of PD-1, CTLA-4, LAG-3 with PD-L1, CD80/86, and MHC-II, respectively. Consequently, TCR and CD28 bind to MHC-II and CD80/86, respectively, resulting in the detection and neutralization of tumor cells.
Abbreviations: APC, antigen presenting cell; CD, cluster of differentiation; CTLA-4, cytotoxic T-lymphocyte associated protein-4; IC,immune checkpoint; ICI, immune checkpoint inhibitor; LAG-3, lymphocyte activation gene-3; MHC, major histocompatibility complex; PD-1, programmed cell death protein-1; PD-L1, programmed cell death protein ligand-1; TCR,T-cell receptor.

PD-1 and PD-L1 Inhibitors in Brain Metastasis

PD-1 is an immunosuppressive component on the surface of tumor-infiltrating lymphocytes (TILs), NK cells, and innate lymphoid cells, which is crucial to boost the host's immune-mediated-antitumor response by downregulating the immune system and promoting self-tolerance (48, 49). PD-L1, its ligand, is overexpressed on the surface of malignant tumor cells (48). PD-1/PD-L1 binding inhibits PD-1 positive cell proliferation, resulting in tumor immune evasion and treatment failure (48, 49). Therefore, targeting the PD-1/PD-L1 signaling pathway with inhibitory monoclonal antibodies against PD-1 has emerged as an issue of interest for immunotherapy of various types of malignancies, including primary and metastatic melanoma (46, 50-93), NSCLC (such as adenocarcinoma and squamous cell carcinoma [SCC])(46, 50, 54, 55, 94-134), RCC (46, 50, 55, 135-144), gastrointestinal malignancies (145, 146), breast cancer (46, 147), cervical cancer (148), and hematologic malignancies (149). There are also reports of patients with other types of malignancies with BM, in whom favorable outcomes are reported following treatment with PD-1 or PD-L1 inhibitors, including pulmonary large-cell neuroendocrine carcinoma (150), giant cell carcinoma of the lung (151, 152), metastatic primary pulmonary melanoma (153), SCCHN (154), spindle cell SCC (155), parotid carcinoma (156), porocarcinoma (157), metastatic castration-resistant, mismatch repair-deficient prostate cancer (158), widely metastatic sebaceous carcinoma (159), and advanced male primary choriocarcinoma (160). Notably, the wide use of PD-1 inhibitors across an array of cancer types is mostly based on clinical trials with specific eligibility criteria, limiting its generalizability to specific populations such as the elderly, patients with autoimmune conditions, patients with organ transplant, organ dysfunction, and BM (particularly, symptomatic or progressive BM) (161). However, real-world data have indicated acceptable PD-1 inhibitors' safety and efficacy among different populations of trial-ineligible patients (i.e., elderly), except for solid organ transplant recipients (161-164).

Various approaches have been adopted to investigate the anti-tumor effects of PD-1 inhibitors, including PD-1 inhibitors monotherapy (98, 109, 112, 113, 165, 166) or combination therapies with other ICIs (CTLA-4 inhibitors (56, 57, 79, 80, 83, 91, 92, 123, 141, 167, 168), LAG-3 inhibitors (169, 170), and indoleamine 2 3-dioxygenase 1 inhibitors (171)), targeted therapies (tyrosine kinase inhibitors [TKIs], v-raf murine sarcoma viral oncogene homolog B1 [BRAF] inhibitors, and MAPK kinase (MEK) inhibitors (56, 140,

Table 1. Prospective clinical trials assessing the efficacy of ICIs in BM.

Author, year	Drug	Tumor type	Number of patients	Type of Study	results	ORR	AEs
Page et al (302), 2022	Tremelimumab + Radiotherapy ± Trastuzumab (if HER2+)	Breast cancer	26	Trial (NCT02563925)	Intracranial responses: DCR: 50%, CR: 7.6%, PR: 11.5%, SD: 30.7%	19.1%	84% No grade 4 AEs, Tremelimumab + Radiotherapy ± Trastuzumab was well tolerated
Emamekhoo et al (141), 2022	Ipilimumab + Nivolumab	Advanced renal cell carcinoma	25	Phase IIIb/IV trial (Checkmate 920; NCT02982954)	CR: 0%, PR: 32%, SD: 40%, OR: 32%, median duration of response: 24 months, median PFS: 9 months	32%	Grade 3 or 4: 54%, Any grade: 93%
Gogishvili et al. (134), 2022	Cemiplimab + CT vs. Placebo + CT	NSCLC	466, 31 of whom had BMs (6.7%) (adequately treated and clinically stable brain) Cohort A: Cemiplimab + CT (312, 24 with BMs (7.7%)) - Cohort B: Placebo + CT (154, 7 with BMs (4.5%))	Phase-III study (a double-blind, placebo-controlled) (EMPOWER-Lung 3; NCT03409614)	Cohort A: - CR: 8/312 (2.6) - PR: 127/312 (40.7) - SD: 121/312 (38.8) - PD: 22 /312 (7.1) Cohort B: - CR: 0 - PR: 35/154 (22.7) - SD: 74/154 (48.1) - PD: 24/154 (15.6) Cohort A vs. B: - PFS *: 8.2 vs. 5.0 months (HR = 0.56; P < 0.0001) - OS *: 21.9 vs. 13.0 months (HR = 0.71; P = 0.014)	Cohort A vs. B: ORR (Primary tumor response)*: 135/312 vs. 35/154 (P < 0.0001)	Cohort A vs. B: * Any grade AEs: 95.8% vs. 94.1% * Grade ≥ 3 AEs: 43.6% vs. 31.4%
Di Giacomo et al (83), 2021 (Cohort A)	Ipilimumab + Fotemustine (chemotherapy)	Melanoma	26	Phase III trial (NIBIT-M2 study; NCT02460068)	OS: 8.2 months, 4-year survival: 10.3%, intracranial CR: 7.7%, PR: 11.5%, SD: 15.4%, **OR: 19.2%**	19.3%	Grade 3 or 4: 69%
Di Giacomo et al (83), 2021 (Cohort B)	Ipilimumab + Nivolumab	Melanoma	27	Phase III trial (NIBIT-M2 study; NCT02460068)	OS: 29.2 months, 4-year survival: 41%, Intracranial: CR: 37%, PR: 7.4%, SD: 11.1%, **OR: 44.4%**	11.1%	Grade 3 or 4: 30%
Ahmed et al. (147), 2021	Nivolumab + SRS Previous CNS therapy: - None: 6/12 (50%) resection + stereotactic - Radiation therapy: 1/12 (8%) - Stereotactic radiation therapy: 2/12 (17%) - Surgery: 3/12 (25%) -	Breast cancer-BMs (ECOG PS ≤2 with ≤10 BMs)	12 patients, 17 BMs	Phase-Ib trial (Single-arm, nonrandomized, open-label) (NCT03807765)	Intracranial response: - CR: 6/12 (50%) - PR: 5/12 (42%) - PD: 1/12 (8%) - Median intracranial control: 6.2 months - 6-month control rates: 55% 22% - Local failure: 2/17 lesions (12%) - Median LC: NR - 6-month rate of LC: 100% - 12-month rates of LC: 89% - Median DIC: 9.3 months - 6-month DIC rate:55% - 12-month DIC rate: 28% - distant intracranial failure: 8/12 patients Systemic response: - Systemic progression: 4/12 - Median time to systemic PFS: NR - 6-month PFS rate: 63% - 12-month PFS rate: 51% - Median OS: NR - 12-month OS rate: 89%	iORR: 11/12 (92%)	* No dose-limiting toxicities * Most common neurologic adverse events: grade 1 to 2 headaches and occurring in 5/12 (42%) * RNB: 0 * Treatment-related deaths: 0
Goldberg et al. (114), 2020	Pembrolizumab * Prior local CNS therapy: - None: 21(50%) - SRS: 16 (38%) - WBRT: 8 (19%) - Craniotomy/resection: 4 (10%)	NSCLC-BMs (≥1 brain metastasis 5-20mm not previously treated or progressing after prior radiation, no neurologic symptoms or corticosteroid requirement, and performance status <2)	42 Group A: PD-L1 ≥1% (37) Group B: PD-L1 <1% or unevaluable (5)	Phase-II trial (Non-randomized, open-label) (NCT0208507: updated analysis of the full NSCLC cohort)	Group A: - CR: 7/37 - PR: 4/37 - SD: 4/37 - PD: 16/37 - Unevaluable: 6/37 - Median time to response: 1.8 m - Median PFS: 1·9 m - CNS PFS: 2·3 m - Mortality by the time of data lack: 26/37 - OS: 9·9 m	BM response - Group A: 11/37 (29.7%) * DOR in the brain among the 11 CNS responders: 5.7 m - Group B: No response	* trAEs grade 3 or 4: 2 patients with pneumonitis, and 1 each with constitutional symptoms, colitis, adrenal insufficiency, hyperglycemia, and hypokalemia * Serious trAEs: 6/42 (14%) patients: pneumonitis acute kidney injury, colitis, hypokalemia, and adrenal insufficiency * Treatment-related deaths: 0
Chiang et al. (314), 2020	Atezolizumab	SCLC	17 patients	Phase-I randomized control trial (PCD4989g, NCT01375842)	CNS PFS: 1.9%, median PFS: 1.5 months, median OS: 5.9 months	CNS ORR: 6%,	Grade>III: 29.4%, any grade: 64.7%
Chih-Hsin Yang, (265), 2019	Durvalumab + Osimertinib	Advanced SCLC	21 patients (15 patients received durvalumab and osimertinib)	Phase-I clinical trial (NCT01693562)	CNS ORR: 9.5%, median CNS PFS: 1.5 months, median PFS: 2.3 months, median OS: 4.8 months	ORR: 64%	>Grade III: 0%

Table 1. Continued

Flippot et al. (143), 2019	Nivolumab	ccRCC-BMs (previously untreated or focally treated asymptomatic BMs) ccRCC who failed VEGF–directed therapies	73 - Cohort A: previously untreated BMs (39) - Cohort B: previously treated BMs (34), mostly stereotactic radiation therapy (88%)	Phase-II trial (non-randomized) (NCT03013335)	Cohort A: - CR: 4/34 (12%) - PR: 0 - SD: 13/34 (38%) - PD: 17/34 (50%) - OS rate (12 months): 67% - Median iPFS: 2.7 * Most patients in cohort A (72%) needed subsequent focal brain therapy. Cohort B: - OS rate (12 months): 59% - Median iPFS: 4.8 months Cohort A vs. B: - iPFS*: 2.7 vs. 4.8 months (aHR: 2.04 (95% CI, 1.08 to 3.83)	Cohort A: 12% * No OR was reported in patients with brain lesions that were multiple > 1 cm	* Nivolumab was permanently discontinued in one patient of cohort A after treatment-related atrioventricular block. * There was no other occurrence of trAEs leading to treatment discontinuation. * trAEs (any grade)> 10% in each group * trAEs grade 3 or 4: - Cohort A: 10% - Cohort B: 15%
Kluger et al. (64), 2019	Pembrolizumab (24 months)	MBMs (one or more asymptomatic, untreated 5- to 20-mm BMs) not requiring corticosteroids)	23	Phase-II clinical trial (NCT02085070)	BMs response (CR + PR): 6/23 (26%) CR: 4/23 PR: 2/23 SD: 1/23 PD: 8/23 - Unevaluable for BMs response (due to progression or need for radiation): 8/23 (35%) • Extracranial response (15 evaluable patients): - CR: 4/15 - PR: 3/15 - SD: 1/15 - PD: 7/15 • Median PFS: 2 months • Median OS: 17 months • Mortality at 24 months: 12/23 (52%)	BMs OR: 26%	Neurologic adverse events: 65% All AEs but one were grade 1 or 2 Seizure: 3/23
Long et al. (92), 2018	Nivolumab ± ipilimumab	MBMs (immunotherapy-naive patients with asymptomatic active BMs with no previous local brain therapy)	79 - Cohort A: nivolumab + ipilimumab (36) - Cohort B: nivolumab (27) - Cohort C: nivolumab in non-randomized patients within whom local therapy had failed, or who had neurological symptoms, or leptomeningeal disease (16)	Phase-II trial (Multicenter open label randomized) (ABC trial; NCT02374242)	Cohort A: - CR: 6/35 (17%) - PR: 10/35 (29%) - SD: 4/35 (11%) - PD: 14/35 (40%) - Intracranial PFS: NR - OS: NR Cohort B: - CR: 3/25 (12%) - PR: 2/25 (8%) - SD: 0 - PD: 19/25 (76%) - Intracranial PFS: 2·5 - OS: 18·5 Cohort C: - CR: 0 - PR: 1/25 (6%) - SD: 2/25 (13%) - PD: 13/25 (81%) - Intracranial PFS: 2·3 - OS: 5·1	Intracranial response (median follow-up of 17 months) - Cohort A: 16/35 (46%) - Cohort B: 5/25 (20%) - Cohort C: 1/16 (6%)	* trAEs: - Cohort A: 34/35 (97%) - Cohort B: 17/25 (68%) - Cohort C: 8/16 (50%) * Grade 3 or 4 trAEs: - Cohort A: 19/35 (54%) - Cohort B: 4/25 (16%) - Cohort C: 2/16 (13%) * Treatment-related deaths: 0
Spigel et al. (315), 2018	Atezolizumab	NSCLC	13 NSCLC patients with brain metastasis	Phase-II clinical trial (FIR study, NCT01846416)	OS: 6.3 months, medium PFS: 4.3 months, ORR: 23%	23%	Treatment-related AEs: 69%
Tawbi et el. (91), 2018	Nivolumab + ipilimumab	MBMs (at least one measurable, nonirradiated BMs with a tumor diameter of 0.5 to 3 cm and no neurologic symptoms)	94	Phase-II trial (non-randomized open-label, multicenter) (CheckMate 204, NCT02320058)	- CR: 24/94 (26%) - PR: 28/94 (30%) - SD: 2/94 (2%) - PD: 31/94 (33%)	Intracranial OR: 52/94 (55%) Intracranial clinical benefit: 54/94 (57%)	* trAEs of any grade: 96% * trAEs grade 3 or 4: 55% * CNS involvement grade 3 or 4: 7% * Treatment-related death: 1 patient (immune-related myocarditis)
Long et al. (92), 2018	Nivolumab ± ipilimumab	MBMs (immunotherapy-naive patients with asymptomatic active BMs with no previous local brain therapy)	79 Cohort A: nivolumab + ipilimumab (36) - Cohort B: nivolumab (27) - Cohort C: nivolumab in non-randomized patients within whom local therapy had failed, or who had neurological symptoms, or leptomeningeal disease (16)	Phase-II trial (Multicenter open label randomized) (ABC trial; NCT02374242)	Cohort A: - CR: 6/35 (17%) - PR: 10/35 (29%) - SD: 4/35 (11%) - PD: 14/35 (40%) - Intracranial PFS: NR - OS: NR Cohort B: - CR: 3/25 (12%) - PR: 2/25 (8%) - SD: 0 - PD: 19/25 (76%) - Intracranial PFS: 2·5 - OS: 18·5 Cohort C: - CR: 0 - PR: 1/25 (6%) - SD: 2/25 (13%) - PD: 13/25 (81%) - Intracranial PFS: 2·3 - OS: 5·1	Intracranial response (median follow-up of 17 months) - Cohort A: 16/35 (46%) - Cohort B: 5/25 (20%) - Cohort C: 1/16 (6%)	* trAEs: - Cohort A: 34/35 (97%) - Cohort B: 17/25 (68%) - Cohort C: 8/16 (50%) * Grade 3 or 4 trAEs: - Cohort A: 19/35 (54%) - Cohort B: 4/25 (16%) - Cohort C: 2/16 (13%) * Treatment-related deaths: 0

Table 1. Continued

Tawbi et al (80, 298), 2018, (Cohort A)	Ipilimumab + Nivolumab	Melanoma	101 asymptomatic melanoma patients with BM	Phase-II trial (CheckMate 204 (NCT02320058)	Intracranial: OR: 54.4%, CR: 29%, PR: 26%, SD: 4%, 36-month PFS: 54.1%, 36-month OS: 71.9%	83.3%	Grade 3 or 4: 54.5 %
Tawbi et al (80, 298), 2018, (Cohort B)	Ipilimumab + Nivolumab	Melanoma	18 melanoma patients with BM who were symptomatic or previously treated with corticosteroids	Phase-II trial (CheckMate 204 (NCT02320058)	Intracranial: OR: 16.6%, CR: 11%, PR: 5.6%, SD: 5.6%, 36-month PFS: 18.9%, 36-month OS: 36.6%	16.6%	Grade 3 or 4: 55.6 %
Antonia et al. (316), 2017	Durvalumab	NSCLC	23 patients	Phase-III clinical trial (PACIFIC, NCT02125461)	lower incidence of new brain metastases with durvalumab VS. placebo (11% vs. 5.5%) CNS ORR: 30%, Median CNS PFS: 3.7 months, Median PFS: 16.8 months	-	Grade III or IV: 29,9%,
Williams et al (292), 2017	Arm A: Ipilimumab + SRS Arm B: WBRT + Ipilimumab	Melanoma	Arm A: 5 Arm B: 11	Phase-I clinical trial (NCT01703507)	Arm A: OS: 8 months, PFS: 2.5 months Arm B: PFS: 2.1 months (OS not reached)		The combination of radiotherapy and Ipi added no specific AEs (no grade 4 AEs)
Fehrenbacher et al. (317), 2016	Atezolizumab	NSCLC	27 patients	Phase-II randomized clinical trial (POPLAR, NCT01903993)	Median OS: 12.6 months	30%	Grade III and IV: 57%
Goldberg et al. (70), 2016	Pembrolizumab	- MBMs - NSCLC-BMs (at least one untreated or progressive BM, between 5 and 20 mm in longest diameter without associated neurologic symptoms or the need for corticosteroids)	36 - MBMs (18) - NSCLC- BMs (18)	Phase-II clinical trial (NCT02085070)	- BM RR: MBMs: 22% - CR: 0/18 - PR: 4/18 - SD: 2 - PD: 8 - Unevaluable: 4/18 NSCLC-BMs: 6/18 (33%) - CR: 4/18 - PR: 2/18	BM RR: MBMs: 22% NSCLC-BMs: 33%	- Serious grade 3–4 trAEs: transaminitis, colitis, pneumonitis, fatigue, endocrine abnormalities, and acute kidney injury (1 patient each)
					- SD: 2 - PD: 6 - Unevaluable: 4 * OS: - MBMs: NR - NSCLC-BMs: 7.7 months - mortality: MBMs: 6/18 NSCLC-BMs: 9/18 (all but one due to disease progression, one with unknown cause of death many months after discontinuing treatment).		- Serious neurological AEs: cognitive dysfunction (1) and seizures (3) due to pembrolizumab, metastases, or both - no treatment-related deaths.
Haanen et al (296), 2016	Ipilimumab + Nivolumab	Melanoma	10	Phase-I trial	**BORR: 50%,** PR: 50%	50%	
Long et al (297), 2015 (Cohort A)	Ipilimumab + Nivolumab	Melanoma	35	Phase-II trial (NCT02374242)	Intracranial: CR: 17%, PR: 29%, SD: 11%, **OR: 46 %,** 6-months OS: 78%	46%	Grade 3 or 4: 63%
Long et al (297), 2015 (Cohort B)	Nivolumab	Melanoma	25	Phase-II trial (NCT02374242)	Intracranial: CR: 12%, PR: 8%, SD: 0%, **OR: 20%**, 6-months OS: 68%	20%	Grade 3 or 4: 16%
Margolin et al (282), 2012	Ipilimumab	Melanoma	51 (cohort A) without neurological symptoms or corticosteroid treatment 21 (Cohort B) with corticosteroid usage	Phase-II clinical trial (NCT00623766)	Cohort A (intracranial): PR: 16%, CR: 0%, **BORR: 16%**, SD: 10%, OS: 7 months Cohort B (intracranial): CR: 5%, PR: 0%, **BORR: 5%,** SD: 5%, OS: 3.7 months	Cohort A: 16%, Cohort B: 5%	Cohort A: 55% (CNS-associated) Cohort B: 39% (CNS-associated)
Camacho et al (301), 2009	Tremelimumab	Melanoma	3	Phase-II trial (NCT00086489)	OR: 0%, CR: 0%, PR: 0%, DCR: 0%, PD: 100%	0%	Progression of disease in all three patients with BM
Downey et al (285), 2007	Ipilimumab	Melanoma	10	Two trials	PR: 20%, CR: 10%, **BORR: 30%**,	30%	81.2% (in all 139 metastatic melanoma patients)

OR, objective response; AE, adverse effect; BORR, best overall response rate; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate; OS, overall survival; CNS, central nervous system EAP, expanded access program, SRS, stereotactic radiosurgery, BM, brain metastasis, MBM, melanoma brain metastasis, HER2, human epidermal growth factor receptor 2; PFS, progression-free survival, irRC; immune-related response criteria; RN, radiation necrosis; RNFS, radiation necrosis-free survival; MBM, melanoma brain metastasis.

172), anti-angiogenic agents (i.e., bevacizumab) (111)), CT (99, 123, 173, 174), RT (stereotactic RT (SRT) or WBRT)(50, 53, 55, 68, 69, 74, 78, 95, 100-102, 175-178), surgery (179), and SRS (50, 58, 59, 66, 69, 71, 72, 88, 102, 147, 180-189). A combination of CNS-directed and systemic treatment seems to improve survival in patients with BMs (185). However, findings regarding the best treatment strategy for BMs are still contradictory (52-56, 58, 66, 80, 85, 95, 100, 101, 177, 182, 183, 185, 190-192).

Various prognostic factors have been suggested in patients with BMs treated with PD-1 inhibitors (54, 94, 100, 108, 168, 193-196). According to Naik *et al.*, baseline score > 1 in diagnosis-specific graded prognostic assessment (DS-GPA), as well

as a neutrophil-to-lymphocyte ratio < 4 were significant predictors of long-term survival to PD-1 inhibitors in patients with MBM who had not previously received anti-PD-1 therapy (168). According to Zeijl *et al.* Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≥1, symptomatic BMs, liver metastasis, and elevated LDH were important survival prognostic factors among patients with advanced melanoma treated with first-line anti-PD-1 therapy (193). Another study by Lee *et al.* among patients with MBMs suggested circulating tumor DNA (ctDNA) as a strong prognostic biomarker in patients with concurrent extracranial disease. However, ctDNA was unable to identify or monitor intracranial disease activity (194). Turiello *et al.* suggested the prognostic value of serum CD73 in patients with advanced melanoma receiving anti-PD-1 (195). Trommer *et al.* indicated the following independent survival predictors in patients with BMs treated with combined RT and anti-PD-1 therapy; concurrent RT- and ICI, ECOG-PS = 0, and BM volume ≤ 3 cm3 (54). According to Huang *et al.*, being a never smoker and an ECOG ≥ 2 were adverse OS prognostic factors among patients with lung cancer-BMs treated with anti-PD-1 ± RT (100). Furthermore, the authors suggested a lack of concurrent brain RT as an independent prognostic factor of a shorter intracranial PFS (iPFS) (100). Steroid use is another suggested poor prognostic factor in patients with advanced NSCLC-BMs and PD-L1 expression > 50%, who were treated with first-line pembrolizumab (108). Other suggested adverse prognostic factors include active BMs, use of anti-PD-1 in later lines, worsened performance status, Karnofsky Performance Status of < 90, higher LDH level, elevated protein S100B levels, higher total metabolic tumor volume, as well as lower albumin, absolute lymphocyte count, not developing irAEs, steroid use, platinum resistance, etc. (61-63, 85, 108, 112, 127, 132). From a molecular point of view, Zhou *et al.* indicated that lower stromal $CD8^+$ TIL number in NSCLC-BMs was significantly associated with shorter OS (196). Consistently, according to Kluger *et al.*, most pembrolizumab responder patients with asymptomatic MBMs had higher pretreatment tumor $CD8^+$ cell density and PD-L1 expression (64). Notably, Descourt *et al.* suggested that BM was not an independent negative factor for OS among first-line single-agent pembrolizumab receivers with PD-L1-positive (tumor proportion score ≥ 50%) advanced NSCLC (104). Similarly, Metro *et al.* suggested that the presence of BM per se was not associated with a worse outcome in NSCLC patients receiving pembrolizumab monotherapy (112).

Albeit their clinical benefits, an array of irAEs have also been reported with PD-1 inhibitors, such as thyroiditis, pneumonitis, colitis, hepatitis, mucositis, pancreatitis, hypothyroidism, adrenal insufficiency, etc. (57, 197). Thromboembolic events have also been increasingly reported as AEs associated with ICSs (198, 199). A large study on patients with BM revealed a significantly increased incidence of status epilepticus since the approval of ICIs in 2014 (200). Other neurologic AEs include gait disturbances, headache, cognitive dysfunction, seizure, etc. (64). There are also reports of less common AEs, including occasional hypopituitarism, diffuse pneumonitis following coronavirus HKU1, leptomeningeal carcinomatosis, radiation-induced vasculitic leukoencephalopathy, hyper-progression (acute progressive disease without subsequent regression), pseudo-regression, myasthenic-like syndrome, asymptomatic reversible CNS demyelination, thrombocytopenia, severe exacerbation of the primary disease, and bullous pemphigoid (54, 59, 67, 188, 197, 201-214). Notably, studies have suggested an association between developing irAEs and PD-1 inhibitors efficacy, which may depend on the type and severity of toxicity, as well as the timing of irAE onset (54, 105, 215-218). According to Otsuka *et al.*, irAEs might be correlated with improved survival in patients with advanced mucosal melanoma on nivolumab monotherapy (216). According to Zhang *et al.*, irAE was an independent predictor of longer OS, and systemic and intracranial time to treatment failure (TTF) (105). On the other hand, specific AEs of ICIs, such as thromboembolic complications, are associated with worsening survival (198). Additionally, when used as combination therapies, specific considerations are required regarding the AEs. For instance, radionecrosis is considered significant toxicity in patients with BMs treated with RT -anti-PD-1 combination (207). However, evaluating a series of 17 NSCLC patients with 49 BMs treated with stereotactic radiation (SRS or frac-

tionated stereotactic radiation therapy) before, during, or after nivolumab/durvalumab therapy, Ahmed *et al*. found no evidence of increased toxicity when anti-PD-1/PD-L1 treatments were combined with stereotactic radiation to the brain (132).

Treatment failure and poor efficacy with PD-1 inhibitors (i.e., developing new metastatic brain lesions or intracranial progression of the previous BMs) have also been reported among patients with BMs on PD-1 inhibitors (98, 139, 140, 219-221). In a study by Schvartsman *et al*., 8.6% of patients with MM without prior MBM developed BM while on anti-PD-1 therapy (221). Among those with prior MBMs, 45.3% progressed intracranially while receiving anti-PD-1 (221). The authors suggested that PD-1 inhibitors may alter the natural history of patients with preexisting MBMs (221). According to Lau *et al*., second-line ipilimumab-nivolumab for MBM after progression with BRAF-MEK inhibitors showed poor efficacy, with an intracranial response rate of 4.8% (1/21) and median PFS of 1.3 months (222). Wang *et al*. suggested a potential survival benefit with first-line BRAF/MEK inhibitor therapy compared to first-line anti-PD-1 therapy for patients with *BRAF*-mutated MBMs (223). Ishihara *et al*. suggested a higher incidence of newly developing BM in RCC in patients receiving nivolumab compared to those who received second or later-line TKIs (220). Evaluating 24 patients with active BMs, Tozuka *et al*. suggested poor efficacy of anti-PD-1/anti-PD-L1 in NSCLC patients with active BMs (98). The authors also suggested the efficacy of anti-PD-1/PD-L1 may be lower for intracranial than for extracranial tumors (98).

Pembrolizumab

Melanoma

In 2015, first-line PD-1 inhibitors were approved by the food and drug administration (FDA) and National Comprehensive Cancer Network for patients with stage IV melanoma, resulting in substantial OS improvement among these patients, including those with BM (60). Nevertheless, according to a nationwide study, 38% of US patients were not receiving first-line ICIs as of 2019 (60). In 2019 and 2021, pembrolizumab received FDA approvals for adjuvant treatment of patients with melanoma with lymph node involvement following complete resection (FDA approves pembrolizumab for adjuvant treatment of melanoma, FDA) and stage IIB or IIC melanoma following complete resection (FDA approves pembrolizumab for adjuvant treatment of Stage IIB or IIC melanoma | FDA), respectively. These approvals were based on the results from EORTC1325/KEYNOTE-054 (NCT02362594 (224-226)) and KEYNOTE-716 (NCT03553836 (227-229)) trials.

Several studies have evaluated the safety and efficacy of pembrolizumab among patients with primary and metastatic melanoma (61-71). According to a phase-II clinical trial (NCT02085070; 2019), pembrolizumab has acceptable toxicity and produces long-lasting effects when treating untreated, asymptomatic, and small-size (5-20 mm) MBM (64). The authors reported a similar two-year survival in this subgroup of patients to that in patients without BM (64). Additionally, all patients with extracerebral responses had CNS responses, too (64). Their findings were consistent with the interim results from this trial published in 2016 (NCT02085070; 2016) (70). Compared to other studies of pembrolizumab, the NCT02085070 clinical trial indicated relatively low BM response rates for MBM (2016: 22%, 2019: 26%) or NSCLC-BMs (2016: 33%) (64, 70). The authors speculate this may understate pembrolizumab clinical benefit and reflect the difficulties of conducting clinical trials in this population (70). The authors also mentioned the necessity of combination therapy strategies and biomarker development to improve the patient's outcomes (70).

Regarding the combination therapy strategies, Nardin *et al*. revealed local lesional control of 80% and prolonged OS with acceptable tolerance in patients with MBM treated with the pembrolizumab-SRS combination (66). Consistently, Anderson *et al*. revealed the safety and efficacy of concurrent pembrolizumab-SRS in reducing MBM size among patients who had progression on multiple prior systemic therapy courses (69). The authors suggested concurrent pembrolizumab-SRS outperforms ipilimumab-SRS combination and SRS without concurrent IT (69). Radiation necrosis of the brain (RNB) is one of the AEs that should be considered in patients treated

with RT-anti-PD-1 combination therapy (66, 67). Evaluating pembrolizumab-receiver patients with MBM who were previously treated with RT, Du Four *et al.* indicated an RNB incidence of 12.8% (after a median follow-up of 50 months) in these patients (67). Nardin *et al.* reported RNB in 6.8% of the MBMs treated with the pembrolizumab-SRS combination (66).

Non-Small-Cell Lung Cancer

Following the results of the phase-III randomized trials of KEYNOTE-024 (PD-L1 tumor proportion score [TPS] ≥ 50%)(NCT02142738; 2016 (230)) and KEYNOTE-042 (PD-L1 TPS ≥ 1%)(NCT02220894; 2019 (118)), pembrolizumab was approved as the first-line treatment of patients with metastatic NSCLC who are not candidates for surgical resection or definitive chemoradiation, and their tumors express PD-L1 (TPS ≥1%) without EGFR or ALK genomic aberrations (FDA expands pembrolizumab indication for first-line treatment of NSCLC (TPS ≥1%) | FDA) (117, 118, 120). Real-life observations were also almost comparable with pivotal clinical trials (115, 116). Surveys conducted to evaluate the safety and efficacy of pembrolizumab in patients with NSCLC-BM are mostly based on real-world data since these patients have been excluded from most trials (particularly those with symptomatic or progressive BMs) (70, 96, 97, 103-116, 119). Nevertheless, clinical trials also indicated the beneficial effects of pembrolizumab in patients with NSCLC-BM (107, 109, 114).

A real-world study (ESCKEYP GFPC study) on 845 patients with PD-L1-positive (TPS ≥ 50%) advanced NSCLC who initiated first-line treatment with pembrolizumab, of whom 176 (20.8%) had BMs revealed no significant differences in PFS, OS, or the ORR in patients with and without BMs (ORR: 47% and 45%, respectively) (104). Their findings were in line with a previous study by Sun *et al.*, revealing no significant survival difference between NSCLC patients with and without BM after treatment with pembrolizumab (106). These findings suggest not immediately excluding patients with BM from pembrolizumab-based therapies since they may not have a lower chance of survival (106). Consistently, Metro *et al.* recommended that BM presence does not imply a poorer pembrolizumab antitumor activity in patients with NSCLC-BM treated with first-line pembrolizumab (patients with BMs vs. without BMs; ORR: 39.2% vs. 44.4% (p = 0.48), OS: 9.9 vs. 26.5 months (p = 0.05), and TTF: 4.2 vs. 10.8 (p = 0.06)) (112). Evaluating 30 patients with non-oncogene addicted NSCLC (i.e., EGFR- and ALK-negative) with PD-L1 TPS ≥ 50% and asymptomatic BMs who were treated with pembrolizumab ± RT, Metro *et al.* suggested the efficacy of upfront pembrolizumab in this subgroup of patients (97). According to Frost *et al.*, while upfront pembrolizumab resulted in durable responses in NSCLC patients with asymptomatic BMs, those with symptomatic BMs did not take such a benefit (110).

After reporting the primary results of a phase-II trial of pembrolizumab (NCT02085070) in 18 patients with NSCLC-BM and 18 patients with MBM in 2016 (70), Goldberg *et al.* published an updated analysis of the full NSCLC cohort (N= 42) with BM (5 - 20 mm) in 2020 (114). Confirmed BM response was observed in 29·7% of patients with PD-L1 TPS ≥ 1%, which met the prespecified success criteria for the trial (114). Notably, PD-L1 and TIL biomarker analyses revealed no statistically significant association between both PD-L1 expression and TIL levels with the response or PFS (114). Results regarding the OS did not also reach statistical significance (114). Additionally, targeted messenger ribonucleic acid (mRNA) immune profiling of 23 tumor biopsies showed that compared to the non-responders, pembrolizumab-responders' tumors had significantly higher pro-inflammatory genes levels, including key effector molecules and chemokines such as Granzyme-B, C-X-C Motif Chemokine 9 (CXCL9), CXCL10, and granulysin (114). Of note, this trial lacked a control arm (treats patients with radiation followed by systemic therapy), making it difficult to conclude which strategy is superior (114).

A pooled analysis of KEYNOTE-001 (NCT01295827), 010 (NCT01905657), 024 (NCT02142738), and 042 (NCT02220894) revealed improved outcomes with pembrolizumab monotherapy in patients with PD-L1-positive (TPS ≥ 1% and TPS ≥ 50%) NSCLC with BMs (109). According to the authors, compared to CT, pembrolizumab monotherapy improved OS, PFS, ORR, and response duration, with lower treat-

ment-related adverse events (trAEs) regardless of the presence of treated, stable baseline BMs (109). Notably, the authors found greater beneficial effects of pembrolizumab in patients with PD-L1 TPS ≥ 50% vs. those with TPS ≥1% (109). Concerning the combination therapies, a recent pooled analysis of KEYNOTE-021 (NCT02039674; 2016 (231)), KEYNOTE-189 (NCT02578680; 2018 (232)), and KEYNOTE-407 (NCT02775435; 2018 (233)) indicated a higher ORR and longer response duration with pembrolizumab plus CT versus CT alone, across all PD-L1 subgroups (< 1%, 1-49%, and ≥50%) and irrespective of BM status (107). The authors suggested the use of pembrolizumab plus platinum-based histology-specific CT for treatment-naive patients with advanced NSCLC, including those with stable BMs (107). In line with this study, Afzal *et al.* previously had indicated a higher ORR, and a lower proportion of patients with BM progression in NSCLC patients treated with carboplatin/pemetrexed plus pembrolizumab compared to those treated with carboplatin/pemetrexed alone (96).

Renal Cell Carcinoma

While the FDA has approved pembrolizumab-axitinib and pembrolizumab-lenvatinib combinations for metastatic RCC based on KEYNOTE-426 (NCT02853331; 2019 (234)), KEYNOTE-564 (NCT03142334; 2021 (235)), and CLEAR (Study 307/KEYNOTE-581; NCT02811861, 2021 (236))(FDA approves pembrolizumab for adjuvant treatment of renal cell carcinoma; FDA)(FDA approves pembrolizumab plus axitinib for advanced renal cell carcinoma; FDA)(FDA approves lenvatinib plus pembrolizumab for advanced renal cell carcinoma; FDA), to our knowledge these key clinical studies in patients with metastatic RCC did not include individuals with BM or did not separately disclose the results in the subgroup of patients with BMs.

Breast Cancer and Other Cancer Types

Recently, pembrolizumab was approved for high-risk early-stage TNBC, according to the phase-III trial KEYNOTE-522 (NCT03036488; 2020 (237)). Subsequently, based on the results of the KEYNOTE-355 trial (NCT02819518; 2022 (238)) (with 3% of patients with stable and treated breast cancer-BM [BCBM]), pembrolizumab combined with CT was approved as the first-line treatment for patients with PD-L1 positive advanced triple-negative breast cancer (Pembrolizumab for Advanced Triple-Negative Breast Cancer - NCI). However, CNS-specific results have not been reported separately for patients with BM (239).

Albeit limited to case reports, pembrolizumab has also shown to be a possible promising treatment option for other types of cancers with BM, including pulmonary large cell neuroendocrine carcinoma (150), breast cancer (240), mismatch repair-deficient prostate cancer (158), refractory male primary choriocarcinoma (160), spindle cell SCC (155), metastatic porocarcinoma (157), giant cell carcinoma of the lung (151), non-small cell lung carcinoma with giant cell features (152), microsatellite-stable metastatic sebaceous carcinoma (159), metastatic primary pulmonary melanoma (153), and gastric cancer with BMs (146). Further investigations are required to determine the safety and efficacy of pembrolizumab among these individuals.

Nivolumab

Melanoma

A combination of nivolumab and relatlimab, a LAG-3 inhibitor, has been FDA approved since March 18, 2022, for the treatment of patients aged ≥ 12 years old with unresectable or metastatic melanoma (FDA approves Opdualag for unresectable or metastatic melanoma, FDA). According to phase-II and phase-III studies, nivolumab seems to be one of the most effective treatment options for patients with asymptomatic BM, particularly when combined with therapies such as ipilimumab (80, 82, 83, 86, 87, 91, 92). Nevertheless, symptomatic MBM remains difficult to treat (79, 80). While PD-1 inhibitors are established as adjuvant therapy in high-risk resected stage III or IV melanoma (241), Rassy *et al.* also suggested the use of ICIs in "early disease" to prevent CNS metastasis (242). A retrospective bicentric analysis of 293 patients with metastatic melanoma suggested the protective role of anti-PD-1 by lowering the risk of BMs by almost 70% (243). Neoadjuvant use of nivolumab for resectable stage III melanoma is currently limited to clinical trials (NADINA study, NCT04949113; estimated study

completion date: January 2027)(Neoadjuvant Ipilimumab Plus Nivolumab Versus Standard Adjuvant Nivolumab in Macroscopic Stage III Melanoma - Full Text View - ClinicalTrials.gov)(241).

Several studies have assessed nivolumab safety and efficacy in MBM (72-80, 83, 84, 86-88, 91-93), either as monotherapy or in combination with ipilimumab (76, 77, 79, 80, 82, 91, 92), SRT (74, 78, 81, 85, 90), CT (83), and SRS (88, 93). Results from a multicenter randomized phase-II study (ABC trial; NCT02374242; 2018) revealed nivolumab activity, as monotherapy or in combination with ipilimumab, in immunotherapy-naive patients with active asymptomatic MBM with no previous local brain therapy (92). The authors reported intracranial response rates of 46% and 20% in patients treated with nivolumab plus ipilimumab and nivolumab alone, respectively (92). The corresponding values for complete response rate were 17% and 12%, supporting the nivolumab-ipilimumab combination as the first-line therapy for patients with asymptomatic untreated MBM (92). The 5-year follow-up data from all patients enrolled in the ABC trial (NCT02374242; 2021) corroborated durable responses in most of the patients with MBM treated with upfront ipilimumab plus nivolumab (82). In line with these findings, the CheckMate 204 clinical trial (NCT02320058; 2018) confirmed the concordant intracranial and extracranial activity of the nivolumab-ipilimumab combination in patients with untreated MBM, with intracranial and extracranial clinical benefit rates (CBR) of 57% and 56%, respectively (benefit rate is defined as the percentage of patients who achieved CR, PR, or had stable disease [SD] for at least six months) (91). The authors also reported a similar safety profile of this regimen in melanoma patients with and without BM (91). The NIBIT-M2 study (NCT02460068; 2021), a recent phase-III clinical trial, compared the safety and efficacy of ipilimumab plus fotemustine (cohort A) and ipilimumab plus nivolumab (cohort B) to fotemustine without IT (cohort C) in patients with BRAF wild-type or mutant melanoma with active, untreated, asymptomatic BM (83). In this study, Di Giacomo *et al.* indicated median OSs of 8.5, 8.2, and 29.2 months in the fotemustine arm, ipilimumab plus fotemustine arm, and ipilimumab plus nivolumab arm (83). Compared to fotemustine, ipilimumab plus nivolumab was significantly associated with a better median OS, as well as a better 4-year survival rate (83). The final 3-year follow-up data analysis of CheckMate 204 (NCT02320058; 2021) evaluated 101 patients with asymptomatic (cohort A) and 18 patients with symptomatic MBMs (cohort B)(80). The authors found intracranial CBR of 57·4% and 16·7% in cohorts A and B, respectively (80). Intracranial ORRs (iORRs) were 53.5% and 16.7% in asymptomatic and symptomatic MBMs, respectively (80). While the observed durable 3-year response, OS, and PFS rates among those with asymptomatic MBM supported the first-line use of nivolumab-ipilimumab combination therapy, treatment of symptomatic MBM is still challenging and requires alternative approaches to reduce corticosteroids dependency (79, 80). However, some patients with symptomatic disease may also benefit from a long-term response with this combination (80).

Studies on the best dosage of the nivolumab-ipilimumab combination are very limited (76, 89). A recent meta-analysis compared the safety profile of two different nivolumab-ipilimumab combination regimens; the N1I3 regimen suggested by Tawbi *et al.* (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every three weeks for four doses) (80) vs. the N3I1 regimen (nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every three weeks for four doses) (76, 244). According to the results, the N3I1 regimen more frequently induced any AEs (96% vs. 85%, $p = 0.003$), grade ≥ 3 AEs (64% vs. 36%, $p < 0.001$), and serious AEs (61% vs. 48%, $p = 0.004$), as well as hepatic dysfunction, diarrhea, colitis, and pyrexia (76, 244). Previously, a phase IIIb/IV clinical trial of CheckMate 511 (NCT02714218; 2019) among patients with previously untreated, unresectable stage III/IV melanoma had achieved consistent results, indicating trAEs grade 3 to 5 incidences of 34% and 48% in N3I1 and N3I1 regimens, respectively ($p = 0.006$) (89). The authors found no significant efficacy differences between these regimens at a minimum follow-up of 12 months (89).

Using the TriNetX dataset (a global health network dataset), a recent real-world study assessed the impact of cranial stereotactic RT (SRT) in patients with MBM treated with combined nivolumab and ipilimumab (CNI)(78). This study revealed improved OS and decreased mortality

when adding stereotactic RT to CNI in patients with MBM, supporting previous findings regarding the importance of local therapy with SRT or surgery along with systemic therapy (78, 81, 85, 90). The ABC-X study (NCT03340129; estimated study completion date: August 2025) is an ongoing open-label, phase-II trial evaluating the effect of SRT addition to the nivolumab-ipilimumab combination in systemic treatment-naïve patients with MBM (≥ one asymptomatic BM, 5- 40 mm, no history of previous treatment with SRT) (Anti-PD 1 Brain Collaboration + RT Extension (ABC-X Study) - Full Text View - ClinicalTrials.gov)(90). Regarding the best sequence of radio-immunotherapy (RIT), a recent observational, nonrandomized phase-II clinical trial (the ELEKTRA trial) indicated that sequencing RT followed by ICI (RT-ICI vs. ICI-RT sequencing) was associated with better clinical outcomes in patients with MBM, including better ORR, disease control rate, a trend toward a better PFS, and higher frequencies of memory T cells and activated CD8 T cells in the blood (74).

Evaluating 26 patients with advanced resected and unresectable melanoma and 73 BM who were treated with a nivolumab-SRS combination (within six months of receiving nivolumab), Ahmed *et al.* revealed OSs of 11.8 and 12.0 months from date of SRS and nivolumab initiation, respectively (93). Local BM failure with ≥20% volume increase was observed in 11% of lesions, and 12-month post-radiation local BM control was 85% (93). Consistently, Minniti *et al.* revealed meaningful intracranial activity of concurrent SRS and ipilimumab/nivolumab in patients with either asymptomatic or symptomatic MBM, despite an RNB frequency of 15% (88). The nivolumab-SRS combination resulted in significantly better intracranial PFS, OS, and DBC (88). ORRs were 76% and 60% in nivolumab-SRS and ipilimumab-SRS groups, respectively (88). Notably, the authors suggested better iPFS associated with multi-fraction SRS (70%) compared to single-fraction SRS (46%) at six months, particularly in combination with nivolumab (88).

Non-Small-Cell Lung Cancer

According to the results from the CA2099LA study (CheckMate 9LA), the FDA approved nivolumab in combination with ipilimumab and two cycles of platinum-doublet CT on May 2020, as the first-line treatment for people with metastatic or recurrent NSCLC who do not have genomic tumor aberrations for EGFR or ALK (FDA approves nivolumab plus ipilimumab and chemotherapy for first-line treatment of metastatic NSCLC, FDA)(122, 124). Previously, in the CheckMate 227 study (NCT02477826, 2019), advanced NSCLC patients who received nivolumab with ipilimumab had a longer OS than those who received platinum-based CT, independent of PD-L1 expression (245). On March 2022, the FDA approved nivolumab with platinum-doublet CT for adult patients with resectable NSCLC in the neoadjuvant setting based on the CheckMate-816 trial results (NCT02998528; 2022 (246))(FDA D.I.S.C.O Burst Edition: FDA approvals of Opdivo (nivolumab) for early-stage non-small cell lung cancer and Lynparza (olaparib) for the adjuvant treatment of high-risk early breast cancer | FDA). The NIVIPI-Brain is an open-label, non-randomized, phase-II ongoing trial (NCT05012254; estimated study completion date: December 15, 2026) evaluating the safety and efficacy of first-line nivolumab plus Ipilimumab plus platinum-based CT (two cycles) in patients with stage IV or recurrent NSCLC with synchronous BMs (Nivolumab and Ipilimumab Plus Chemotherapy for Patients With Stage IV Lung Cancer With Brain Metastases - Full Text View - ClinicalTrials.gov). The NIke Trial (LOGiK2004) is another single-arm phase-II ongoing trial conducted in Japan to evaluate the efficacy of nivolumab-ipilimumab combined with platinum-based CT for untreated symptomatic and asymptomatic BMs (at least one BM measuring ≥5 mm) in CT-naïve patients with NSCLC (123). This investigation began in May 2021 and will take 2.5 years to complete (123).

Several studies have been conducted to investigate nivolumab safety and efficacy in patients with NSCLC-BMs (121, 123, 125-133, 247, 248). In their 2016 study, Dudnik *et al.* investigated nivolumab CNS activity among five patients with advanced NSCLC and new/progressing asymptomatic intracranial metastases (133). The iORR was 40% (2/5 patients), one patient had SD, and two progressed in the CNS (133). They reported concordant intra- and extracranial responses with nivolumab and suggested the possible efficacy of nivolumab in NSCLC-CNS metastasis

(133). Later, in 2018, Gauvain *et al.* evaluated 43 patients with NSCLC-BMs who were treated with nivolumab (131). They also observed similar intracerebral and extracerebral nivolumab efficacy (iORR: 9%, eORR: 11%), with an acceptable safety profile (131). According to Cortinovis *et al.* survey on the Italian cohort of the Expanded Access Program (EAP), the safety and efficacy of nivolumab in NSCLC patients with CNS metastases (N = 37) were similar to that in the overall Italian EAP cohort (N = 371)(130). Another analysis from the EAP cohort on 409 stage IIIB/IV NSCLC patients with asymptomatic or controlled BMs who progressed after at least one systemic treatment further confirmed these observations (129). Consistently, Rossi *et al.* found no differences in OS or TTF according to BM presence in patients with NSCLC treated with nivolumab (127), which was further confirmed by Zhang *et al.* study in 2020 (126). Among various evaluated factors in Rossi *et al.* study (performance status, age, presence of baseline BM, high disease burden, and platinum resistance), platinum resistance (not baseline BMs) was the only independent predictive factor (127). On the other hand, Gounant *et al.* suggested BM presence as a worse survival predictor among patients with NSCLC and PS 3-4, with median OSs of 2.1 vs. 8 months in patients with and without BMs, respectively (p = 0.003) (125). Altogether, although these findings suggest that BM presence in patients with NSCLC might not considerably affect nivolumab efficacy, verification of these results in large-scale prospective studies is still necessary. Patients with poor predictive factors, such as those who have received long-term treatment with high-dose corticosteroids or those with low PD-L1 expression, are considered challenging populations for IT (249, 250). The deleterious effects of glucocorticoids on immune response are well known, particularly in patients with cancer (251). However, de Jong *et al.* showed an exceptionally durable BM response to a short course of nivolumab in a patient on high-dose steroids (128). In another case report, Kitadai *et al.* suggested nivolumab intracranial efficacy in a patient with PD-L1-negative NSCLC with asymptomatic multiple BMs (121). However, the authors did not evaluate the BM PD-L1 expression (121). Another population with almost unknown nivolumab efficacy is patients with PS 3-4 (125). Evaluating 35 NSCLC patients with PS 3-4 (29% of whom presented BMs), Gounant *et al.* suggested some individuals with extremely poor general conditions may benefit long-term from nivolumab salvage therapy (125).

Renal Cell Carcinoma

The FDA has approved the nivolumab plus ipilimumab combination and nivolumab plus cabozantinib, a TKI, for advanced RCC based on the results from CheckMate 214 (NCT02231749; 2018 (144)) and CheckMate-9ER (NCT03141177; 2021 (142)) trials (FDA approves nivolumab plus ipilimumab combination for intermediate or poor-risk advanced renal cell carcinoma | FDA, FDA approves nivolumab plus cabozantinib for advanced renal cell carcinoma | FDA). Limited studies have been conducted to assess nivolumab safety and efficacy in BMs from RCC, and these patients are underrepresented in clinical trials (135, 137, 140, 141, 143). Therefore, patients with RCC and BMs have a high unmet medical need. The GETUG-AFU 26 NIVOREN phase-II trial (NCT03013335; 2019) is the first prospective study evaluating IT RCC-BMs (143). In this study, 73 RCC patients with previously untreated (cohort A; N = 39) or treated (cohort B; N = 34) asymptomatic BMs who failed VEGF–directed therapies were included (143). The iORR was 12%, indicating limited intracranial activity of nivolumab in RCC patients with untreated BMs (143). Notably, each of the four patients who demonstrated intracranial response had a unique lesion with a baseline length diameter of less than 10 mm (143). Additionally, in comparison to 39% of individuals with unique lesions, 73% of patients with multiple target lesions showed progressive intracranial disease as their best response (143). Although all four patients with intracranial response also had an extracranial response, discordant intra-, and extracranial responses were observed in 18% of patients in cohort A (143). Most cohort A patients (72%) needed subsequent focal brain therapy (143). According to the authors, prior focal brain therapy (cohort B) lowered the hazard of intracranial progression after adjusting for baseline variables (iPFS cohort A vs. B: 2.7 vs. 4.8 months, aHR: 0.49 [95% CI, 0.26 to 0.92])(143). Altogether, this study indicated the limited efficacy of nivolumab in RCC-BM with-

out local therapies (143). Accordingly, Chowdhry *et al.* mentioned the importance of local control with either radiation or surgery in the treatment of RCC-BMs (137). Recently published primary results from phase IIIb/IV CheckMate 920 (NCT02982954; 2022) indicated the encouraging antitumor activity of the nivolumab-ipilimumab combination in patients with previously untreated aRCC with asymptomatic BMs, with a median PFS of 9.0 months (141). Twenty- eight patients were included in this study, of whom no one developed grade 5 irAEs (141). iORR among response-evaluable patients was 32%, and half of the responders remained without progression (141). Reporting two patients with RCC who developed BMs, Nakagawa *et al.* suggested that cabozantinib (a multitargeted TKI targeting VEGF, MET, and AXL receptor tyrosine kinase) monotherapy or combination therapy with ICIs such as nivolumab may be an effective treatment option for these patients (140). Nevertheless, treatment responses differed from one patient to another. For instance, rapid postoperative progression of BMs responded to cabozantinib-nivolumab therapy in the second patient, whereas the first patient developed a new BM 6 months after the initial postoperative BMs regression with stereotactic RT followed by ipilimumab-nivolumab therapy (140).

Breast Cancer

Ahmed *et al.* designed a single-arm, non-randomized, open-label, phase-Ib trial (NCT03807765; 2021) to assess the safety and efficacy of nivolumab-SRS combination among patients with metastatic breast cancer (ECOG PS ≤2) with ≤10 BMs (147). This study indicated that the nivolumab-SRS combination was well tolerated in this population without dose-limiting toxicities (147). There were no cases of RNB or treatment-related deaths (147). With a median follow-up of 9.6 months, the authors indicated an iORR of 92%, as well as a 12-month intracranial control rate, DIC rate, and OS rate of 22%, 28%, and 89%, respectively (147). Notably, while the primary factor affecting the incidence and prognosis of BCBM is the subtype of breast cancer (252), subtypes were not separated in this study. Altogether, there is still a strong need for phase-II studies to assess nivolumab efficacy in BM from breast cancers; according to a recent systematic review by Schlam *et al.*, although nearly half of the patients with triple-negative and human epidermal growth factor receptor 2 $(HER2)^+$ metastatic breast cancer experience BM, these patients constitutes only 3.3% of the ICI trials on breast cancer population (239). There is a critical need in oncology to assess the safety and efficacy of ICIs in patients with BCBM (239).

Other Cancer Types

Although the CheckMate 141 phase-III trial of nivolumab (NCT02105636; 2016 (253)) suggested prolonged OS with nivolumab among patients with recurrent platinum-refractory SCCHN, patients with BM were excluded from this study (253). Limited case reports have suggested nivolumab efficacy in SCCHN patients with BM (156). Takemoto *et al.* reported a patient with BM from parotid carcinoma who achieved a remarkable BM shrinkage following treatment with six cycles of nivolumab (156). Consistently, Cabezas-Camarero *et al.* revealed a complete intracranial response ten weeks after receiving third-line nivolumab in a PD-L1 negative metastatic SCCHN patient who progressed on cetuximab-based CT, suggesting possible nivolumab efficacy in biomarker-negative SCCHN (154).

Cemiplimab

Melanoma

There is an ongoing clinical trial of cemiplimab plus fianlimab (a LAG-3 inhibitor) compared with pembrolizumab in patients with previously untreated unresectable locally advanced or metastatic melanoma (NCT05352672; estimated study completion date: April 20, 2031). Patients with active or untreated BM are not eligible for this study. However, BMs meeting prespecified criteria, such as BM not requiring immunosuppressive corticosteroids doses or asymptomatic BM with a single untreated BM size <10 mm, will be included (Clinical Study of Fianlimab in Combination With Cemiplimab in Adolescent and Adult Patients With Previously Untreated Unresectable Locally Advanced or Metastatic Melanoma - Full Text View - ClinicalTrials.gov).

Non-Small-Cell Lung Cancer

Recently, cemiplimab-rwlc in combination with

platinum-based CT was FDA-approved for adult patients with advanced NSCLC (aNSCLC) without EGFR, ALK, or ROS1 aberrations based on a multicenter randomized open-label trial (Study 16113, EMPOWER-Lung 3 (NCT034096142022) (134)) (FDA approves cemiplimab-rwlc in combination with platinum-based chemotherapy for non-small cell lung cancer | FDA). While patients with previously treated and controlled BM were eligible to be included, those with active or untreated BM were excluded (134). Of 466 patients with stage III/IV aNSCLC with any PD-L1 expression, 6.7% had BM (adequately treated and clinically stable)(134). However, the study did not separately report the results for the subgroup with BM (134). This study revealed a significantly longer OS in patients receiving cemiplimab-CT vs. those who received placebo-CT (21.9 months vs. 13.0 months; HR = 0.71 ($p = 0.014$))(134). Nevertheless, OS did not significantly differ when it came to certain subgroups, including patients with PD-L1 < 1%, never smokers, and women (134). Notably, superior PFS and ORR in favor of the cemiplimab-CT cohort were observed across all subgroups, and the authors are awaiting longer-term follow-up data for OS results (134). This study indicated the combination of cemiplimab and platinum-doublet CT as a potential first-line treatment for patients with advanced squamous and non-squamous NSCLC without EGFR, ALK, or ROS1 aberrations, regardless of PD-L1 expression level (134). To our knowledge, there is currently no study specifically reporting the safety and efficacy of cemiplimab among patients with BM.

Atezolizumab

Atezolizumab is an IgG1 human monoclonal antibody that has been engineered to inhibit PD-L1 signaling. Atezolizumab has been approved by the U.S. FDA for being administered as single-agent therapy or in adjunction with chemotherapeutic agents in different types of malignancies (254). Different studies indicated the therapeutic benefits of atezolizumab in patients with BM.

Non-Small-Cell Lung Cancer

A phase-II clinical trial (FIR study, NCT01846416) investigated the effectiveness of single-agent therapy with atezolizumab in reducing PD-L1 progression or metastasis in patients with advanced NSCLC. This study enrolled a total number of 138 patients in three cohorts, the third of which included 13 NSCLC patients with BM. The results indicated the clinical benefits of atezolizumab in treating NSCLC patients with BM as shown by OS, medium PFS, and ORR of 6.3 months, 4.3 months, and 23%, respectively (255). In a phase-III open-label clinical trial (OAK study, NCT02008227), the efficacy of the treatment with atezolizumab was compared with docetaxel in asymptomatic NSCLCs patients, whose disease progressed despite formerly platinum therapy and a group of them suffered from steady metastatic encephaloma. The results comparing 38 and 47 NSCLCs patients treated with atezolizumab and docetaxel, respectively, demonstrated a more significant amelioration in disease progression (39%) and fatalities (45%) by atezolizumab compared to CT in the POPLAR study (NCT01903993), suggesting the beneficiary roles of atezolizumab in treating NSCLC-induced BM (256). In this regard, atezolizumab increases the OS by 5.4 months, and 3.7 months, in patients with PD-L1 expression of more than 1% and those with below 1% PD-L1 expression levels. Therefore, the clinical usefulness of atezolizumab compared to CT can benefit patients with either high or low PD-L1 expression levels (256, 257). Another study using subgroup analysis of Japanese patients participating in the OAK study reported also the beneficiary effects of atezolizumab in the mentioned group of NSCLC patients (258). A subgroup analysis of a phase-III clinical trial (IMpower150, NCT02366143) demonstrated that adding atezolizumab to bevacizumab plus carboplatin and paclitaxel could delay the time to development of BM in NSCLC patients (Hazard ratio: 0.68)(259). These promising results indicating the safety and efficacy of atezolizumab have led to the approval of this drug by the U.S. FDA for being applied in NSCLC patients with BM, who previously experienced unsuccessful treatment with CT or targeted therapy.

Small-cell Lung Cancer

A phase-I clinical trial (PCD4989g, NCT01375842) investigated the clinical efficiency of the treatment with atezolizumab in patients

with different solid tumors, including small cell lung cancer (SCLC). In this study, 17 SCLC patients with BM were included, from whom 65% had received atezolizumab as a third-line or above treatment. The results indicated the promising therapeutic benefits of atezolizumab in these patients, with median OS and median PFS of 5.9 and 1.9 months, respectively. These findings illustrated that atezolizumab extends PFS and ORR and can be well tolerated in SCLC patients with BM (260).

Another phase-III clinical trial namely IMPower-133 compared the clinical effectiveness of atezolizumab plus CT (etoposide and carboplatin) and CT alone in 403 SCLC patients with BM who had been unsuccessfully treated. The findings demonstrated the beneficiary roles of atezolizumab in improving median PFS (from 4.3 to 5.2 months) and OS (from 10.3 to 12.3 months) of the SCLC patients compared to CT alone (261). In this context, atezolizumab was the first drug that had been applied as a first-line treatment of SCLC (262). These findings overall point toward the effectiveness of atezolizumab in patients with brain metastases originating from lung cancers. However, for benefiting more patients from this novel immunotherapy approach the composition of this drug should be optimized and its high cost should be managed.

Durvalumab

Non-Small-Cell Lung Cancer

Durvalumab is another PD-L1 inhibitor, gaining FDA approval for the first time in May 2017 for treating metastatic bladder cancer (263). The risk of developing brain abscesses should be considered when using durvalumab (263). In a phase-III clinical trial (PACIFIC, NCT02125461), the efficacy of durvalumab was evaluated in 713 stage-III NSCLC patients, some of whom suffered from BM. The results showed no significant tumor growth during 16.8 months after administering durvalumab compared to 5.6 months after placebo therapy. The findings showed a median PFS of 11.2 months, along with no significant increase in AEs in the investigated group (264). A phase-I clinical trial (CAURAL, NCT02454933) comparing the efficacy of combination therapy with osimertinib and durvalumab versus osimertinib monotherapy in 21 terminal NSCLC patients with BM reported an ORR of 64% after combination therapy (265). However, the limited sample size of this study limited its generalizability, and there is a need for more qualified trials assessing durvalumab efficacy in BM. There is evidence that durvalumab has a favorable safety profile when being used for treating NSLC, but this requires the completion of a course of cardiac resynchronization therapy before using the drug. To our knowledge, there is only one cohort study demonstrating its efficacy in increasing the OS (132, 266).

Small-Cell Lung Cancer

Durvalumab is considered a first-line treatment as an adjuvant to CT in SCLC. Durvalumab has also shown promising results in treating BM stemming from SCLC when used in conjunction with CT and RT. In a study, durvalumab was administered in combination with CT to treat BM originating from SCLC. According to the results, combining durvalumab with etoposide and cisplatin CT (EP) can significantly improve OS, whereas sole administration of EP showed no favorable results. There was no difference in OS between the cohort receiving EP and durvalumab and the cohort treated with brain RT as an adjuvant (267, 268).

The major barrier limiting the efficacy of durvalumab is its low penetrance rate through BBB, resulting in its low concentration within the brain. A case report presenting a patient with stage-III SCLC reported that an oral multitarget TKI, named anlotinib, can serve as a factor in increasing the penetrating ability of durvalumab leading to its sufficient availability within the brain (269). However, further studies are required to determine whether this combination is effective. Furthermore, this specific PD-L1 inhibitor is more effective when combined with poly-ADP ribose polymerase inhibitors, such as Olaparib. In this regard, a combination of these two is more tolerated and has a better long-term outcome, leading to a more favorable prognosis. RT has also been demonstrated to play an important role in increasing the permeability of the BBB to enhance the amount of anti-PD-L1 in the brain; therefore, it can serve as a novel adjuvant to durvalumab. However, a study on breast can-

cer patients with BM did not support the administration of durvalumab as a first-line treatment in these patients (270).

Avelumab

Non-Small-Cell Lung Cancer

Avelumab is a humanized IgG1 lambda antibody with anti-PD-L1 characteristics. The efficacy of avelumab on BM is currently under investigation by a registered phase-II clinical trial (PAVE study, NCT03568097), which will investigate the effects of the combination therapy of avelumab and CT on 55 NSCLC patients with BM.

Renal Cell Carcinoma

Avelumab has been used in treating urothelial carcinomas (271). Although platinum-based CT approaches are considered the gold-standard treatment for metastatic urothelial carcinomas, avelumab is currently found to help treat RCC due to its promising effects on enhancing the patients' PFS. The administration of avelumab and axitinib in a male patient suffering from multiple metastatic lesions in the lung and hilar lymph nodes secondary to RCC led to a significant reduction in the size of metastases, as reported by Uekawa *et al.* (272, 273).

Merkel Cell Carcinoma

A case series reported effective results of the combination of CT and etoposide and avelumab in patients with metastasis stemming from a rare type of skin cancer, namely Merkel cell carcinoma (MCC), as this approach improved their OS and reduced their brain metastatic lesions' sizes. Therefore, this drug was approved in March 2017 by the FDA for treating MCC and is primarily used as a second-line treatment (136). Currently, there is no published clinical trial on the utility of avelumab in brain-metastatic patients.

CTLA-4 Inhibitors and Brain Metastasis

T cells activation for fighting cancer cells is enabled by the engagement of T-cell receptors (TCRs) with antigen-bound MHC-1 expressed on APCs and the co-stimulatory signal from the attachment of T cells associated CD28 and the B7 family (e.g., B7.1 and B7.2) on APCs (274). Moreover, attaching CD28 to the B7 family leads to an upregulated expression of CTLA-4 on T cells, which is a regulatory receptor with a higher affinity to bind with the B7 family on APCs compared to CD28 (274). As a result, the upregulated expression of CTLA-4 outcompetes the co-stimulatory signal of CD28 and B7 for T-cell activation, thereby weakening T cells' immune response to cancer cells (274). In this regard, inhibiting CTLA-4 receptors through anti-CTLA4 monoclonal antibodies has been introduced as an IC-inhibiting approach to strengthen and prolong the immune response of T cells against various types of cancers (275). This increased immune response was evidenced by an induced production of cytokines of Il-2, Il-10, and Interferon gamma (IFN-Y)(275). Accordingly, CTLA4-knocked-out mice tended to develop lethal lymphoproliferative conditions leading to tissue degeneration (276). Moreover, inhibiting CTLA4 in murine models using monoclonal antibodies resulted in enhanced T-cell function for killing various types of solid cancers, including prostate, fibrosarcoma, and colon (277-279). In this regard, two fully human-based anti-CTLA4 monoclonal antibodies, ipilimumab, and Tremelimumab have been developed for combating cancers, the efficacy of which was also studied in patients with brain metastases.

Ipilimumab

Melanoma

Ipilimumab, a complete human IgG1 monoclonal anti-CTLA-4 antibody, was the first ICI authorized by leading regulatory organizations. In this regard, the United States FDA approved ipilimumab as adjuvant therapy in completely-resected stage-III melanoma and also for treating metastatic or unresectable melanoma in monotherapy or concurrent therapy with nivolumab (280).

Weber *et al.* used the data from a phase-II controlled trial in which 115 patients with unresectable stage III (3.5%) or stage IV (96.5%) melanoma were treated with ipilimumab at a dosage of 10 mg/kg every three weeks (for a maximum of four doses)(281). They randomized the patients into two cohorts, in which either budesonide or placebo was administered. Twelve of the 115 (10.4%) enrolled patients had stable BM at the baseline. The results indicated that two of the 12 brain-metas-

tasized melanoma patients (16.7%) showed a PR, and three of them (25%) had SD. In contrast, no patient demonstrated a CR, resulting in an overall DCR of 41.7%. The BORR, defined as the proportion of patients with PR or CR by modified World Health Organization (WHO) criteria, was reported to be 16.7% in these patients (not mentioned whether intra- or extracranial). Furthermore, the median overall survival (OS) of these MBM patients was 14 months (range: 2.7–56.4). This study overall contributed to evidence of the efficacy and safety of ipilimumab in MBM patients (281). In another phase-II open-label clinical trial, Margolin *et al*. studied whether the corticosteroid treatment in advanced MBM patients who received ipilimumab (10 mg/kg, every three weeks up to four doses) could affect the antitumor activity of ipilimumab (282). They enrolled 72 MBM patients from ten centers in the US, dividing them into two cohorts consisting of 51 patients without neurological symptoms and prior corticosteroid usage (Cohort A) and 21 patients with symptomatized BM. The latter had been treated with stable doses of corticosteroids at study entry to relieve their manifestations (Cohort B). The results indicated an iORR of 16% and a brain DCR (defined as CR plus PR plus SD) of 26%, assessed by immune-related response criteria (irRC) in cohort A. In contrast, patients in cohort B demonstrated much less effective outcomes by 5% iORR and 10% DCR as defined by irRC. The results indicated less efficiency of ipilimumab in MBM patients who were previously treated with corticosteroids. However, whether this reduced effectiveness is attributable to the greater extent of BM in cohort B or the immunosuppressive properties of corticosteroids should be further elucidated in future studies. In summary, this study underlined that corticosteroid treatment could not completely prevent the beneficiary effects of ipilimumab in MBM patients (282).

Queirolo *et al.* studied 146 asymptomatic melanoma patients with BM treated with ipilimumab (3 mg/kg every three weeks for four doses)(283). The data of these patients were obtained from the EAP program, which is a program designed in Italy for evaluating the effects of ipilimumab on unresectable (stage III), stage IV, or asymptomatic brain metastatic melanoma patients who failed or could not endure previous treatments and had no further available therapeutic choices. Of these 146 patients, four showed CR (2.7%), 13 had PR (8.9%), and 22 had SD (15.0%), resulting in an overall DCR of 26.7% (283). The OS and PFS were reported as 4.3 and 2.8 months, respectively. Moreover, 29% of patients showed trAEs, with diarrhea as the most observed AE, which showed to be reversible by ipilimumab treatment protocol guidelines. In this regard, only 6% of the mentioned population showed grade 3/4 AEs. Hence, the safety of ipilimumab treatment in this study was comparable with other clinical trials, and no unexpected or higher rates of serious AEs for ipilimumab were reported (283). This study collectively suggested the durable clinical response of ipilimumab and its controllable AEs in MBM patients (283). Other clinical trials evaluating the efficacy of ipilimumab in MBM also indicated its promising clinical outcomes (284, 285). In this regard, Downey showed a CR of 10% and PR of 20% in 139 metastatic melanoma patients after receiving ipilimumab (285). From this population, ten patients had BM at study entry, three of which (30%) showed PR and two of which had PR (20%)(285). Another study reported a promising clinical benefit of combined ipilimumab and fotemustin as a chemotherapeutic drug used in melanoma patients with or without BM in three-year follow-ups (286, 287).

The combination of ipilimumab and SRS also appeared to be well tolerated and associated with better OS in MBM patients who received both SRS and ipilimumab than in patients receiving SRS alone (288-290). For instance, a study compared the efficacy and AEs between 20 MBM patients who received ipilimumab-SRS, and 34 patients who underwent only SRS. The results indicated that administering ipilimumab combined with SRS does not expose patients to excessive AEs, including hemorrhage or RNB (291). These results were in line with previous studies (288, 290, 292). Moreover, patients in the ipilimumab cohort had longer OS than the SRS-only treated group, but this difference was not statistically significant (291). Accordingly, a phase-I clinical trial illustrated that the combined therapy of 10 mg/kg ipilimumab with SRS and 3 mg/kg ipilimumab with WBRT is safe and tolerable (292). Overall, ipilimumab seems to be a proper ICI associated with promising outcomes in metastatic brain

patients, either administered alone or combined with conventional approaches. However, more prospective studies with higher sample sizes are warranted to elucidate the ipilimumab efficacy in BM comprehensively.

Paired Immunotherapy: Ipilimumab-Nivolumab Combination Therapy

Concurrent blockade of different classes of ICIs could theoretically lead to a more potent immune response than monotherapy against BM. To examine this theory, various studies have assessed the combinatory therapy efficacy of nivolumab and ipilimumab in MBM, most of which were discussed in the "Nivolumab" section (76, 77, 79, 80, 82, 91, 92). The synergistic properties of combination therapies are not well recognized (293, 294). One of the suggested mechanisms for the favorable clinical response of PD-1 inhibitors, when used in combination with CTLA-4 inhibitors (paired immunotherapies), is that PD-1/PD-L1 are unlikely to recruit immune cells into the metastasis, while CTLA-4 inhibitors promote T-cell recruitment into the tumor (295). Therefore, Téglási *et al.* suggested that patients with reduced immune cells infiltration into the tumor microenvironment may benefit more from combination therapy (94).

Melanoma

A phase-I trial studied the concurrent treatment with nivolumab-ipilimumab, followed by nivolumab maintenance therapy in ten MBM patients (280, 296). The results indicated a BORR and PR of 50% (296). A phase-II clinical trial in four sites in Australia compared the effects of the co-administration of nivolumab and ipilimumab versus nivolumab monotherapy in adult MBM patients (297). In this regard, 35 patients were assigned to cohort A to receive 1 mg/kg nivolumab combined with 3 mg/kg ipilimumab every three weeks (for four doses), followed by 3 mg/kg nivolumab every two weeks. On the other hand, 25 patients were assigned to cohort B, in which they were given 3 mg/kg nivolumab every two weeks. Intracranial OR was reported to be significantly higher in cohort A than in B (46% vs. 20%) as a primary endpoint of the study. Moreover, intracranial CR was observed in 17% of patients in cohort A and 12% in cohort B. However, trAEs were significantly higher in cohort A (97%) than in cohort B (68%), with 63% grade 3 or 4 AEs in cohort A compared with 16% in Cohort B (297). However, no new or unexpected toxicities were detected in this study.

In another phase-II trial (CheckMate 204), brain metastatic melanoma patients were enrolled into cohort A if they were asymptomatic and their brain lesions were between 0.5-3 cm and into cohort B if they had stable neurological symptoms or were previously treated with corticoids (298). Both cohorts were administered intravenously a combination of ipilimumab and nivolumab followed by nivolumab maintenance at the dosage mentioned in the previous study. The results indicated an intracranial ORR of 54.4% in 101 asymptomatic patients with no new observed safety signals versus 22.2% in 18 patients with neurological symptoms or a history of corticosteroid therapy. Moreover, the median PFS and OS of symptomatic patients were reported to be 1.2 and 8.7 months, respectively. Based on these results, it can be concluded that the combinatory therapy of ipilimumab and nivolumab could be effective in asymptomatic MBM patients and has the potential to be administered as first-line therapy. However, patients with neurological symptoms or corticosteroid requirements might need alternative therapy approaches (298). The long-term results of this study indicated an ORR of 53.5% in cohort A and 16.7% in cohort B (80). Moreover, cohort A showed a 36-month intracranial median PFS and OS of 54.1% and 71.9%, respectively, compared to a 36-month intracranial PFS of 18.9% and OS of 36.6% in cohort B. Hence, the long-term outcomes of this study were in line with its preliminary report after a median follow-up of 20.6 months regarding the clinical benefit of a combination of nivolumab and ipilimumab in asymptomatic MBM patients (80). Apart from the higher rates of trAEs than monotherapy, the co-administration of ipilimumab and nivolumab showed encouraging outcomes in melanoma patients with BM. This combinatory suppression of checkpoint inhibitors of CTLA-4 and PD1-PD/L1 is mostly effective in asymptomatic MBM patients and has shown an acceptable safety profile (75). However, it needs to be more studied in future trials with higher sample sizes to be administered as first-line treatment in these patients.

Renal Cell Carcinoma

In a phase-IIIb/IV trial monitoring the efficacy of ipilimumab and nivolumab in advanced RCC patients suffering from asymptomatic BM, the patients were given 3 mg/kg ipilimumab and 1 mg/kg nivolumab every three weeks for four doses, followed by 489 mg nivolumab every four weeks. The results demonstrated a 32% ORR and a median duration response of 24.0 months. Moreover, no new safety signals were reported, and the median PFS of patients was reported at nine months. This study indicated potential promising outcomes of combinatory therapy of ipilimumab and nivolumab in advanced RCC patients with asymptomatic BM (141).

Tremelimumab

Tremelimumab is another fully human monoclonal antibody blocking CTLA-4 receptors on cytotoxic T lymphocytes, thereby preventing the normal suppression of T cells and prolonging their activation. The Pfizer company first developed this IgG2 antibody to fight against advanced cancers (299). Currently, the FDA approved the administration of Tremelimumab in combination with durvalumab, an anti-PD-L1 antibody, in treating unresectable hepatocellular carcinoma. Tremelimumab has shown OR but not increased OS in cancer metastatic patients in the primary phases of clinical trials. Based on phase-I/II studies, tremelimumab is considered a well-tolerable anti-CTLA-4 with manageable AEs (274).

Melanoma

According to a phase-III clinical trial conducted by Ribas *et al*., although the OR and OS of 328 metastatic melanoma patients receiving tremelimumab were not statistically better than 327 patients who were treated with standard-of-care CT, the response duration of the tremelimumab-treated group was significantly longer (300). The most frequently observed AEs associated with tremelimumab were pruritus, diarrhea, and rash (300). However, in the mentioned study, patients with BM were excluded. In contrast, Camacho *et al.* conducted a phase I/II trial to study the effects of tremelimumab on metastatic melanoma patients, three of whom had stable or previously treated BM. The results indicated the progression of the disease in all three patients, either intracranially by developing new BM or size enhancement of prior BM or extracranially by developing new lesions in the lung, chest wall, and subcutaneous regions (301).

Breast Cancer

According to Page *et al*. study, breast cancer patients with BM who were treated with tremelimumab plus RT with or without Trastuzumab (based on the expression of human epidermal growth factor receptor-2) showed promising intracranial responses with manageable AEs (302). There are also clinical trials that studied tremelimumab in other advanced solid cancers but not in patients with BM. Therefore, based on the low number of conducted trials with insufficient sample sizes, monotherapy with tremelimumab did not show superior effects to standard-of-care treatments in patients with BM. Overall, there is a substantial need for more clinical trials to monitor tremelimumab effects and safety concerns in patients with BM (280).

LAG-3 Inhibitors and Brain Metastasis

LAG-3 is a type-1 transmembrane protein and a regulatory cell-surface molecule playing roles in inhibiting the proliferation and activation of T cells. LAG-3 is expressed not only on various immune cells like activated T cells, NKs, and B cells but also it is upregulated in many tumors (303, 304). Either cytokines like Il2, Il7, Il12, Il15, and Il27 or TCR stimulation could significantly induce the expression of LAG-3 (304, 305). This receptor is considered an ICI, playing several roles in suppressing the immune system, like negatively regulating the proliferation and homeostasis of $CD4^+$ and $CD8^+$ T cells, known as T-cell exhaustion, reducing cytokine production, and encouraging the development of T-regulatory cells (303, 304). In this regard, LAG-3 proteins are suggested to contribute to cancer immune evasion. Therefore, monoclonal antibodies targeting LAG-3 might play beneficiary roles in inducing the body's immune system against different tumors. In this sense, patients with BM might also profit from this treatment.

Relatlimab

Relatlimab is a newly-developed anti-LAG3 antibody belonging to the IgG4 subclass used to

Table 2. Other studies investigating the effects of ICIs in patients.

Author, Year	Drug	Tumor type	Number of patients	Type of study	results	ORR	AEs
Trommer et al. (54), 2022	Concurrent RT + anti-PD-1 vs. Non-concurrent RT + anti-PD-1	MBMs (65) NSCLC-BMs (21) Other-BMs (6)	93 - Group A: concurrent RT: 63 - Group B: sequential (30) - Before anti-PD-1: 19 - After anti-PD-1: 11	Retrospective analysis	Total: - OS: 12.19 (4.36–20.02) - 12-month OS rate: 50.7% - PFS: 4.70 (2.53–6.86) - LC at 3 months: 69.3% - LC at 6 months: s 89.3%. - CR + PR + SD: 40.2% - PD: 59.8% - Cerebral response rate: 42.9% - overall progression (cerebral + systemic): 42.9% - Only cerebral progression: 16.5%, - Only systemic progression: 14.3% Group A vs. group B - OS: 17.61 vs. 6.83 months (P = 0.173) - PFS: 5.49 vs. 4.70 (0.383) - LC at 3 months: 64.2 vs. 81.8 (0.131) - LC at 6 months*: 95.3% vs. - 69.2% (p = 0.008) - Overall RR (P = 0.151) -CR: 9.7% vs. 3.3% -PR: 12.9% vs. 23.3% -SD: 21% vs. 6.7% -PD: 56.5% vs. 66.7% - Clinical benefit (CR + PR + SD): 43.5% vs. 33.3% (P = 0.151)	- Overall RR (P = 0.151) -CR: 9.7% vs. 3.3% -PR: 12.9% vs. 23.3% -SD: 21% vs. 6.7% PD: 56.5% vs. 66.7% -Clinical benefit (CR + PR + SD): 43.5% vs. 33.3% (P = 0.151)	- Total AEs: 74.1% - Grade 1 or 2 (71.7%)
Zhu et al. (99), 2022	Anti-PD-1 + CT ± bevacizumab	NSCLC-BMs (EGFR-mutated or ALK-rearranged) who progressed after previous EGFR/ALK-TKIs with BMs	19	Retrospective analysis	- ORR: 15.8% - DCR: 57.9% - PFS: 4.7 months - OS: 19.2 months - iORR: 10.5% - eORR: 15.8% - iDCR: 68.4% - eDCR: 63.2%	15.8%	• Grade 3-4: - Leukopenia: 31.6% - Neutropenia: 26.3% - Thrombocytopenia: 10.5 - Rash: 5.3% • Grade 5: 0
Serra-Bellver et al. (57), 2022	Ipilimumab + nivolumab	Advanced melanoma (stage 3 unresectable and stage 4)	697, 240 of whom with BMs Group A: Treatment naïve with BMs (138) Group B: Previously treated with BMs (102)	Retrospective	Group A: CR: 13.8% PR: 42.0 SD: 8.0 PD: 36.2 ORR: 55.8 DCR: 63.8% OS: 38.7 months PFS: 10 months 3-year PFS rate: 35.3% 3-year OS rate: 54.5% Group B: CR: 2.0% PR: 18.6% SD: 10.8% PD: 68.6% ORR: 20.6% DCR: 31.4% PFS: 2.3 months OS: 7.6 months	Group A: 55.8% Group B: 20.6%	Group A: - All grade trAEs: 85.5% - Grade 3 or 4 trAEs: 52.9% - Death due to adverse events: 0.7% Group B: - All grade trAEs: 46.1% - Grade 3 or 4 trAEs: 27.5% - Death due to adverse events: 0
Descourt et al. (104), 2022	Pembrolizumab	Advanced NSCLC (PD-L1-positive; TPS ≥ 50%)	845 patients, 176 of whom had BMs - Group A: with BM (176) - Group B: w/o BMs (669)	Retrospective	Group A vs. B: PFS: 9.2 vs. 8 (p = 0.3) OS: 29.5 vs. 22.0, p = 0.3) ORR: 47% vs. 45% SD: 20% vs. 23% PD: 31% vs. 31%		
de Castro et al. (78), 2022	Combined nivolumab-ipilimumab ± stereotactic RT	MBMs	228 Group A: Combined nivolumab-ipilimumab + stereotactic RT (114) Group B: Combined nivolumab-ipilimumab w/o stereotactic RT (114)	Retrospective	Group A vs. B: - Median OS: NR vs. 327 days - OS probability *: 40.9% vs. 54.4% (P = .0057)		
Patrinely *et al.* (179), 2021	Local therapy (Surgery/SRS) + adjuvant therapy with ICIs: - Nivolumab (5) - Nivolumab + ipilimumab (4) - Pembrolizumab (1) - Ipilimumab (1)	Isolated BMs: - Primary cutaneous lesions (6) - unknown origin (5)	11	Clinical series	Group A: Local therapy + ICI monotherapy - Intracranial recurrence: 3/7 - Extracranial recurrence: 0 - Mortality: 2/7 Group B: Local therapy + Dual ICIs - Intracranial recurrence: 1/4 - Extracranial recurrence: 0 - Mortality: 0	N/A	- Total irAEs: 8/11 - Grade III/IV irAE: 3/11 (hepatitis, colitis, cerebral radiation necrosis)

Table 2. Continued

Huang et al. (100), 2021	Anti-PD-1 + concurrent RT vs. anti-PD-1 + non-concurrent RT vs. anti-PD-1 monotherapy	Lung cancer-BMs (Lung adenocarcinoma, squamous cell lung carcinoma, and SCLC)	60 Group A: anti-PD-1 + concurrent RT (21) Group B: anti-PD-1 + non-concurrent RT (20) Group C: anti-PD-1 w/o RT (19)	Retrospective observational	Group A vs. B vs. C: - PFS: 9.2 vs. 5.7 vs. 4.6 months (P=0.347) - OS: not reached vs. 12.1 vs. 6.9 months (P=0.206) - iORR: 61.1% vs. 29.4% vs. 25.0% - iDCR: 83.3% vs. 58.8% - vs. 56.3% - iPFS*: 9.8 vs. 5.7 vs. 4.8 months (P=0.039)	iORR: 61.1% vs. 29.4% vs. 25.0%	N/A
Liao et al. (95), 2021	WBRT ± anti-PD-1	NSCLC-BMs	70 - Group A: WBRT alone (41) - Group B: anti-PD-1 + WBRT (29)	Retrospective	Total cohort: - Median survival: 24 months Group A vs. B: - Median survival*: 20 months vs. 27 months (p=0.035) - PFS: 7 months vs. 12 months (p=0.247)	N/A	- At least one AE: 47/70 - Most adverse events were of grade 1 or 2 severity - Grade 3 AE: 2/70 - No significant difference between group A vs. B
Hilbers et al. (56), 2021	ipilimumab + nivolumab/ ICI + targeted therapy	MBMs	116 Group A: ipilimumab + nivolumab (N = 53, 32% of which had symptomatic BMs) Group B: ICI + targeted therapy (N = 63, 55.6% of which had symptomatic BMs)	Retrospective	Group A: DCR: 60.3% iRR at 3 months: 43.8% iRR at 6 months: 46.5% iRR at 12 months: 53.1% eRR at 3 months: 44.7% eRR at 6 months: 56.8% eRR at 12 months: 50.0% PFS: 9.6 months OS: 44.8 months CR: 24.5% PR: 20.8% PD: 37.7% SD: 7.5% MR: 7.5% Group B: DCR: 60.4% iRR at 3 months: 50% iRR at 6 months: 20.9% iRR at 12 months: 13.9% eRR at 3 months: 69.2 eRR at 6 months: 48.6% eRR at 12 months: 17.6% PFS: 5.8 months OS: 14.2 months CR: 3.2% PR: 41.3% PD: 31.7% SD: 15.9% MR: 3.2%	Group A: 45.3% - CR: 24.5% - PR: 20.8% Group B: 44.5% CR: 3.2% PR: 41.3%	irAEs Group A: - Grade 3 or 4: 60.4% - Grade 5: 1.9% Group B: - Grade 3 or 4: 7.9% - Grade 5: 0
Du et al. (46), 2021	ICI receivers vs. non-receivers	- NSCLC-BMs (104,765) - TNBC-BMs (30,820) - MBMs (11,338) - RCC-BMs (6,973)	227,255 Group A: ICI exposed (25,220) Group B: non-ICI-exposed (25,243)	Retrospective	OS in ICI exposed vs non-ICI-exposed - Total cohort*: 14.0 vs. 7.9 months (HR: 0.88; 95% CI: 0.85–0.91) - NSCLC cohort*: 14.4 vs. 8.2 months (HR: 0.86, 95% CI: 0.82–0.90) - TNBC cohort*: 23.9 vs. 11.6 (HR: 0.87, 95% CI: 0.82–0.92) - Melanoma cohort*: 27.6 vs. 16.8 months (HR: 0.80; 95% CI: 0.73–0.88) - RCC cohort: 16.7 vs. 14.0 months (HR: 0.96, 95% CI: 0.86–1.10)	N/A	N/A
Sun et al. (106), 2021	Pembrolizumab-based therapies	NSCLC	570, 126 of whom had BMs Group A: with BMs (126) - Local therapy before pembrolizumab (SRS, surgical resection, WBRT): 96 - untreated BM: 30 (17 received radiation a month after pembrolizumab, 13 pembrolizumab alone with small asymptomatic BM) Group B: w/o BMs (444)	Retrospective	Group A vs. B: Systemic ORR: 27.8% vs. 29.7% (P = 671) PFS: 9.2 vs. 7.7 months (P = 0.609) OS: 18.0 vs. 18.7 months (P = 0.966) * Best intracranial responses - CR: 2/13 - PR: 2/13 - SD: 3/13 - PD: 4/13 - Unevaluable: 2/13		
Powell et al. (107), 2021	Platinum-doublet chemotherapy ± pembrolizumab	advanced NSCLC (non squamous and squamous) with previously treated or untreated stable BMs	1298, 171 of whom had BMs • Group A + B: with BMs (171) - Group A: Pembrolizumab + CT (105) - Group B: CT alone (66)	Retrospective pooled analysis of KEYNOTE-021, -189, and -407	Group A+B vs. C+D (HRs): OS: 0.48 vs. 0.63 PFS: 0.44 vs. 0.55 Group A vs. B: OS: 18.8 vs. 7.6		

Table 2. Continued

			* Group C + D: without BMs (1127) - Group C: Pembrolizumab + CT (643) - Group D: CT alone (484)		PFS: 6.9 vs. 4.1 Group A: - CR: 0 - PR: 39.0% - SD: 37.1% - PD: 8.6% Group B: - CR: 0 - PR: 19.7% - SD: 34.8% - PD: 24.2% Group C: - CR: 1.6% - PR: 53.0% - SD: 32.3% - PD: 7.3% Group D: - CR: 1.7% - PR: 30.2% - SD: 43.6% - PD: 14.5%		
Metro et al. (97), 2021	Pembrolizumab ± RT Group A: upfront pembrolizumab alone (9) Group B: WBRT + pembrolizumab (8) Group C: SRS + pembrolizumab (13)	NSCLC-BMs (PD-L1 ≥ 50% non-oncogene addicted NSCLC and asymptomatic BMs)	30	Retrospective	Intracranial responses: Group A: - CR: 1 (11.1%) - PR: 4 (44.4%) - SD: 1 (11.1%) - PD: 1 (11.1%) Group B: - CR: 1 (12.5) - PR: 5 (62.5) - SD: 1 (12.5) - PD: 0 Group C: - CR: 0 - PR: 4 (30.7) - SD: 2 (15.4) - PD: 3 (23.1) Group A vs. B vs. C: - Median survival: NR vs. NR vs. 7.6 months (P = 0.09) - 12 months survival rates: 55.5% vs. 62.5% vs. 23.0%		
Mansfield et al. (109), 2021	Pembrolizumab vs. CT	NSCLC-BMs (PD-L1-positive; TPS ≥ 1% and ≥ 50%)	3170 • With BMs: 293 - Group A: pembrolizumab (199) - Group B: CT (94) • Without BMs: 2877 - Group C: pembrolizumab (1754) - Group D: CT (1123)	Retrospective pooled analysis of KEYNOTE-001, 010, 024, and 042	Group A: - CR: 1.5% - PR: 24.6% - SD: 18.6% - PD: 40.2% Group B: - CR: 1.1 - PR: 17.0% - SD: 43.6% - PD: 19.1% Group C: - CR: 1.7% - PR: 24.1% - SD: 34.4% - PD: 27.0% Group D: - CR: 0.3% - PR: 21.9% - SD: 46.0% - PD: 15.5% PFS HR in patients with BMs (TPS ≥ 1%) (A vs. B): 0.96 (95% CI: 0.73–1.25) PFS HR in patients without BMs (TPS ≥ 1%) (C vs. D): 0.91 (95% CI: 0.84–0.99) OS HR in patients with BMs (TPS ≥ 1%) (A vs. B): 0.83 (95% CI: 0.62–1.10) OS HR in patients without BMs (TPS ≥ 1%) (C vs. D): 0.78 (95% CI: 0.71–0.85)		
Nakamura et al. (52), 2020	Anti-PD-1 vs. Anti-BRAF/MEK	Melanoma	71 Group A: PD-1 inhibitors (61) Nivolumab (55) Pembrolizumab (6) Group B: BRAF/MEK inhibitors (10)	Retrospective analysis	Group A vs. B: - CR: N/A vs 5/10 - PR: N/A vs 3/10 - Developing BM on treatment*: 3/61 vs 4/10 (P = 0.006) - BM free survival*: P = 0.017	BOR for group A: N/A BOR for group B: 8/10	Group A: N/A Group B: - Pyrexia (3/10)
Knispel et al. (53), 2020	Anti-PD-1/ Anti-CTLA-4 + preceding RT vs. Anti-PD-1/	Unresectable MM	835, 223 of whom had BM Group A: preceding	Multicenter retrospective cohort	Group A vs. B - PFS: After multivariable	Subgroup E vs F 8.8% vs 3.5%; RR=2.54; p=0.14	N/A

Table 2. Continued

	Anti-CTLA-4 w/o preceding RT		radiotherapy + anti-CTLA-4 (150) Group B: Anti-CTLA-4 w/o preceding radiotherapy (446) Group C: preceding radiotherapy+ anti-PD-1 inhibitors (85) Group D: Anti-PD-1 inhibitors w/o preceding radiotherapy (154) Subgroup E: Patients with BM with preceding radiotherapy + anti-PD-1 (137) Subgroup F: Patients with BM w/o preceding radiotherapy + anti-PD-1 (86)		adjustment, no - difference was detected (HR=1.02, p=0.74) - OS (HR=1.08, p=0.61) - OR: 8.7% vs 13.0%, RR=1.47, p=0.20) Group C vs. D: - PFS: (HR=0.84, p=0.41) - OS (HR=0.73, p=0.26) - OR: 16.5% vs 25.3%, RR=0.93, p=0.82) Subgroup E vs F: - PFS: HR=0.85, p=0.29 - OS: HR=0.77; p=0.18 - OR: 8.8% vs 3.5%; RR=2.54; p=0.14)		
Tozuka et al. (98), 2020	Anti-PD-1/ anti-PD-L1 monotherapy (nivolumab, pembrolizumab, or atezolizumab) in active BMs vs. non-active BMs	NSCLC-active BMs	197 - Group A: Active BMs (24): 3 patients received local treatment for BMs, but they received steroid treatment - during initiation of anti-PD-1/PD-L1 - Group B: Without active BM (no BM or treated asymptomatic BMs) (173): all patients with BMs received local treatment. 4 received WBRT, 21 received SRS, 2 received WBRT and SRS, and 1 underwent surgery.	Retrospective analysis	Group A vs. B: - PFS*: 1.3 vs. 2.7 months; P < 0.001 - OS*: 4.5 vs. 16.3 months; P = 0.001 Group A (active BMs) - Intracranial response rate: 2/15 (13.3%) - Extracranial response rate: 4/15 (26.7%) - Progression of intracranial lesions (while having PR or stable extracranial disease): 3/15 (20%) - Intracranial PFS: 1.4 months - Extracranial PFS: 2.2 months	N/A	N/A
Qian et al. (101), 2020	Concurrent ICIs + RT (brain-directed)/ non-concurrent ICIs + RT (but within 90 days) ICIs: - Anti-CTLA-4 monotherapy (43) - Anti-PD-1 monotherapy (39) - Sequential anti–CTLA-4 and anti–PD-1 (16) - Simultaneous anti–CTLA-4 and anti–PD-1 (12)	MBMs NSCLC-BMs	110 patients with 340 BMs Group A: Concurrent ICIs + RT (brain-directed) (102 BMs) Group B: Non-concurrent ICIs + RT (but within 90 days) (238 BMs)	Retrospective	Group A vs. group B: - Best response (any)*: 70% vs. 47% (P < 0.001) - CR: 41% vs. 26% - PR: 29% vs. 21% - SD: 25% vs. 26% - PD: 5% vs. 26% - Time to response*: HR: 1.76 P = (0.006) - Local recurrence*: HR 0.42 (P = 0.006)	Group A vs. group B: 67% vs. 50%	N/A
Amaral et al. (85), 2020	Nivolumab + ipilimumab ± local therapies * Regardless of treatment line	MBMs (Asymptomatic and symptomatic)	380 Symptomatic MBM: 60/193 with data available (31%)	Retrospective	- Median OS: 19 months - 1 year OS: 69% - 2 years OS: 41% - 3 years OS: 30%		
Zhang et al. (126), 2020	Nivolumab	NSCLC	73 - Group A: With BMs: 32 (7 of which were symptomatic BMs) - Group B: Without BMs: 41	Retrospective	Group A: - iORR: 28.1% - iDCR: 46.9% - iPFS: 2.2 months Group A vs. B: - ORR: 25.0% vs. 19.5% (p = 0.574) - DCR: 53.1% vs. 56.1% (p = 0.800) - PFS: 2.8 vs. 4.9 months (p = 0.204 - DOR*: 9.8 vs. 28.8 months (p = 0.003) - OS: 14.8 vs. 20.2 months (p = 0.114)		
Cortinovis et al (318), 2019	Nivolumab	Squamous NSCLC	37	EAP program	OS: 5.8 months, OR: 19%, DCR: 49%, CR: 3%, PR: 16%, SD: 30%, PFS: 4.9 months	19%	Any grade: 32%, Grade 3 or 4: 8%
Lanier *et al.* (177), 2019	ICIs + SRS vs. SRS alone	Lung-BMs: 226 MBMs: 45	271 - Group A: Immunotherapy+ SRS: 101 - Nivolumab (44) - Pembrolizumab (37) - Ipilimumab (15) - Nivolumab/Ipilimumab (1) - Atezolizumab (1) - Other (3)	Retrospective analysis	Group A vs B: - OS*: 15.9 vs 6.1 months (P < 0.01) - 1-year cumulative incidence of neurologic death*: 9% vs 23% (P = .01) - Risk of DBF*: 54% vs. 34% (P < 0.01) - Rates of death without DBF at 1 year*: 16% vs 45% (P < .01)	N/A	- Overall rates of neurologic toxicity requiring intervention: 33%. - Grade 3 or 4 CNS toxicity in patients receiving immunotherapy: 21%

Table 2. Continued

			* SRS timing: - Before immunotherapy (83) - Concurrent (13) - After immunotherapy (5) - Group B: SRS alone: 170		- Non-neurologic death: 29% vs 41%, P = 0.51) - Median brain metastasis velocity (BMV): 6.4 vs. 10.1 (P = 0.57). - 1-year cumulative incidence - of local failure: 9% vs. 4% (P = 0.17)		
Minniti et al. (88), 2019	SRS + nivolumab/ipilimumab (Concurrent)	MBMs (untreated)	80 patients, 326 BM lesions Group A: SRS + nivolumab (35) Group B: SRS + ipilimumab (45)	Retrospective	Group A: - CR: 41% - PR: 35% Group B: - CR: 23% - PR: 37% Group A vs. B: - Intracranial PFS rate (6-month) *: 69% vs. 48% (p = 0.02) - Intracranial PFS rate (12-month) *: 42% vs. 17% (p = 0.02) - OS *: 22.0 vs. 14.7 months (p = 0.015) - DBC rates (6 and 12 months) *: 75% and 46% vs. 52% and 20% (P = 0.027)		
Cortinovis et al. (130), 2019	Nivolumab	NSCLC-BMs	37 (Italian cohort of the EAP) - Prior RT: 57% - Receiving CS: 22%	Retrospective	- CR: 1/37 (3%) - PR: 6/37 (16%) - SD: 11/37 (30%) - PD: 19/37 (51%) - ORR: 7/37 (19%) - OS: 5.8 m - PFS: 4.9 m - DCR: 18/37 (49)		
Crinò et al. (129), 2019	Nivolumab	NSCLC-BMs	409 (Italian cohort of the EAP) Receiving CS: 118 Concomitant radiotherapy: 74	Retrospective	- DCR: 164/409 (40%) - CR: 4/409 (1%) - PR: 64/409 (16%) - SD: 96/409 (23%) - PD: 192 /409 (47%) - OS: 8.6 months - Death: 35/409 (9%)		
Trommer-Nestler et al. (59), 2018	Robotic SRS± anti-PD-1 - Pembrolizumab (10) - Nivolumab (2)	MBMs	26 Group A: SRS + anti-PD-1 (13 patients, 28 lesions) Group B: SRS alone (13 patients, 20 lesions)	Retrospective	Group A vs. B: - Local control at 6 months: 86% vs. 80% - Lesion size increase rate at 3 months*: 21% vs. 5% (0.028) - Lesion size increase rate at 6 months*: 14% vs. 20% (0.005)	Group A vs. B: Local response rate at 3 months: 79% vs. 95% Local response rate at 6 months: 86% vs. 80%	Group A vs. B: Intracranial pressure symptoms: 8/13 vs. 5/13 Gastrointestinal symptoms: Group A: 2/13 (enterocolitis accompanied by diarrhea, CTCAE grade 2) Group B: 1/13 (non-specific gastroenterological symptoms CTCAE grade 0–1) New thyroid disorder: 4 vs. 0 (P = 0.096)
Hubbeling et al. (102), 2018	Cranial RT ± anti-PD-1/anti-PD-L1 Radiation therapy: SRS (94) PBI (28) WBRT (101)	NSCLC-BMs	163 Group A: Cranial RT + anti-PD-1 (50) Group B: Cranial RT alone (113)	Retrospective	N/A	N/A	Group A vs. B: No significant difference in rates of all-grade AEs and grade ≥ 3 AEs
Afzal et al. (96), 2018	carboplatin/pemetrexed ± pembrolizumab	Non-squamous NSCLC	54, 17 of whom had BMs Group A: carboplatin/pemetrexed (12) Group B: carboplatin/pemetrexed + pembrolizumab (5)	Retrospective	Group A vs. B: Best response: P = 0.36 - CR: 0/12 vs. 1/5 - PR: 7/12 vs. 3/5 - SD: 2/12 vs. 0/5 - PD: 3/12 vs. 1/5 DCR: 75% vs. 80% (P = 0.68) Median time to achieve response: 1.67 vs. 1.1 month	Group A vs. B: 58.3% vs. 80% (P = 0.75)	N/A
Nardin et al. (66), 2018	SRS + pembrolizumab Concurrent: 22/58 (38%) SRS before PB: 21/58 (36%) SRS after PB: 17/58 (26%)	MBMs	25 patients, 58 MBMs	Retrospective analysis	Local control 46/58 MBMs (80%): CR: 7/58 PR:14/58 SD:25/58 DP: 12/58 (20.7%) Local control: 17/25 patients (68%) Distant intracranial progression: 16/25 (64%) Median OS: 15.3 months Intracranial PFS: 4 months	Local control rate: 80% of lesions OR: 21/58 (36.2%)	Neurotoxicity - Radiation necrosis (within a median time of 6.5 months): 4/58 MBMs (6.8%), 4/25 patients (16%) - No other significant SRS-related adverse event was observed.

Table 2. Continued

Gauvain et al. (131), 2018	Nivolumab	NSCLC-BMs	43 - Local BM pretreatment: 34/43 (79%) - Active BMs: 16/43 (37%)	Retrospective	- iORR: 9% - eORR: 11% - Intracerebral control rate: 51% - Intracerebral PFS: 3.9 months - Global PFS: 2.8 month - OS: 7.5 m		
Fang et al (310), 2017	SRS + Ipilimumab and/or Pembrolizumab	Melanoma	137	Trial (retrospective analysis)	OS: 16.9 months, 2-year RNFS: 81.2%		RN: 27%
Pike et al. (55), 2017	Anti-PD-1 (pembrolizumab, nivolumab, or both) + RT - Radiation only prior to anti-PD-1 (78) - Radiation both before and after anti-PD-1 or only after PD-1: (59, 25 of whom continued to receive PD-1 inhibitors following radiation)	- NSCLC - MM - RCC	137 - NSCLC (79) - MM (48) - RCC (10)	Retrospective	• Median survival - NSCLC: 192 - MM: 394 - RCC: 121 • OS following the first instance of brain-directed radiation: 21 months - NSCLC: 18 - Melanoma: 52 - RCC: 27 • Median survival following PD-1-directed therapy: 249 days - NSCLC: 192 - Melanoma: 394 - RCC: 121	N/A	Grade 4 or 5 radiation-specific or irAE: 0
Patel et al (291), 2017	Ipilimumab + SRS	Melanoma	20	Retrospective analysis of the effects of SRS + ipilimumab Vs. SRS alone in MBM patients	Intracranial DCR: 29.1%, 1-year OS: 38.5%		RN and hemorrhage in patients co-treated with SRS and ipilimumab was similar to patients treated with SRS
Anderson et al. (69), 2017	• Concurrent pembrolizumab + RT - Group A: SRS (11 patients, 23 lesions) - Hypofractionated radiation (7) - WBRT (3) • Group B: concurrent SRS + ipilimumab (20 patients, 31 lesions) • Group C: SRS without concurrent IT (15 patients, including 13 with no concurrent therapy, 1 with concurrent vemurafenib, and 1 with recent temozolomide 27 treated lesions)	MBMs	21 concurrent pembrolizumab + RT	Retrospective analysis	Group A on first planned follow-up MRI - CR: 8/23 lesions (35%) - PR: 8/23 (35%) - SD: 6/23 (26%) - PD:1/23 Group B: On first follow-up scan - CR: 4/31 (13%) - PR: 6/31 (19%) - SD: 19/31(61%) - PD: 2/31 (6%) Group C on first follow-up scan : - CR: 1/27 (3.7%) - PR: 5/27 (18.5%) - SD: 18/27 (66.7%) - PD: 3/27 (11.1%)	Intracranial RR: - Group A: 70.0% - Group B: 32.0% - Group c: 22.0%	Concurrent pembrolizumab + RT: - Grade 1: 25 events - Grade 2: 8 events - Grade 3: 1 event - Grade 4 and 5: 0 * Mortality after a median follow up of 276 days: 11/21 patients - In the 11 patients who had died, 13/14 BMs that were treated with SRS were controlled at the time of death (93%)) - At the time of death, 8/11 patients had suffered recurrence within the brain, and were treated with repeat SRS, surgery, or observation, as dictated by their clinical course.
Ahmed et al (93), 2016	Nivolumab + SRS	Melanoma	26	Trial (retrospective analysis)	OS: 12 months (From Nivolumab initiation), 12-moths local BM control: 85%		Neurologic toxicity (grade 2): 3.8%
Anderson et al. (71) [abstract], 2016	Concurrent pembrolizumab + SRS/hypofractionated RT - Group A: Pembrolizumab + RT (n = 19; 31 lesions) - Group B: Ipilimumab + RT: (n = 53; 89 lesions) - Group C: systemic chemotherapy or BRAF inhibitors w/o concurrent IT (n = 59 patients; 92 lesions)	MBMs	131 patients, 212 lesions - SRS (169) - hypofractionated (43)	Retrospective	Group A: - CR: 33% - PR: 29% - SD: 33% - PD: 4% Group B: - CR = 13% - PR = 19% - SD = 66% - PD = 3% Group C: - CR = 3% - PR = 20% - SD = 70% - PD = 7% Response distribution Group A vs. B*: P = 0.01 Response distribution Group A vs. C*: P < 0.01		
Johnson et al (288), 2015	Group A: Ipilimumab (or BRAF inhibitors) + SRS Group B: SRS	Melanoma	Group A: 20 Group B: 97	Retrospective trial	Group A: Survival: 18 months, 1-year survival: 65% Group B: survival: 7 months, 1-year survival: 30%		-
Kiess et al (290), 2015	Ipilumumab + SRS	Melanoma	46	Retrospective trial	Median survival:12.4 months 1-year OS: 65%		Grade 3 or 4 AEs in 20% of patients (combination of SRS

Table 2. Continued

					(concurrent), (SRS before): 56%, (Ipilimumab before): 40%		and ipilimumab is well-tolerated)
Gerber et al (309), 2015	Ipilimumab + WBRT	Melanoma	13 (10 had follow-up imaging for assessing treatment response)	Trial (retrospective analysis)	CR: 10%, PR: 10%, SD: 20%, DCR: 56% (irRC), PFS: 102 days (irRC), OS: 4 months, 1-year survival: 15.4%	20%	Grade 3 or 4 neurologic toxicity: 11.1%
Queirolo et al (283), 2014	Ipilimumab	Melanoma	146	EAP (retrospective)	CR: 3%, PR: 9%, SD: 15%, BORR: 12%, OS: 4.3 months	12%	All grades: 29%
Kniesely et al (289), 2012	Group A: Ipilimumab + SRS Group B: SRS only	Melanoma	Group A: 27 Group B: 50	Retrospective assessment of prospectively collected cohort	Group A: Median survival: 21.3 months, 2-year survival: 47.2% Group B: Median survival: 4.9 months, 2-year survival: 19.7%		ipilimumab administration was associated with higher rate of AEs
Weber et al (281), 2011	Ipilimumab	Melanoma	12	Retrospective analysis of a phase-II clinical trial	BORR: 16.7%, CR: 0%, PR: 16.7%, SD: 25%, DCR: 41.6%, OS: 14 months	16.7%	31.25% (CNS-associated)

OR: objective response, AE: adverse effect, BORR: best overall response rate, CR: complete response, PR: partial response, SD: stable disease, DCR: disease control rate, OS: overall survival, CNS: central nervous system, EAP: expanded access program, SRS: stereotactic radiosurgery, BM: brain metastasis, MBM: melanoma brain metastasis, HER2: human epidermal growth factor receptor 2, PFS: progression-free survival, irRC: immune-related response criteria, RN: radiation necrosis, RNFS: radiation necrosis-free survival, MBM: melanoma brain metastasis

re-establish the exhausted T cells' immune activity for killing cancer cells. There is currently no clinical trial assessing the effectiveness of monotherapy with relatlimab in patients with BM. However, the combinatory therapy of relatlimab and nivolumab in advanced melanoma patients (patients with BM were excluded) who were older than 12 years and weigh more than 40 Kg was approved by the FDA in March 2022 (306). In this regard, a phase-II/III double-blind, randomized trial has shown that administering a fixed combinatory dose of nivolumab and relatlimab in 355 patients with metastatic or unresectable melanoma was more effective compared to giving only nivolumab. This study reported a mean PFS of 10.1 months in the nivolumab-relatlimab group compared with 4.6 months in the nivolumab-only group (p<0.001)(307). Even though grade 3 or 4 of trAEs was more frequently observed in the patients treated with nivolumab-relatlimab than those treated only with nivolumab (18.9% vs. 9.7%, respectively), no new safety signals were associated with this combinatory therapy (307). This promising result can pave the road for designing trials studying relatlimab efficacy and safety in patients with BM.

Immune Checkpoint Inhibitors Combined with Conventional Treatments

With the advent of ICIs and the identification of their CNS efficacy, their addition to the previous conventional therapies received much attention. Nevertheless, findings regarding combinatory therapies are still inconclusive. The combined use of conventional therapies with ICIs raised important efficacy and safety questions, concerning their possible synergistic activities in the brain. Various studies have assessed the combined use of ICIs with conventional therapies for patients with BM, including SRS, SRT, WBRT (53-55, 58, 59, 66, 93, 95, 100, 101, 132, 147, 182, 183, 191, 192, 288, 290, 292, 308-310), and CT (83, 99, 123, 173, 174, 286, 287, 311). Several combination therapy studies were reviewed in the relevant sections for each ICI. In the next section, we will briefly discuss some of the other studies.

ICI-SRS

According to Ahmed *et al.* retrospective study on 26 MBM patients, combined treatment with nivolumab and SRS could be well-tolerated and lead to prolonged OS and BM control compared with standard therapy (93). Regarding the RT sequencing, Le *et al.* suggested that compared to NSCLC/melanoma patients with BM who received no ICIs or non-concurrent ICIs, concurrent SRS-ICI was significantly associated with decreased DBF (182). However, they found no association between concurrent ICI-SRS treatment with local control (182). On the other hand, evaluating 75 patients with 566 MBM, Qian *et al.* indicated a significantly greater lesion volume reduction in patients receiving concurrent ICI-SRS in comparison with nonconcurrent therapy (58). In Nardin *et al.* study, the sequencing of SRS and pembrolizumab administration did not significantly affect intracranial control or OS (66). Contrarily, according to an international meta-analysis (2019), concurrent ICI-SRS was associated with improved safety and efficacy compared to

sequential therapy in patients with BM (191).

In another study on patients with NSCLC, Singh *et al.* found no significant difference between anti-PD-1-SRS and CT-SRS receivers with lesion volume < 500 mm3 in terms of survival, maximal percent lesional shrinkage, and time to maximal shrinkage (183). However, anti-PD-1 receivers with lesion volume > 500 mm3 had a significantly higher amount of lesional shrinkage after SRS and faster time to initial response and time to maximal shrinkage (183). According to the authors, in contrast to patients with melanoma, those with NSCLC-BM who received SRS did not significantly benefit from anti-PD-1 therapy in terms of survival or total lesional response (183). Nevertheless, better volumetric response in those with lesion volume higher than 500 mm3 might be beneficial in lesions causing mass effects (183). Concerning the safety of the SRS-ICI combination, Fang *et al.* reported a 27% RNB rate, with a six-month median duration to RNB development. However, co-administration of CT-SRS was associated with worse RNB-free survival at one year compared to co-treatment with ICI-SRS (310).

ICI-SRT/WBRT

A multicenter retrospective cohort study on 835 patients with unresectable metastatic melanoma, of whom 223 had BM, revealed no significant survival or OR difference among patients with BM on ICIs with and without preceding RT (53). Additionally, according to the authors, there was no survival difference between preceding WBRT and SRT (53). On the other hand, another study on 13 MBM patients illustrated that co-treatment with WBRT and ipilimumab could lead to an effective response with an iDCR of 56%. However, this study showed that combining ipilimumab and SRS mostly leads to SD rather than BM regression (309). Albeit not conclusive, these findings, together with other studies, suggested promising efficacy and safety profile of ICI-RT co-administration in MBM (288, 290, 292).

Investigating 269 patients (34% with BM) with NSCLC on PD-1 inhibitors, Samuel *et al.* suggested that RT addition during or within three months of starting anti-PD-1 was neither associated with increased toxicity nor with improved survival (192). On the other hand, according to Hang *et al.* study, compared to non-concurrent anti-PD-1-RT and anti-PD-1 monotherapy, concurrent treatment resulted in a higher immune-related (ir)-ORR, ir- DCR, and ir-PFS among patients with treated or newly diagnosed BM from lung cancer (100), although the median OS did not significantly differ (100). Qian *et al.* also indicated higher response rates, as well as lower PD rate, local recurrence, and time to response with concurrent ICI-RT (defined as RT on the same day or in between doses of a CT course) compared to non-concurrent ICI-RT (but within 90 days) among patients with MBM or NSCLC-BM (101). Liao *et al.* indicated a better OS (but not PFS) in patients with NSCLC-BM who received additional anti-PD-1 therapy compared to those receiving WBRT alone, with no significant AE difference (95). A recent study by Trommer *et al.* suggested that despite its delayed therapeutic response, concurrent RT and anti-PD-1 therapy (initiating RT and ICIs within one month) was more effective compared to sequential/non-concurrent treatment (at least one-month interval between therapies) among BM patients, particularly in those with low pre-treatment inflammatory status, more or larger metastasis, and primary cancers other than melanoma (54).

ICI-CT

To date, there are limited studies dealing with ICI-CT combination therapy in patients with BM, including NSCLC-BM (99, 123, 311) and SCLC-BM (174). According to Takayama *et al.* study on patients with NSCLC-BM, those who have previously received brain radiotherapy - including those with larger/more symptomatic BM- benefit more from this combination therapy (311). In a recent study on 19 patients with EGFR/ALK-positive NSCLC with BM, Zhu *et al.* suggested that in patients who progressed after receiving TKI therapy, ICI coupled with CT and bevacizumab may be a safe option with synergistic anti-tumor action for BM (99). Tsuchiya-Kawano *et al.* conducted the first prospective study evaluating the intracranial response to ICI therapy (ipilimumab) combined with platinum-based CT in patients with NSCLC-BM (NIke Trial (LOGiK2004)) (123). Study enrollment was initiated in May 2021 and will last for 2.5 years. According to the researchers, nivolumab-ipilimumab in combination with

platinum-based CT may provide a new treatment option for patients with NSCLC-BM if it shows intracranial activity in this trial (123). Overall, although the combination of ICIs and CT demonstrated promising results in patients with BM, the efficacy and long-term AEs of this combinatory therapy need to be more precisely elucidated in prospective studies.

Conducting a meta-analysis of 6 related studies, accounting for 2905 patients (10.8% with baseline BM) with extensive-stage SCLC, Zhou *et al*. recommend that ICIs-CT was associated with significantly improved OS in the total population (174). However, when combined with CT, PD-1 and PD-L1 inhibitors showed a statistically significant OS improvement, while CTLA-4 inhibitors did not. Additionally, in patients with baseline BM, ICIs-CT showed no survival benefits over CT alone (174). Further studies in the population with BM are required to assess the safety and efficacy of this regimen in SCLC-BM.

Conclusion

Although still inconstancy exists regarding the efficacy/safety of ICIs in patients with BM, the majority of evidence support their use as monotherapy, paired immunotherapy, or combined therapy with conventional treatments. Inconsistencies between the study findings might be due to differences in the study-related characteristics (cross-sectional vs. retrospective vs. prospective, follow-up durations), treatment-related characteristics (systemic pre-treatment, concurrent vs. sequential therapy for combination therapies, fractionation scheme, RT dose, the interval between diagnosis and receiving treatment, etc.), study population-related characteristics (comorbidities, patients' overall status, developing irAEs, staging at treatment initiation, baseline lactate dehydrogenase (LDH) level and other laboratory characteristics, etc.), primary tumor-related characteristics (primary site of the disease, staging, lesion volume, presence and number of extracranial metastases, etc.), and BM-related characteristics (active vs. non-active BMs, the burden of intracranial disease and the number of metastatic sites, tumor mutation status and molecular subtypes (*EGFR* mutated, *ALK* mutated, *BRAF* mutated, *RET* mutated, etc.), and tumor mutational burden (312, 313), etc.). Abid *et al.* also suggested variable CNS penetration of PD-1 antibodies in different individuals (219). With respect to the importance of follow-up duration for interpreting study findings, Hilbers *et al*. showed that while an intracranial response rate of 50% was achieved at three months in patients with MBM who received combined ICI-targeted therapy, it dropped to 13.9% at 12 months (56). All in all, before deciding which treatment approach to choose, specific tumor characteristics, including histology, biomarkers, size, location, and symptomatology, as well as the patient's characteristics should be considered (114).

Although patients with BM were excluded from most clinical trials assessing the effectiveness of ICIs in metastatic cancers, the limited existing evidence regarding the impacts of these drugs on BM is promising. This evidence is mostly acquired from different phases of clinical trials comparing the utility of the immunotherapy approach combined with conventional treatment. In this regard, the current literature shows that ICIs, including anti-PD-1/PD-L1, anti-CTLA-4, and anti-LAG3 can play beneficiary roles in terms of improving different remission indices like ORR, CR, PR, and DCR in patients with BM. Additionally, ICIs usually do not expose patients to more AEs than conventional therapies. Hence, ICIs can be considered attractive therapeutic approaches for improving the prognosis of BM patients and might have even the potential to be used as first-line treatment in BM originating from most solid tumors in the future. Nevertheless, before this point is reached, there is a substantial need for conducting more eligible randomize-controlled clinical trials studying high numbers of individuals with BM to elaborate on these drugs' efficacy more reliably.

Conflict of Interest

The authors report there are no competing interests to declare.

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