The Oncologist, 2022, **27**, 538–547
https://doi.org/10.1093/oncolo/oyac064
Advance access publication 22 May 2022
Review Article

Immune Checkpoint Inhibitors in the Treatment of Breast Cancer Brain Metastases

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Abstract

The management of breast cancer brain metastases (BCBM) has historically involved local therapies. However, as novel systemic treatments have become more effective in controlling visceral disease, BCBM have also been better controlled. Immune checkpoint inhibitors (ICIs) have demonstrated efficacy in brain metastases in patients with lung cancer and melanoma and represent a promising option for patients with triple-negative BCBM, a group with limited systemic therapy options. In this review we summarize current data about the role of ICIs in the treatment BCBM. We identified 15 clinical trials that evaluated ICIs ± chemotherapy in patients with breast cancer. The studies were mostly focused on triple-negative breast cancer (TNBC). Of these trials, 4 excluded patients with BCBM, while 11 allowed patients with stable, treated or asymptomatic BCBM. In total, 2692 patients were enrolled in the identified clinical trials, but only 91 trial patients (3.3%) had BCBM. Furthermore, only 2 of these clinical trials reported BCBM-specific outcomes and none of the clinical trials reported BCBM-specific adverse events. Up to 45% of patients with TNBC will develop BCBM; however, only 3.3% of the patients included in the clinical trials that led to the U.S. Food and Drug Administration approvals for ICIs in advanced breast cancer had brain metastases. This review reinforces that efficacy data are greatly needed for patients with BCBM—this is an area of unmet need in oncology. More inclusive clinical trials and real-world data that evaluate the safety and efficacy of ICIs in patients with BCBM are greatly needed.

Key words: breast neoplasms; brain neoplasms; immune checkpoint inhibitors; triple-negative breast neoplasms.

Implications for Practice

This review summarizes current data about the role of immune checkpoint inhibitors (ICIs) in the treatment breast cancer brain metastases (BCBM). Up to 45% of patients with triple-negative breast cancer will develop BCBM but only 3.3% of patients included in the clinical trials evaluated the role of ICIs in advanced breast cancer have BCBM. This report underscores the need for patients with BCBM to be adequately represented in clinical trials in order to better understand safety and efficacy of ICIs in BCBM as well as optimal combinations to enhance immune response in the central nervous system.

Introduction

Breast cancer is the second leading cause of metastases to the central nervous system (CNS) and up to a third of patients with breast cancer are diagnosed with CNS disease.[1-3] The role of systemic therapies in the treatment of breast cancer brain metastases (BCBM) has increased in significance, with particularly promising advances in the human epidermal growth factor receptor 2 (HER2)-positive breast cancer subtype.[4,5] Conversely, the role of systemic therapy has remained relatively unchanged in triple-negative breast cancer (TNBC).[6,7] Brain metastases often develop in the setting of progression of systemic disease[8]; there is an unmet need for improved systemic control to better manage BCBM and extra-CNS disease.

Patients with brain metastases have been historically excluded from clinical trials due to concerns about toxicities, limited efficacy of systemic agents across the blood-brain-barrier and overall poor prognosis; limiting the generatability of trial results across multiple solid tumor types.[9] A recent study showed that out of 446 phase III clinical trials studying advanced solid tumors, 169 (36.4%) excluded all patients with brain metastases, additionally, 140 (30.2%) had conditional brain metastases exclusions. Notably, industry-sponsored trials were more likely to exclude all patients with brain metastases.[9] Another study revealed that out of 223 clinical trials for advanced breast cancer, lung cancer, and melanoma, 52 (23%) excluded all patients with brain metastases, while 124 (56%) had conditional brain metastases exclusions; this study revealed that exclusion of patients with CNS involvement has decreased over the past 5 years.[10] Despite multiple efforts to improve enrollment of this population in clinical trials, many ongoing clinical trials still exclude known and/or active brain metastases.

Received: 16 September 2021; Accepted: 4 March 2022.

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of several cancers commonly associated with brain metastases. Real world data have demonstrated intracranial effects in melanoma and non–small cell lung cancer (NSCLC) with similar responses in visceral and brain metastases.[11,12] In breast cancer, the most promising findings and indications for immunotherapy are currently limited to a subset of patients with TNBC.[13] The aim of this review is to investigate the current evidence related to immunotherapy and CNS metastatic disease in ways it can be applied to BCBM, and more specifically to TNBC.

Methods

For this narrative review, we performed a search on PubMed using the terms "breast cancer", "immunotherapy", and "ICIs" and limited to clinical trials resulted between 2015 and 2020 was performed during February of 2021. Additionally, the 2020 San Antonio Breast Cancer Symposium and American Society of Clinical Oncology meetings were manually searched for relevant abstracts. Finally, clinicaltrials.gov was manually reviewed to select ongoing studies. Initial abstracts were reviewed by I.S. with review of full study manuscripts by I.S. and M.G.M.

Breast Cancer Brain Metastases

Breast cancer subtype is the main factor influencing incidence and prognosis of BCBM. Hormone-receptor-positive (HR+) accounts for 60%-70% of all breast cancers and has the lowest incidence of brain metastases (15%).[14,15] Brain metastases generally appear later in the course of metastatic HR+ breast cancer with an overall survival (OS) after diagnosis of BCBM of around 5-10 months.[16-18] The HER2+ subtype accounts for 20%-30% of all breast cancers but has the highest incidence of brain metastases[19] with 31%-50% of patients with metastatic HR–/HER2+ breast cancer developing BCBM.[14,15,20,21] The OS after the development of BCBM is 11-18 months with some of the novel HER2-targeted agents.[14,17,18,22,23] Around one-third of patients with HR+/HER2+ breast cancer will develop BCBM.[14,17] This triple-positive patient group has a more favorable prognosis with a survival of 16-19 months.[14,17] TNBC accounts for 15% of all breast cancers and the incidence of brain metastases are between 22% and 46%.[7,14,15,24] The OS of patients with TNBC brain metastases is 4-5 months and the onset of BCBM is the earliest after the diagnosis of metastatic disease.[14,17-19] Overall, the incidence of BCBM is increasing, to which multiple factors may be related including better imaging techniques, increased screening for participation in clinical trials, and increased life expectancy for patients due to general advances in systemic cancer therapies.[25,26]

The standard treatment of BCBM is multidisciplinary with local therapeutics including stereotactic radiosurgery (SRS), whole brain radiation (WBRT) and/or surgical resection.[27] Prospective clinical trials in solid tumors demonstrated the addition of WBRT to surgery or to SRS decreased intracranial recurrence but did not improve OS.[28-30] SRS is increasingly being used in the setting of a limited number of brain metastases,[31] while WBRT remains the preferred treatment for diffuse or miliary brain metastases. In patients with solitary lesions and controlled systemic disease, surgical resection combined with adjuvant SRS therapy increases survival and is preferred.[32-34]

Systemic therapy has been overall less effective in the treatment of BCBM than in the treatment of visceral metastases.[35-39] However, in HER2+ breast cancer the addition of anti-HER2 therapies, such as tyrosine kinase inhibitors or antibody-drug conjugates (ADC), has improved OS for patients with BCBM.[22,23,40,41] For example, in the HER2CLIMB trial, the addition of tucatinib to capecitabine and trastuzumab improved clinical outcomes with superior 1-year progression-free survival (PFS; 33% in the tucatinib arm and 12.3% in the placebo, HR 0.54, 95% CI 0.42-0.71, $P = .001$), longer median PFS (7.8 vs 5.6 months, respectively) and a significant improvement in OS at 2 years (44.9% vs 26.6%, respectively; HR 0.66, 95% CI 0.5-0.88, $P = .005$).[42] In HER2CLIMB, almost half of the patients had BCBM and approximately one-third of patients had active and progressing BCBMs. In the patient population with BCBMs, tucatinib's impact was even more pronounced with significant improvements in the CNS-PFS (median CNS-PFS 9.9 vs 4.2 months, respectively) as well as significant improvement in CNS-OS (estimated 1 year survival 70.1% vs 46.7%, respectively).[23,43]

Historically, cytotoxic chemotherapies have limited effect on CNS metastases. Recently, approved targeted agents for metastatic TNBC have demonstrated potential for the treatment of BCBM. In 2019, atezolizumab (anti-program cell death 1 ligand [PD-L1] antibody) in combination with nab-paclitaxel was granted accelerated approval for metastatic TNBC that is PD-L1 positive (immune cells, IC ≥ 1% PD-L1 per the SP142 assay); however, the accelerated approval was voluntarily withdrawn by the pharmaceutical company in August 2021 after the confirmatory trial failed to meet its endpoint.[13] Pembrolizumab (anti-program cell death protein 1 [PD1] antibody) is approved in combination with chemotherapy (paclitaxel, nab-paclitaxel, or carboplatin/gemcitabine) for advanced TNBC that is PD-L1 positive (≥ 10 combined positive score [CPS] per the Dako 22C3 assay). There are growing clinical data that ICIs are able to penetrate the CNS and exert anti-tumor effects on CNS metastases in NSCLC and melanoma.[11,12] Clinical studies have demonstrated similar responses to ICI for brain metastases and visceral metastases in these tumor types. While the biological drivers and tumor microenvironment (TME) of NSCLC and melanoma are different from breast cancer, these clinical observations support ICI activity in the CNS and the potential for ICI efficacy in the treatment of BCBM.

Sacituzumab govitecan (SG) is a novel antibody-drug conjugate (ADC) that targets Trop-2 and is approved for use in metastatic TNBC.[44] There is limited information about the efficacy of SG in BCBM. A recent window of opportunity study (NCT03995706) evaluated concentrations of SG and its payload (SN-38) in the brain tissue of 11 patients who underwent a craniotomy for BCBMs. In this small study, CNS penetrance of SG was confirmed as therapeutically relevant concentrations of SN-38 were found in the surgical specimens. In addition, at 12 weeks post-op 3 patients had partial responses, 5 had stable disease and 4 patients had evidence of progression of disease.[45] Moreover, in a subgroup analysis of the phase III ASCENT trial, the efficacy and safety of SG were assessed in 61 patients with stable brain metastases ($n = 32$ were treated with SG and $n = 29$ with treatment of physician choice [TPC]). Unfortunately, in this small subset of patients with BCBMs, there was no difference in median PFS (2.8 months in the SG arm vs 1.6 months in the TPC arm; hazard ratio 0.65, 95% CI 0.35-1.22) or in median OS (6.8 in SG arm

vs 7.5 months in TPC arm; hazard ratio 0.87, 95% CI 0.47-1.63).[46] There is an ongoing phase II trial (NCT04647916) assessing SG in patients with HER2-negative BCBM.[47]

Central Nervous System Immune Privilege

In 1950s, the CNS was described as an immunologically privileged site. This was attributed to integrity of the blood-brain barrier (BBB), which through the protection of the meninges and the cerebral spinal fluid (CSF) limits the circulation of immune cells and antibodies into the CNS.[48,49] There is now a better understanding that while the BBB prevents most macromolecules from entering into the CNS, some smaller molecules are able to cross and maintain homeostasis, provide nutrients, and immune surveillance to the CNS.[48,50] In addition, immune cells are able to transcend the BBB through a variety of mechanisms. These routes of immune cell trafficking are particularly important in understanding the pathophysiology of brain metastases and the tumor microenvironment (TME), as well as in understanding which novel agents may be effective in treating and/or preventing CNS metastases.[50] Furthermore, direct administration of agents into the CSF may help to directly delivery immunologically active agents to the BCBM without the impedance of the BBB. A recent study of 10 patients with high grade gliomas showed pembrolizumab given at standard dose achieved therapeutic concentrations in the CSF and resulted in effective PD-L1 blockade.[51] Additionally, an ongoing phase I/Ib study (NCT03025256) is assessing the role of concurrent intrathecal and intravenous nivolumab in 23 patients with metastatic melanoma and leptomeningeal disease. This study has shown adequate safety with no new safety signals and no CNS-specific toxicity. Furthermore, there were initial signs of efficacy in this hard-to-treat population. The immunologic assessments are ongoing.[52]

The TME plays a key role in the development of cancer and in the response to cancer-directed therapies.[53-55] Under normal circumstances, lymphocytes are not found in the brain parenchyma; however, small numbers of antigen presenting cells and T cells can be detected in the choroid plexus, CSF and subarachnoid and perivascular spaces present for immune surveillance.[56] Leukocytes can enter the CNS although the choroid plexus, across leptomeningeal vessels or via postcapillary venules in the perivascular space; these routes allow for activated T-cells to enter the CNS when inflammation is present.[56]

Increased BBB permeability has been described in patients with brain metastases which allows not only for the formation of metastatic disease but also the possibility of CNS penetration of agents and immune cells that would normally not cross the BBB.[57,58] These changes allow lymphocytes to enter the CNS, after which activation or inhibition of the immune cells is mediated by cytokines produced by the microglia (astrocytes).[56] In addition, the TME in the CNS has particular characteristics that represent additional challenges for the treatment of brain metastases; for example: the microglia produces cytokines that promote proliferation of "non-inflamed" tumor immune cells, such as type 2 tumor-associated macrophages and astrocytes produce pro-tumorigenic cytokines, such as IL-6 and TNF-α.[59]

Studies comparing the TME of paired primary tumors and BCBM have shown that primary tumors have significantly higher quantities of tumor-infiltrating lymphocytes (TILs) relative to brain metastases.[60] This may be of clinical relevance as tumors with lower number of TILs are associated with a worse prognosis, and decreased responses to ICIs.[61,62] Analysis of the TME of TNBC brain metastases compared to primary breast tumors consistently showed decreased immune infiltration with fewer activated NK cells and T helper cells and more plasma cells.[63,64] Similar findings have been reported in NSCLC and melanoma.[65,66] Further studies are required to elucidate characteristics on BCBM to determine potential prognostic and therapeutic targets.

For systemic therapies to be effective in BCBM, the agent must be able to penetrate the BBB and must be able to evade the immunosuppressive TME of the CNS. In preclinical studies assessing the efficacy of ICIs in brain metastases, 2 major mechanisms have been proposed. The first one is focused on the ability of the antibodies (cytotoxic T-lymphocyte associated antigen 4 [CTLA-4], PD-1, and PD-L1 inhibitors) to cross the BBB via transcytosis.[58] These antibodies can then elicit an effect in tumor cells and/or TILs.[67] The second mechanism is that immune cells stimulated by ICI peripherally can cross the BBB and elicit an antitumor effect in the CNS.[58]

Immunotherapy in Brain Metastases: The Success Story

Patients with CNS metastases were not included in many of the initial ICIs trials; however, recent studies as well as real world data have shown that these agents are effective in the treatment of melanoma and NSCLC brain metastases. Higher systemic and intracranial response rates have been noted with dual checkpoint blockage (anti-CTLA4 plus anti-PD(L)1), as seen in Table 1. Patients with leptomeningeal metastases have a particularly poor prognosis and until recently the role of ICIs in this setting was unknown. A small study evaluated the role of pembrolizumab monotherapy in patients with leptomeningeal metastasis from solid tumors (n = 13), including 5 patients with breast cancer.[68] The CNS-ORR was 38% with a median CNS-PFS of 2.9 months and median OS of 4.9 months. CNS and systemic responses were similar and were more common among tumor subtypes that typically respond to ICIs such as melanoma and lung cancer.

Melanoma

Metastatic melanoma has frequently served as a model for immunotherapy clinical trials. Melanoma is associated with high rates of somatic mutations, which may be a predictor of response to ICIs.[80] Melanoma metastasizes to the CNS in up to 28% of cases and once CNS disease develops the prognosis is very poor.[81] Several studies have shown improved outcomes and a tolerable side effect profile with ICIs in melanoma brain metastases, with an intracranial response rate ranging from 6 to 57% and a 1-year OS of 31% (Table 1).

Non–Small Cell Lung Cancer

Lung cancer is the leading cause of cancer-related deaths in the US and up to 26% of patients with NSCLC will develop brain metastases.[75,81,82] ICIs are standard of care first-line treatment for metastatic NSCLC.[83,84] Patients with brain metastases were not included in the NSCLC pivotal clinical trials. However, several subsequent studies (Table 1) assessing the use of ICI in patients with NSCLC brain metastases have shown efficacy, especially in tumors that are PD-L1 positive, with an intracranial response rate of 16.7 to 33%.[74-79,85]

Table 1. Efficacy of immune checkpoint inhibitors in melanoma and non–small cell lung cancer in patients with brain metastases.

Identifier/trial	Agents	Phase	Patient number/cohorts	Outcomes
Melanoma				
NCT01449279/ CA184-045[69]	Ipilimumab	Pilot study	*N* = 185	1-year OS rate in patients with stable BM=31%
NCT00623766[70]	Ipilimumab	2	*N* = 72 Cohort A = 51 patients (asymptomatic, not receiving steroids) Cohort B = 21patients (symptomatic, receiving steroids)	Cohort A IRR = 24% CohortBIRR = 10%
NCT01654692/ NIBIT-M1[71]	Ipilimumab, fotemustine	2	*N* = 20	IRR = 50%
NCT0237424[72]	Ipilimumab, nivolumab	2	*N* = 79 Cohort A = 36 patients (asymptomatic and untreated ipilimumab/nivolumab) Cohort B = 27 patients (asymptomatic and untreated, nivolumab) Cohort C = 16 patients (symptomatic and treated, nivolumab)	Cohort A IRR= 46% Cohort B IRR= 20% Cohort C IRR= 6%
NCT02320058/CheckMate 204[11]	Nivolumab, ipilimumab	2	*N* = 94	IRR = 57%
NCT02085070[73]	Pembrolizumab	2	*N* = 23	IRR=26%
Non–small cell lung cancer				
NCT01454102/Checkmate 012 (Arm M)[74]	Nivolumab, ipilimumab	1	*N* = 12	IRR = 16.7%
NCT01721759 CheckMate 063CheckMate 017 CheckMate 057[75]	Nivolumab	Pooled analysis 2 3 3	*N* = 46	IRR =33% (stable disease)
NCT02008227/OAK study subgroup[76]	Atezolizumab, docetaxel	I3	*N* = 61	Atezolizumab with greater reduction in new BM, vs docetaxel
NCT02085070[77]	Pembrolizumab	2	*N* = 39 Cohort A = 34 (PD-L1 positive) Cohort B = 5 (PD-L1 negative)	Cohort A IRR = 29% Cohort B IRR = 0%
Nivolumab expanded access program[78]	Nivolumab	Pilot study	*N* = 409	ORR = 17% DCR =39% in CNS metastasis patients (overall response, no CNS disease)
Multiple tumor types				
NCT02085070[79]	Pembrolizumab	2	*N* = 36 (18 with melanoma18 with NSCLC)	IRR melanoma = 22% IRR NSCLC = 33%

Abbreviations: BM, brain metastases; CNS, central nervous system; DCR, disease control rate (complete response = partial response + stable disease); IRR, intracranial response rate; NSCLC, non–small cell lung cancer; ORR, overall response rate; OS, overall survival.

Immunotherapy in Breast Cancer

Though breast cancer was previously considered immunogenically quiescent, recent studies have shown benefit of immunotherapy in a selected group of patients with breast cancer. Several clinical trials have been published assessing the efficacy of ICIs in breast cancer and clinical guidelines for the use of immunotherapy in breast cancer were recently published.[86] Few of these initial trials included patients with BCBM and only 91 of the 2692 (3.3%) patients included in these trials had BCBM (Table 2).

In the phase Ib KEYNOTE-012 study, 32 patients with PD-L1-positive advanced TNBC were treated with pembrolizumab monotherapy, the objective response rate (ORR) was 18.5% and the median time to response 17.9 weeks, but patients with BCBM were excluded from this study.[87] In the phase Ia PCD4989g trial, 116 patients with metastatic TNBC were treated with atezolizumab monotherapy; with a PFS was 1.4 months, median OS of 17.6 months, and ORR of 19%.[88] Patients with ≥1% of PD-L1-positive TIL had longer ORR and OS compared with PD-L1-negative patients. Selected patients with asymptomatic BCBM were allowed in the study; however, the number of patients with CNS involvement was not reported. In the phase Ib, JAVELIN trial, 168 patients with advanced or metastatic breast cancer (34% TNBC, 42% HR+, 15% HER2+) were treated with avelumab, and the ORR was 5% in the TNBC group.[89] Again, patients with BCBM were excluded from this study. In the KEYNOTE-028 trial, 25 patients with HR+/HER2– advanced breast cancer were treated with pembrolizumab; at a median follow up of 9.7 months the ORR was 12% and the median duration

Table 2. Published trials of immune checkpoint inhibitors in metastatic breast cancer.

TrialPhase/agent/name	Included patients with BM	Evaluable patients	Patients with BCBM, *n* (%)
Phase Ib. Pembrolizumab. Keynote-012[87]	Yes. Treated and stable BM	32	3 (9.4%)
Phase Ia. Atezolizumab[88]	Yes. Asymptomatic BM	115	N/A
Phase Ib. Avelumab. JAVELIN[89]	No	168	0
Phase Ib. Pembrolizumab. Keynote-028[90]	Yes. Treated and stable BM	25	N/A
Phase II. Pembrolizumab. Keynote-086 (Cohort A)[91]	No	170	0
Phase II. Pembrolizumab. Keynote-086 (Cohort B)[92]	No	84	0
Phase III. Pembrolizumab + chemotherapy. Keynote-355[93]	Yes. Treated and stable BM	847	26 (3%)
Phase I. Atezolizumab + nab-paclitaxel[94]	Yes. Treated and stable BM	33	N/A
Phase III. Atezolizumab + nab-paclitaxel. Impassion130[95]	Yes. Treated and stable BM	902	61 (6.7%)
Phase I. Pembrolizumab + eribulin mesylate. ENHANCE1[96]	Yes. Treated and stable BM	82	1 (1.2%)
Phase Ib. pembrolizumab + abemaciclib. JPCE[97]	Yes. Asymptomatic BM	28	N/A
Phase II (Basket trial). Durvalumab + olaparib, MEDIOLA[98]	Yes. Asymptomatic BM	32	N/A
Phase II. Niraparib + pembrolizumab. TOPACIO[99]	Yes. Treated BM	47	N/A
Phase I/II. Pembrolizumab + trastuzumab. PANACEA[100]	Yes. Stable BM	58	N/A
Phase II. TDM1 + pembrolizumab. KATE2[101]	No	69	0
Total		2692	91 (3.3%)

Abbreviations: BM, brain metastases; N/A, not available.

of response was 12 months.[90] Only patients with previously treated and stable BCBM were allowed in this study, although the number of patients with BCBM and their outcomes have not been reported.

The KEYNOTE-086, was a phase II study assessing pembrolizumab for patients with TNBC in 2 separate cohorts: cohort A included 170 heavily pretreated patients whose ORR was 5.3% and 5.7% in the PD-L1-positive subgroup; cohort B included 84 newly diagnosed patients, whose ORR was 21%, respectively.[80,91,92] Patients with BCBM were excluded from this study.

In 2019, atezolizumab received accelerated approval from the Food and Drug Administration (FDA) for use in combination with nab-paclitaxel as first-line therapy for metastatic PD-L1-positive TNBC based on the IMpassion130 study.[13] However, the pharmaceutical company voluntarily withdrew this approval in August 2021 after the confirmatory trial (IMpassion131) did not meet its primary endpoint, as described below. In IMpassion130, the combination of atezolizumab and nab-paclitaxel led to a clinically significant improvement in OS in the PD-L1-positive subgroup (25 vs 15.5 months, hazard ratio for death 0.84) and PFS (7.5 vs 5.0 months) when compared with nab-paclitaxel alone.[13,102] This study included 61 patients (6.8%) with asymptomatic or previously treated brain metastases. In the ITT population, there was no significant differences in clinical outcomes among patients with BCBMs (median PFS 4.9 months in atezolizumab + nab-paclitaxel vs 4.4 months in nab-paclitaxel); however, OS trended toward worse OS in patients who received atezolizumab plus nab-paclitaxel (14.3 months vs 16.2 months, respectively). While there was only a small number of patients with PD-L1-positive tumors and BCBM (n = 26), patients with PD-L1-positive tumors and BCBM consistently did worse when they received atezolizumab plus nab-paclitaxel (median PFS = 2.2 months, median OS 14.7 months; n = 15) then those who received nab-paclitaxel alone (median PFS 5.6 months, median OS 28.6; n = 11). However, there was inadequate power to fully investigate this observation (PFS HR 1.40, 95% CI 0.57 to 3.44; OS HR 1.58, 95% CI 0.61-4.10).[13,103] The IMpassion131 was another phase III trial comparing atezolizumab plus paclitaxel vs paclitaxel alone, in this study the combination of chemoimmunotherapy did not lead to an improvement of PFS or OS irrespective of PD-L1 status. Patients with treated asymptomatic BCBM were included in this study but no CNS-specific outcomes have been reported.[104,105]

Pembrolizumab was approved in combination with chemotherapy as a first-line treatment for patients with PD-L1 positive, advanced TNBC based on the KEYNOTE-355 trial. In this study, 847 patients were randomized to receive pembrolizumab in combination with chemotherapy (paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin) or chemotherapy alone. At a median follow-up of 26 months, in patients with CPS of 10 or higher the median PFS was 9.7 months in the pembrolizumab arm versus 5.6 in the chemotherapy arm (HR 0.65, 95% CI 0.49-0.86, P = .0012). The difference in PFS was not statistically significant in the patients with CPS above 1 and in the intention-to-treat population.[93] The improvement in PFS was irrespective of the chemotherapy partner.[106] KEYNOTE-355 included patients with stable and treated BCBM (3% of the intention to treat population); however, the CNS-specific outcomes of those patients have not been reported to date.

There is growing interest in finding markers predictive of response to immunotherapy. Higher levels of TILs have been used as a predictive marker of response to immunotherapy.[95] Lower quantities of TILs have been identified in metastatic tumors relative to primary breast cancer while metastatic tumors have more M2-macrophages when compared with primary tumors.[60,107,108] Small studies have shown that the differences in immune abundance between primary and metastatic breast tumors are more apparent in BCBM, suggesting immune escape; however, the clinical implications of these differences are yet to be elucidated.[108]

PD-L1 expression has been used as a predictive biomarker of response to ICIs. The companion PD-L1 assay for

Table 3. Ongoing clinical trials for immunotherapy in breast cancer brain metastases.

Identifier	Phase	Description	End-points (primary [1], secondary [2])	Status
Immune checkpoint blockers and radiation therapy				
NCT03807765	1	Stereotactic radiosurgery after nivolumab	[1] DLT [2] CNS disease control, CNS PFS, extracranial PFS, OS	Active, not recruiting
NCT03449238	1/2	Stereotactic radiosurgery and pembrolizumab	[1] Tumor response for non-irradiated BM, correlation of abscopal response and radiation dose in CNS-OS [2] Correlation of extracranial abscopal response and radiation dose	Recruiting
NCT04711824	1/2	Stereotactic radiosurgery with olaparib followed by durvalumab with other systemic therapies	[1] Adverse events, CNS-DCR [2] CNS-PFS, CNS-OS, CNS-ORR, CNS-DFS, extracranial DFS, extracranial response rate	Not yet recruiting
NCT03483012	2	Stereotactic radiosurgery and atezolizumab	[1] PFS [2] Extracranial ORR, PFS, CBR, OS, PRO, radiation necrosis, neurologic evaluation, DLT, abscopal response rate	Active, not recruiting
NCT02563925	N/A	Whole brain irradiation or sterotactic radiosurgery and tremelimumab and durvalumab ±- trastuzumab	[1] Extracranial DCR [2] Immune-related PFS, safety profile	Completed
Immune check point blockers and/or chemotherapy and/or targeted agents				
NCT04512261 (TOPAZ)	1/2	Tucatinib, pembrolizumab, and trastuzumab	[1] DCR, RP2D [2] CNS-ORR,extracranial-ORR, PFS, OS, toxicity profile	Recruiting
NCT04508803 (CHANGEABLE)	2	HX008 and niraparib in patients with germline mutations who progressed after radiation therapy	[1] ORR [2] OS, PFS, CBR, DOR	Not yet recruiting
NCT04303988	2	Cohort A = HER2+/HR−: pyrotinib plus temozolomide Cohort B = HER2−/HR−: bevacizumab, SHR1316 (PD-L1 inhibitor) combined with cisplatin/carboplatin	[1] CNS ORR [2] CNS CBR, PFS, OS, first progression site, safety	Not yet recruiting
NCT03417544	2	Atezolizumab, trastuzumab, and pertuzumab	[1] CNS-ORR [2] PFS, extracranial-CNS ORR, DOR, CBR, OS, DLT, PRO, neurological evaluation	Active, not recruiting
NCT04789668	1/2	Bintrafusp Alfa and Pimasertib for the treatment of patients with brain metastases	[1] CBR, intracranial and extracranial DLT, RP2D, time to CNS progression, OS [2] CNS progression, time to extracranial progression, extracranial ORR, DOR, steroid use	Recruiting
Cellular therapies/vaccines/bispecific antibodies				
NCT03661424	1	Bi-specific antibody (HER2Bi) armed activated T-cells (HER2 BATs)	[1]Toxicity [2] Immune changes, correlation between clinical and immune response, ORR, PFS, OS, PRO	Recruiting
NCT03696030	1	HER2-CAR-T Cells in recurrent brain or leptomeningeal metastases	[1] DLT [2] HER2 CAR-T cells, cytokine levels, circulating tumor cells and immune cells in CSF, YME and PB, CNS-ORR, extracranial ORR, CNS-PFS, OS	Recruiting
NCT04348747	2	Dendritic cell vaccines against Her2/Her3 and pembrolizumab for BCBM	[1] Best CNS response [2] Systemic ORR, CNS PFS, systemic PFS, CNS OS, systemic OS, rate of failure of irradiated lesions	Not yet recruiting

Status of studies verified on clinicaltrials.gov on September 15, 2021.
Abbreviations: BM, brain metastases; CAR-T cell, chimeric antigen receptor T cell; CBR, clinical benefit rate; CFS, cerebrospinal fluid, CNS, central nervous system; DCR, disease control rate; DLT, dose limiting toxicities; DFS, disease-free survival; DOR, duration of response; HER2, human epidermal growth factor receptor 2; ORR, overall response rate; OS, overall survival, PB, peripheral blood; PFS, progression-free survival; PRO, patient-reported outcomes; RP2D, recommended phase II dose; TME, tumor microenvironment.

pembrolizumab is the Dako 22C3 assay; however, PD-L1 is an imperfect biomarker of effect for breast cancer. Differences in expression have also been reported with primary tumors often having higher expression of this marker.[107] These differences have also been reported in BCBM.[60] There are however limited data about PDL1 expression in BCBM. A recent retrospective study revealed that only 9 out of 59 (15%) BCBM were positive for PDL1 (SP142 assay). While the sample size was limited, PD-L1 expression among BCBM subtypes were similar to visceral metastases with TNBC and HER2+/HR- tumors more likely to express PDL1 than HR+/HER2- or HR+/HER2+.[109]

Pembrolizumab was recently approved for high risk early stage TNBC based on the phase III trial KEYNOTE-522.[110] In this study, patients were randomized to receive standard neoadjuvant anthracycline and platinum containing chemotherapy or the same chemotherapy regimen with pembrolizumab in the neoadjuvant and adjuvant setting. The addition of pembrolizumab led to an improvement in pathologic complete response (51.2 vs 64.8%, P = .00055) and event-free survival (76.8 vs 84.5, hazard ratio 0.63, P = .00031). There was also a numerical improvement in OS, although longer follow-up is needed. Improvement in clinical outcomes was irrespective of PD-L1 status. With longer follow-up it may become clear if early incorporation of ICIs in high-risk, early stage TNBC can achieve better systemic control and therefore, potentially prevent or delay the development of BCBM in these high-risk patients.

Clinical Trials in Breast Cancer Brain Metastases: Eliciting Immune Response

Several trials have been published assessing the safety and effectiveness of ICI in metastatic breast cancer (Table 2). Out of the 15 studies, 11 included patients with brain metastases that were stable and/or asymptomatic; however, only 2 of these published studies reported CNS-specific outcomes in patients with CNS disease. The KEYNOTE-012 study included 3 (9.4%) patients with BCBM and the IMpassion130 included 61 patients (6.7%).[13,87] Neither study reported specific outcomes or adverse events for the BCBM population. There are multiple ongoing trials to assess ICIs in combination with other agents or treatment modalities with the goal of increasing the immune response in the metastatic sites (Table 3); however, only a very small number of published trials include patients with CNS involvement (Table 2). Again, this highlights the need to expand eligibility criteria to include more patients with BCBMs as recommended by both the American Society of Clinical Oncology and the US FDA.

Conclusions and Future Directions

BCBM occur in almost half of the patients with triple-negative and HER2+ metastatic breast cancer. These patients are underrepresented in clinical trials, as only 3.3% of the patients in the published ICI studies in breast cancer had BCBM. Clinical trials are encouraged to include patients with CNS metastases, as these patients are in great need of effective therapeutic options and there is growing evidence of clinical activity and therapeutic safety in brain metastases. Investigators are also encouraged to publish the CNS-specific outcomes of patients with BCBM, even when the numbers are small, as they can inform further research and clinical decisions.

ICIs represent a promising option for patients with BCBM, particularly for those with TNBC that otherwise have very limited non-chemotherapy systemic therapy options. ICIs are safe and effective in patients with melanoma and NSCLC brain metastases. Further studies are needed to understand the tumor biology and TME of BCBM in order to determine the role of ICI and optimal treatment combinations for different breast cancer subtypes.

Acknowledgments

We would like to express our gratitude to Dr Alexandra Zimmer (National Cancer Institute; Bethesda, MD) who provided invaluable input for this paper. The authors would also like to thank Kamila Jaroniec for her editing and thoughtful review.

Conflict of Interest

Margaret Gatti-Mays: EMD Serono, Regeneron (RF—inst) SeaGen (tucatinib) (SAB). The other author indicated no financial relationships.

(C/A) consulting/advisory relationship; (RF) research funding; (E) employment; (ET) expert testimony; (H) honoraria received; (OI) ownership interests; (IP) intellectual property rights/inventor/patent holder, and (SAB) scientific advisory board.

Author Contributions

Conception/design: I.S. and M.E.G.-M. Provision of study material/patients: I.S. and M.E.G.-M. Collection and/or assembly of data: I.S. and M.E.G.-M. Data analysis and interpretation: I.S. and M.E.G.-M. Manuscript writing: I.S. and M.E.G.-M. Final approval of manuscript: I.S. and M.E.G.-M.

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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