Update on the Management of Brain Metastasis

Karanvir Singh1 · Shreya Saxena1 · Atulya A. Khosla1 · Michael W. McDermott2,4 · Rupesh R. Kotecha3,4 · Manmeet S. Ahluwalia1,4

Accepted: 3 October 2022 / Published online: 23 November 2022 © The Author(s) 2022

Abstract
Brain metastases occur in almost one-third of adult patients with solid tumor malignancies and lead to considerable patient morbidity and mortality. The rising incidence of brain metastases has been ascribed to the development of better imaging and screening techniques and the formulation of better systemic therapies. Until recently, the multimodal management of brain metastases focused primarily on the utilization of neurosurgical techniques, with varying combinations of whole-brain radiation therapy and stereotactic radio-surgical procedures. Over the past 2 decades, in particular, the increment in knowledge pertaining to molecular genetics and the pathogenesis of brain metastases has led to significant developments in targeted therapies and immunotherapies. This review article highlights the recent updates in the management of brain metastases with an emphasis on novel systemic therapies.

Keywords Brain metastases · Systematic review · Systemic therapy · Immunotherapy · Targeted therapy · Actionable mutations

Introduction
Brain metastases (BM) affect up to one-third of adults with solid tumor malignancies and are associated with significant cancer patient morbidity, anxiety, and mortality. Approximately 70,000–400,000 patients will develop BM each year in the USA [1–3]. Consequentially, BM represent an important public health care burden that is also ten times more common than primary malignant brain tumors. The rising incidence of BM has partly been attributed to the availability of better imaging modalities (MRI), increased systematic screening for at-risk patients, and improved systemic therapies with extra-cranial control but limited intracranial protection as the central nervous system (CNS) is a sanctuary site [4, 5]. Despite the staggering incidence of brain metastases, cancer-specific incidence ratios are not well described in the literature.

As most systemic therapies had limited blood barrier penetration, the traditional practice was comprised of regional, brain-directed therapies including radiation therapy and surgical resection [6, 7]. However, recently, the paradigm has shifted to immunotherapy as a first-line choice for well-selected, asymptomatic patients with specific histologies and the use of targeted agents in oncogenic-driven tumors with actionable mutations [8–10]. Additionally, these novel therapies with CNS activity have also significantly contributed to the improved prognosis of BM patients [4, 11]. The purpose of this article is to highlight the treatment of BM with a specific focus on novel systemic therapy agents.

Prognosis
Earlier studies estimating the prognosis of BM patients led to the development and application of various prognostic indices, such as the recursive partitioning analysis (RPA, a tiered prognostic system based on age, extra-cranial disease status, and the Karnofsky performance status) and the disease-specific graded prognostic assessment (DS-GPA) which is a more modern scoring system based on four objective
risk factors [12–16]. The DS-GPA is based on accumulated data of brain metastases patients from several institutions and has recognized important prognostic factors within each major primary tumor site, including Karnofsky performance status (lung, melanoma, renal cell, breast, and gastrointestinal primaries), age (lung, breast), presence of extra-cranial metastases (lung), and the number of brain metastases (lung, melanoma, and renal cell) [12, 17–20]. More recent studies demonstrated differences in outcomes based on breast cancer, melanoma [20], and NSCLC subsets [21–23]. The most recent versions of the prognostic scoring systems have also now integrated tumor biology and molecular profiles, such as EGFR and ALK alterations in NSCLC adenocarcinoma (Lung-molGPA) [21], estrogen/progesterone and HER2-receptor status for breast cancer (Breast-GPA) [19], and BRAF status in melanoma (Melanoma-molGPA) [20] to more accurately estimate a modern BM patient’s outcome. It is important to make an accurate prognostication, as this guides efficient treatment decision making and identifies the population requiring an aggressive brain-directed therapy, as opposed to a palliative approach.

**Treatment**

**Neuro-Oncology**

Brain metastasis patients face neurologic symptoms from both underlying intracranial disease and treatment-related sequelae [22–25] such as symptoms related to vasogenic edema, seizures, venous thromboembolism, radiation necrosis, and neurocognitive decline [26, 27]. Often these symptoms require medication management, including corticosteroids, antiepileptic drugs, analgesics, and other supportive medications [28–31]. Routine prophylactic use of antiepileptic drugs is, however, not recommended [32]. Dexamethasone is the main glucocorticoid employed to reduce perilesional edema and inflammation, in the setting of symptomatic brain metastases [33]. Finally, bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF) has been explored as a steroid-sparing agent. It has been demonstrated to reduce radiation necrosis-associated capillary leakage and brain edema [34].

**Neurosurgery**

Neurosurgical intervention plays a significant role in the management of brain metastases patients [35]. The craniotomy is typically performed in (1) newly-diagnosed patients without a known underlying primary, (2) BM-associated symptoms resistant to corticosteroids, (3) large metastases, and (4) solitary BM (i.e., one BM without extra-cranial disease) [36, 37]. Multidisciplinary management is the best alternative to the management of finding any brain metastases and may require a carefully evaluated methodology [38, 39].

In the case of a single BM, surgical resection is preferred over WBRT alone [1, 2]. The efficacy of surgery as compared to WBRT for the management of solitary BMs has been supported by two randomized clinical trials. Patchell et al. compared resection combined with WBRT with WBRT alone. This showed an increased survival (40 weeks vs 15 weeks), fewer local recurrences (20% vs 52%), and a better quality of life in patients undergoing resection with WBRT [6]. Vecht et al. found a longer overall survival in patients with a single BM, undergoing resection and WBRT (10 months vs 6 months) in addition to a longer period of functional independence [40]. Muacevic et al. conducted a phase III trial comparing WBRT and microsurgery in combination with gamma knife surgery alone and noted similar survival and local tumor control rates but improved quality of life metrics after radiosurgery alone (p < 0.05) [41]. Moreover, for the treatment of solitary brain metastases, Roos et al. compared surgery and radiosurgery, both with adjuvant WBRT, and a reported better median OS with radiosurgery and WBRT (6.2 vs 2.8 months, p = 0.20) [42].

**Radiation Therapy**

The most common form of local therapy used in patients with BM is radiation therapy. There are multiple different options, including whole-brain radiation therapy (WBRT) with or without hippocampal avoidance (HA-WBRT), stereotactic radiosurgery (SRS), and brachytherapy.

**WBRT—Whole Brain Radiation Therapy**

WBRT is currently used for patients with leptomeningeal disease or those with multiple brain metastases (> 4 lesions) [43]. Conventional WBRT is associated with several short- and long-term side effects, such as fatigue, anorexia, xerostomia, nausea, and alopecia, as well as cognitive dysfunction, balance problems, and hearing loss [44]. Pharmacologic strategies have been developed to help mitigate these side effects. RTOG 0614, a randomized trial compared memantine (used for 24 weeks including a 4 week up-titration period), an N-methyl-D-aspartate (NMDA) receptor antagonist, against placebo among patients receiving WBRT [45]. This trial showed preservation in the delayed recall at 24 weeks (primary endpoint) and a significantly longer time to cognitive decline noted among patients receiving memantine [45]. Hence, memantine is a valuable adjunctive therapy for patients receiving WBRT. Radiotherapeutic advances, such as the use of hippocampal avoidance (HA-WBRT), have also demonstrated reductions in neurocognitive dysfunction [46–48]. Most recently, NRG CC001 compared
these two strategies and demonstrated lower rates of cognitive failure with HA-WBRT and memantine compared to conventional WBRT and memantine, proving HA-WBRT and memantine as the standard in most patients lacking brain metastases in or around 5 mm of the hippocampi or leptomeningeal disease [48, 49].

SRT—Stereotactic Radiosurgery

SRS can be delivered as either a single fraction of extremely conformal, high-dose treatment (generally 18–24 Gy) or as moderately-dosed fractions termed fractionated SRS (FSRS) ranging from 24 to 27 Gy in 3 fractions, or 30 Gy in 5 fractions [50]. This is commonly used for patients with intact brain metastases and is supported for those with limited intracranial disease (1–4 lesions) [51] as well as select patients with multiple lesions (4–15 BM) [52, 53]. In addition, there is increasing interest in combining SRS with select systemic therapy agents to improve response rates and duration of disease control [54–56]. Given the significant paradigm shift to focal therapy alone for intact lesions, SRS is also increasingly being utilized around operable brain metastases as well [57]. Although no high-quality prospective data exists to compare primary SRS to surgery, retrospective data demonstrate higher rates of tumor control with surgery and SRS compared to SRS alone for patients with large brain metastasis (≥4 cc or 2 cm in diameter) [58, 59]. A randomized trial of post-operative SRS vs WBRT was associated with similar survival but the preservation of neurocognitive decline in those treated with focal therapy, supporting its use in patients with limited intracranial disease [60]. Although focal therapy following surgery is seemingly attractive in comparison to WBRT, there are also significant drawbacks to this approach, such as difficulties in target volume delineation, high rates of local failure, and the risk of leptomeningeal spread. Two strategies are underway to further improve patient outcomes with focal therapy. First, to increase to the dose to the resection cavity and local tumor control rates, fractionated SRS is often utilized in clinical practice. Prospective randomized trials are in current study comparing post-operative SRS to FSRS (NCT04114981). Second, one can perform SRS prior to surgery, which is associated with an improved ability to delineate the target as well as a smaller treatment volume (intact brain metastasis vs post-operative cavity) and has been associated with higher rates of disease control even for very large brain metastases [61]. Retrospective comparisons between pre-operative SRS and post-operative SRS for operable brain metastases have demonstrated similar rates of local recurrence ($p=0.24$) and overall survival ($p=0.1$) and reduced rates of leptomeningeal disease failure (3.2 vs 16.6%, $p=0.10$) and radiation necrosis (4.9% vs 16.4%) with pre-operative SRS supporting this approach [59]. Current and future trials (NCT03750227 and NCT03741673) will compare pre-operative SRS vs post-operative SRS to provide prospective randomized evidence to guide clinical practice.

Brachytherapy

Brachytherapy allows for the placement of radioactive isotopes intraoperatively within a resection cavity, so highly conformal high-dose radiation is delivered to the targeted area with a limited dose to the remainder of the brain parenchyma [62]. Newer brachytherapy carriers have allowed for more uniform dose distributions and protection against the brain parenchyma and have resulted in a resurgence of the utilization of this technique, and ongoing registries are prospectively collecting clinical outcomes (NCT04427384). The brachytherapy sources used in modern practice consist of Cesium-131 (C-131) seeds, and prospective phase 1/2 trials have demonstrated impressive local disease control rates in patients with large (>2 cm) newly-diagnosed brain metastases [63]. Ongoing trials are also comparing post-operative brachytherapy to post-operative SRS/FSRS in patients with large operable brain metastases (NCT04365374). Brachytherapy can also be used as an efficient salvage therapy for patients with locally recurrent tumors after prior radiation therapy [64]. Therefore, this provides an additional valuable resource for managing intracranial disease in operable patients with resectable BM.

Systemic Therapy

Traditionally, systemic therapy agents had limited efficacy in CNS metastasis, and therefore, local brain-directed therapy was the treatment of choice for almost all patients [65]. However, this has changed substantially in recent years due to the advent of targeted and immunotherapy as detailed in the next sections.

Non-Small Cell Lung Cancer (NSCLC)

Systemic therapy in patients with NSCLC with brain metastasis is dependent on the presence of targetable mutations. In the USA, about 33–45% of lung adenocarcinomas harbor such genetic changes. The number is significantly greater in nonsmokers [9, 65, 66]. Anti-PD1 agents like pembrolizumab [67] and nivolumab especially in PD-L1 positive patients or who harbor other biomarkers for immunogenicity, or anti-folate chemotherapeutic agent, pemetrexed [68, 69] in patients with adenocarcinomas may aid in controlling intracranial disease in some patients, although responses can be limited.

In NSCLC, EGFR mutations are quite common and occur in 15–30% of cases. Ninety percent of patients with EGFR alterations in NSCLC harbor exon 19 deletions or exon 21
L858R substitutions and are sensitive to EGFR-targeting TKIs. 1st, 2nd, and 3rd generation EGFR TKIs may prove helpful in uncommon EGFR mutations barring exon 20 insertions [70, 71]. Prospective trials for erlotinib, gefitinib, and afatinib in patients with EGFR alterations and brain metastases have documented 70–88% intracranial response rates [72–74]. Osimertinib, a 3rd generation inhibitor, is the present choice of treatment in brain metastases patients with EGFR-mutant lung cancer [75]. Initially, osimertinib had shown great promise with high intracranial response in patients with extracranial T790 resistance mutation who have received prior EGFR-TKI therapy [76, 77]. More recently, osimertinib has become the drug of choice for newly diagnosed EGFR lung cancer patients. The FLAURA study compared osimertinib with TKIs (gefitinib and erlotinib) that demonstrated increased progression-free interval and overall survival and an improved intracranial response with osimertinib (91% vs 68%, respectively) [73–75, 78, 79]. A dual inhibitor of EGFR and HER2, Neratinib may be helpful in patients with select EGFR mutations [80]. Studies to analyze tumor DNA in CSF may help explore CNS progression after the previous intracranial response [81]. ALK targeting therapies such as alectinib, ceritinib, lorlatinib, and brigatinib have demonstrated high intracranial disease control rates [65, 82–91]. Lorlatinib has proved helpful after the progression of symptoms with other ALK targeting therapies [88], but the side effects such as speech changes, mood changes, weight gain, peripheral neuropathy, and gastrointestinal effects have made its use as a first-line treatment challenging in ALK-rearrangement patients [92–94]. The LIBRETTO-001 trial evaluated the efficacy of selpercatinib, a specific RET inhibitor for BMs in patients with RET fusion-positive NSCLC. The iORR reported was 82%, and the median intracranial PFS was determined to be 13.7 months at a follow-up duration of 11.0 months [95]. Adding radiation to standard TKI therapy for NSCLC patients may prove beneficial, and there are trials exploring the combination studies [94]. Further randomized studies are needed to evaluate the role of combined modalities and sequencing of these therapies.

There has been tremendous excitement about the use of immunotherapy in NSCLC and brain metastases. A phase II study out of Yale Cancer Center by Goldberg et al. showed that pembrolizumab is effective in treating NSCLC with untreated brain metastases in PD-L1 expression of at least 1%. A total of 29.7% of brain metastasis patients in this cohort responded to pembrolizumab, and the median follow-up was 8.3 months [67]. The Checkmate 227 trial showcased an increase in overall survival in the nivolumab and ipilimumab group as compared to chemotherapy in patients with PD-L1 expression of > 1% or < 1%. The 4-year survival rate was 29% versus 18% in PD-L1 > 1% and 24% versus 10% in PD-L1 < 1% for nivolumab and ipilimumab versus chemotherapy, respectively [96]. The group with brain metastases derived benefit as well as patients who did not have brain metastases (Table 1).

**Breast Cancer**

Most breast cancers are HER2-negative. HER2-positive alterations occur in 20% of breast cancers [97]. The LANDSCAPE study showed an intracranial response rate of 66% with lapatinib and capecitabine in newly diagnosed radiation-naïve patients [98] with a median duration of response of 5.5 months in HER2+ metastatic breast cancer patients, PATRICIA trial demonstrated an intracranial response rate of 11% with a greater dose of trastuzumab (6 mg/kg) and pertuzumab in patients who did not respond positively to prior trastuzumab as well as radiotherapy. Fifty-one percent of patients achieved clinical benefit at 6 months. Trastuzumab emtansine (T-DM1) has shown efficacy in intracranial disease control. The KAMILLA study of T-DM1 demonstrated the overall response rate as 21% in advanced or metastatic HER2+ breast cancer patients who had received prior HER2-based management along with chemotherapy with no positive effect [99].

**Table 1** Summary of different drugs for brain metastasis

| Study            | Drug      | Patient population | N  | CR | PR | SD | PD | ORR | OS (months) | PFS (months) |
|------------------|-----------|--------------------|----|----|----|----|----|-----|------------|-------------|
| AURA3 [76]       | Osimertinib | 419                | 30 | 7% | 63%| 23%| 3% | 70%| N/A        | 11.7        |
| FLAURA [124]     | Osimertinib | 200                | 22 | 23%| 68%| 5% | 0% | 80%| 38.6       | 18.9        |
| ASCEND 4 [82]    | Ceritinib  | 376                | 35 | 11%| 60%| 17%| 6% | 73%| N/A        | 10.7        |
| NCT01801111 [83] | Alectinib  | 138                | 35 | 20%| 37%| 29%| 9% | 57%| N/A        | 8.9         |
| ALTA [87]        | Brigatinib | 275                | 44 | 5% | 48%| 32%| N/A| 71%| N/A        | N/A         |
| NCT01970865 [88] | Lorlatinib | 276                | 81 | 20%| 43%| 25%| 9% | 51%| N/A        | 7.3         |
| LANDSCAPE [98]   | Lapatinib  | 45                 | 44 | 5% | 52%| 36%| 7% | 66%| 17.0       | N/A         |
| HER2CLIMB [102]  | Tucatinib  | 291                | 55 | 6% | 42%| 44%| 4% | 47%| 18.1       | 9.9         |
| Break MB [125]   | Dabrafenib | 325                | 74 | 0% | 7% | 27%| 40%| 39%| 33.1       | 16.1        |
median duration of exposure was 9.5 months. PERME-ATE was an investigator-initiated, multi-centric study of pyrotnib plus capecitabine in HER2-positive breast cancer brain metastasis patients of 78 patients, cohort A included 59 patients that were radiation naïve and cohort B included 19 patients that had progressed on radiation. The combination resulted in an IRR rate of 74.6% in cohort A and 42.1% in cohort B [100]. Neratinib in combination with capecitabine has shown intracranial response rates of 33–49% in patients with progressive disease post-radiation [101]. The HER2CLIMB study randomized patients who earlier received trastuzumab, pertuzumab, and T-DM1 to the regimen of tucatinib, capecitabine, and trastuzumab versus capecitabine and trastuzumab alone, recognized a complete intracranial response rate of 47% with tucatinib in brain metastases patients with a median duration of response of 6.8 months; respective guesses in patients just receiving trastuzumab and capecitabine were 3 months and 20%, respectively [102]. The DESTINY-Breast 01 trial demonstrated an overall response rate of 58% and a CNS response rate of 41% in 24 brain metastases patients who were heavily pretreated (median = 6 prior regimens). Additionally, the median duration of response was 18.1 months [103]. Another trial that is ongoing (DESTINY breast-12) will enroll up to 250 patients with stable or progressive HER2+ breast cancer brain metastases to further define the intracranial activity of trastuzumab deruxtecan (T-DXd). Systemic therapy options are limited for patients with triple-negative breast cancer (TNBC) and brain metastases. The ASCENT trial evaluates sacituzumab govitecan in TNBC patients with brain metastases. It is an antibody–drug conjugate comprising of an anti-Trop-2 antibody attached to an active metabolite called irinotecan, SN-38. The clinical benefit rate and intracranial response rate were 9% and 3%, respectively [104]. A current SWOG trial is assessing the CNS activity of sacituzumab govitecan, especially in active brain metastases patients (NCT04647916). Alpelisib, a PI3K inhibitor, may have intracranial efficacy for HER2-negative breast cancer patients, after its use led to improved outcomes in a case series of 4 patients [105] and, Abemaciclib showed a response rate of 5% for HER2 negative and 0% for HER2 positive patients [106]. Efficacy of PARP inhibitors such as olaparib is limited in BRCA mutated breast cancers although there is limited data in brain metastases [107]. Bevacizumab in combination with carboplatin in breast cancer brain metastases patients has shown clinical efficacy, and in a phase II trial, their combination demonstrated a CNS ORR of 63% (95%CI, 46–78), a median PFS of 5.62 months, and an OS of 14.10 months [108]. Erribulin was utilized in the EBRAIM prospective observational trial among patients with HER2-negative breast cancer brain metastases, lead to 14 patients with disease control and a prolonged PFS of 10 months (vs 4 months) [109]. Capecitabine has also shown activity in HER2-negative breast cancer brain metastases, as it demonstrated median OS of 13 months and a PFS of 8 months, among a cohort of 7 patients after capecitabine initiation [110].

Iniparib, a PARP inhibitor which also acts by changing reactive oxygen species metabolism in tumor cells, has been evaluated in combination with irinotecan in patients with TNBC brain metastases, and an intracranial response rate of 12% was reported among 34 evaluable patients [111]. The IMpassion 130 reported the efficacy of atezolizumab with nab-paclitaxel or placebo, for treatment of metastatic TNBC and reported a median OS of 14.3 months in patients with concomitant brain metastases [112]. A phase I study of capecitabine in combination with temozolomide for the management of TNBC brain metastases reported significant antitumor activity, with 1 complete and 3 partial responses leading to an ORR of 18% in the brain [113]. Temozolomide was also assessed in combination with cisplatin, in a phase II study, and lead to six patients with breast cancer brain metastases achieving stable disease [114].

There are several ongoing studies in triple-negative breast cancer brain metastases including atezolizumab in combination with SRS is currently being evaluated in a phase II trial, to evaluate its efficacy in this patient population (NCT03483012). Another phase II trial currently underway is assessing the efficacy of cisplatin in combination with vemurafenib, another PARP inhibitor; to treat recurrent triple-negative breast cancer–associated brain metastases (NCT02595905). Finally, the CONTESSA TRIO trial which utilized testetaxel in combination with various PD-L1 inhibitors, among patients with triple-negative metastatic breast cancer, recently concluded, and the intracranial efficacy results are awaited (NCT03952325).

Melanoma

The advancement in systemic therapy is beneficial to target actionable mutations (especially BRAF, NRAS) in melanoma patients with brain metastases. The COMBI-MB study studied the effect of dabrafenib and trametinib in patients with the BRAFv600E mutation. The intracranial disease control rate was 75–88% and the median progression-free survival was 4.2–7.2 months as compared to 11.1 months for patients without brain metastasis [115, 116]. Other agents which include BRAF/MEK regimens such as encorafenib and binimetinib or vemurafenib and cobimetinib have shown intracranial activity [117, 118]. More phase I studies are being conducted to evaluate the efficacy of BRAF and MEK inhibitors (NCT04543188, NCT03332589, NCT04190628).

Immunotherapeutic agents such as check-point blockade have shown responses in melanoma brain metastases. Trials with pembrolizumab or nivolumab, yielded only about
20% intracranial response rates as compared to a 35–40% extracranial response rate [119, 120]. Two trials supported dual-agent therapy include Checkmate 204 and the ABC study. CheckMate 204 is a single-arm phase II trial of a combination of ipilimumab and nivolumab in patients with melanoma and active/unirradiated brain metastases. The benefit was primarily seen in asymptomatic melanoma patients with brain metastasis with a clinical benefit rate (CBR) of 58.4%. The symptomatic patients had intracranial CBR of 22.2% and median intracranial progression-free survival of 1.2 months and overall survival of 8.7 months [120–122]. The ABC study is a randomized trial of patients with asymptomatic or unirradiated brain metastases secondary to melanoma assessing the combination of ipilimumab and nivolumab versus nivolumab, along with a single-arm cohort of patients with advanced disease after local therapy, leptomeningeal disease, or neurologic symptoms accomplished with nivolumab monotherapy [8, 120–122]. The trial confirmed superior results with the combination of nivolumab and ipilimumab as compared to nivolumab monotherapy. The PFS at 6 months was 50% for nivolumab plus ipilimumab versus 29% for just nivolumab. The OS at 6 months was 76% for nivolumab plus ipilimumab as compared to 59% for nivolumab alone. Interestingly, patients who had progressed on prior BRAF inhibitor therapy did not have a meaningful result on the combination therapy [120]. This has led to incorporation into the ASCO-SNO-ASTRO guidelines for immunotherapy in NSCLC patients with asymptomatic brain metastases [38]. The use of multimodality therapy has been shown to be useful in retrospective series compared to either drug alone of radiosurgery alone [123]. Surgery can remove tumor mass decreasing the need for steroid use [100]. Studies focusing on BRAF-targeted and immunotherapeutic approaches are going on (NCT04511013).

## Summary

Significant challenges such as diverse patient populations, selection bias, the efficacy of past treatment, patient dropout, and ambiguity in finalizing primary endpoints in addition to FDA approval for novel systemic therapies exist even though progress has been observed in novel agents in brain metastasis. There has been greater awareness to include brain metastases patients in clinical trials and also novel drugs are being developed with the intent to have intracranial efficacy which has led to substantial progress in management in the last decade. Current endeavors such as reducing patient heterogeneity by utilizing molecular profiling to understand the genetic makeup of the patient’s tumor, broadening eligibility criteria to increase diverse demographic enrollments, particularly of ethnic minorities to understand tumor’s biology, and advancements in the conduct of clinical trials have the potential to improve outcomes for this increasingly important cohort of patients. Additional trials with different drug combinations or with radiation are needed to further improve outcomes.

### Abbreviations

- **N**: Number
- **CR**: Complete response
- **PR**: Partial response
- **SD**: Stable disease
- **PD**: Progressive disease
- **ORR**: Objective response rate
- **OS**: Overall survival
- **PFS**: Progression-free survival

### Supplementary Information

The online version contains supplementary material available at [https://doi.org/10.1007/s13311-022-01312-w](https://doi.org/10.1007/s13311-022-01312-w).

### Required Author Forms

Disclosure forms provided by the authors are available with the online version of this article.

### Open Access

This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit [http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/).

### References

1. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep. 2012;14(1):48–54.
2. Lambo N, Wen PY, Aizer AA. Epidemiology of brain metastases and leptomeningeal disease. Neuro Oncol. 2021;23(9):1447–56.
3. Achrol AS, Rennert RC, Anders C, Soffietti R, Ahluwalia MS, Nayak L, et al. Brain metastases. Nat Rev Dis Primers. 2019;5(1):5.
4. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. J Clin Oncol. 2004;22(14):2865–72.
5. Fabi A, Felici A, Metro G, Mirri A, Bria E, Telera S, et al. Brain metastases from solid tumors: disease outcome according to type of treatment and therapeutic resources of the treating center. J Exp Clin Cancer Res. 2011;30(1):10.
6. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med. 1990;322(8):494–500.
7. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet. 2004;363(9422):1665–72.
8. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med. 2018;379(8):722–30.
9. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-Mutated advanced non-small-cell lung cancer. N Engl J Med. 2018;378(2):113–25.
10. Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Weiner A, Jones RT, et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. Cancer Discov. 2015;5(11):1164–77.

11. Lamba N, Kearney RB, Catalano PJ, Hassett MJ, Wen PY, Haas-Kogan DA, et al. Population-based estimates of survival among elderly patients with brain metastases. Neuro Oncol. 2021;23(4):661–76.

12. Sperduto PW, Chao PK, Sneed PK, Luo X, Suh J, Roberge D, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. Int J Radiat Oncol Biol Phys. 2010;77(3):655–61.

13. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys. 1997;37(4):745–51.

14. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. Int J Radiat Oncol Biol Phys. 2008;70(2):510–4.

15. Gaspar LE, Scott C, Murray K, Curran W. Validation of the RTOG recursive partitioning analysis (RPA) classification for brain metastases. Int J Radiat Oncol Biol Phys. 2000;47(4):1001–6.

16. Sperduto CM, Watanabe Y, Mullan J, Hood T, Dyste G, Watts C, et al. A validation study of a new prognostic index for patients with brain metastases: the Graded Prognostic Assessment. J Neurosurg. 2008;109(Suppl):87–9.

17. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, et al. The effect of gene alterations and tyrosine kinase inhibition on survival and cause of death in patients with adenocarcinoma of the lung and brain metastases. Int J Radiat Oncol Biol Phys. 2016;92(2):406–13.

18. Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. Lung Cancer. 2012;77(3):556–60.

19. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, et al. Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases. Int J Radiat Oncol Biol Phys. 2012;82(5):2111–7.

20. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). JAMA Oncol. 2017;3(6):827–31.

21. Miller JA, Kotecha R, Ahluwalia MS, Mohammadi AM, Suh JH, Barnett GH, et al. The impact of tumor biology on survival and response to radiation therapy among patients with non-small cell lung cancer brain metastases. Pract Radiat Oncol. 2017;7(4):263–73.

22. Bezjak A, Adam J, Barton R, Panzarella T, Laperriere N, Wong CS, et al. Symptom response after palliative radiotherapy for patients with brain metastases. Eur J Cancer. 2002;38(4):487–96.

23. Chow E, Fan G, Hadi S, Wong J, Kirou-Mauro A, Filipczak L. Symptom clusters in cancer patients with brain metastases. Clin Oncol (R Coll Radiol). 2008;20(1):76–82.

24. Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD. Radiosurgery with or without whole-brain radiotherapy for brain metastases: the patients’ perspective regarding complications. Am J Clin Oncol. 2005;28(2):173–9.

25. Soffietti R, Kocher M, Abacioglu UM, Villa S, Fauchon F, Baumert BG, et al. A European Organisation for Research and Treatment of Cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiotherapy: quality-of-life results. J Clin Oncol. 2013;31(1):65–72.

26. Roth P, Pace A, Le Rhun E, Weller M, Ay C, Cohen-Jonathan Moyal E, et al. Neurological and vascular complications of primary and secondary brain tumours: EANO-ESMO clinical practice guidelines for prophylaxis, diagnosis, treatment and follow-up. Ann Oncol. 2021;32(2):171–82.

27. Le Rhun E, Guckenberger M, Smits M, Dummer R, Bachelot T, Sahn F, et al. EANO-ESMO clinical practice guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. Ann Oncol. 2021;32(11):1332–47.

28. Lamba N, Mehanna E, Kearney RB, Catalano PJ, Haas-Kogan DA, Alexander BM, et al. Racial disparities in supportive medication use among older patients with brain metastases: a population-based analysis. Neuro Oncol. 2020;22(9):1339–47.

29. Le Rhun E, Preusser M, van den Bent M, Andratschke N, Weller M. How we treat patients with leptomeningeal metastases. ESMO Open. 2019;4(Suppl 2):e000507.

30. Le Rhun E, Devos P, Weller J, Seystahl K, Mo F, Compter A, et al. Prognostic validation and clinical implications of the EANO ESMO classification of leptomeningeal metastasis from solid tumors. Neuro Oncol. 2021;23(7):1100–12.

31. Pellerino A, Brastianos PK, Radia R, Soffietti R. Leptomeningeal metastases from solid tumors: recent advances in diagnosis and molecular approaches. Cancers (Basel). 2021;13(12).

32. Mikkelsen T, Paleologos NA, Robinson PD, Ammirati M, Andrews DW, Asher AL, et al. The role of prophylactic anticoagulants in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2010;96(1):97–102.

33. Ryken TC, McDermott M, Robinson PD, Ammirati M, Andrews DW, Asher AL, et al. The role of steroids in the management of brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol. 2010;96(1):103–14.

34. Gonzalez J, Kumar AJ, Conrad CA, Levin VA. Effect of bevacinumab on radiation necrosis of the brain. Int J Radiat Oncol Biol Phys. 2007;67(2):323–6.

35. Kotecha R, Ahluwalia MS, Siomin V, McDermott MW. Surgery, stereotactic radiosurgery, and systemic therapy in the management of operable brain metastasis. Neurrol Clin. 2020;40(2):421–36.

36. Ratnaike TE, Das S, Gregson BA, Mendelow AD. A review of brain abscess surgical treatment—78 years: aspiration versus excision. World Neurosurg. 2011;76(5):431–6.

37. Lamba N, Cagney DN, Brigell RH, Martin AM, Besse LA, Catalano PJ, et al. Neurosurgical Resection and stereotactic radiation versus stereotactic radiation alone in patients with a single or solitary brain metastasis. World Neurosurg. 2019;122:e1557–61.

38. Vogelbaum MA, Brown PD, Messersmith H, Brastianos PK, Burri S, Cahill D, et al. Treatment for brain metastases: ASCO-SNO-ASTRO Guideline. J Clin Oncol. 2022;40(5):492–516.

39. Bhangoo SS, Linskey ME, Kalkanis SN. Evidence-based guideline. J Neurooncol. 2010;96(1):103–14.

40. Gonzalez J, Kumar AJ, Conrad CA, Levin VA. Effect of bevacinumab on radiation necrosis of the brain. Int J Radiat Oncol Biol Phys. 2007;67(2):323–6.

41. Kotecha R, Ahluwalia MS, Siomin V, McDermott MW. Surgery, stereotactic radiosurgery, and systemic therapy in the management of operable brain metastasis. Neurrol Clin. 2020;40(2):421–36.

42. Ratnaike TE, Das S, Gregson BA, Mendelow AD. A review of brain abscess surgical treatment—78 years: aspiration versus excision. World Neurosurg. 2011;76(5):431–6.

43. Lamba N, Cagney DN, Brigell RH, Martin AM, Besse LA, Catalano PJ, et al. Neurosurgical Resection and stereotactic radiation versus stereotactic radiation alone in patients with a single or solitary brain metastasis. World Neurosurg. 2019;122:e1557–61.

44. Vogelbaum MA, Brown PD, Messersmith H, Brastianos PK, Burri S, Cahill D, et al. Treatment for brain metastases: ASCO-SNO-ASTRO Guideline. J Clin Oncol. 2022;40(5):492–516.

45. Bhangoo SS, Linskey ME, Kalkanis SN. Evidence-based guideline. J Neurooncol. 2010;96(1):103–14.

46. Vecht CJ, Haaxma-Reiche H, Noordijk EM, Padberg GW, Voormolen JH, Hoekstra FH, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? Ann Neurol. 1993;33(6):583–90.

47. Muacevic A, Wowra B, Sievert A, Tonn JC, Steiger HJ, Kreth FW. Microsurgery plus whole brain irradiation versus Gamma Knife surgery alone for treatment of single metastases to the...
brain: a randomized controlled multicentre phase III trial. J Neurooncol. 2008;87(3):299–307.
42. Roos DE, Smith JG, Stephens SW. Radiosurgery versus surgery, both with adjuvant whole brain radiotherapy, for solitary brain metastases: a randomised controlled trial. Clin Oncol (R Coll Radiol). 2011;23(9):646–51.
43. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metasteses to the brain: a randomized trial. JAMA. 1998;280(17):1485–9.
44. Mehta MF. The controversy surrounding the use of whole-brain radiotherapy in brain metastases patients. Neuro Oncol. 2015;17(7):919–23.
45. Brown PD, Pugh S, Laack NN, Wefel JS, Khuntia D, Meyers C, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol. 2013;15(10):1429–37.
46. Gondi V, Deshmukh S, Brown PD, Wefel JS, Tome WA, Bruner DW, et al. Preservation of neurocognitive function (NCF) with conformal avoidance of the hippocampus during whole-brain radiotherapy (HA-WBRT) for brain metastases: preliminary results of phase III trial NRG Oncology CCO001. Int J Radiat Oncol Biol Phys. 2018;102(5):1607.
47. Dixit KS, Kumthekar PU. Optimal management of corticosteroids in patients with intracranial malignancies. Curr Treat Options Oncol. 2020;21(9):77.
48. Brown PD, Gondi V, Pugh S, Tome WA, Wefel JS, Armstrong TS, et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: phase III trial NRG Oncology CCO001. J Clin Oncol. 2020;38(10):1019–29.
49. Gondi V, Pugh S, Brown P, Wefel J, Gilbert M, Bovi J, et al. NCOG-01. Preservation of neurocognitive function (NCF) with hippocampal avoidance during whole-brain radiotherapy (WBRT) for brain metastases: preliminary results of phase III trial NRG Oncology CCO001. Neuro Oncol. 2018;20(suppl 6):vi172–vi.
50. Mahajan A, Ahmed S, McAleer MF, Weinberg JS, Li J, Brown P, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(8):1040–8.
51. Brown PD, Jaekle K, Ballman KV, Parace E, Cerhan JH, Anderson SK, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. JAMA. 2016;316(4):401–9.
52. Li J, Ludmir EB, Wang Y, Guha-Thakurta N, McAleer MF, Settle SH, et al. Stereotactic radiosurgery versus whole-brain radiation therapy for patients with 4–15 brain metastases: a phase III randomized controlled trial. Int J Radiat Oncol Biol Phys. 2020;108(3, Supplement):S21–2.
53. Kayama T, Sato S, Sakurada K, Mizzawa J, Nishikawa R, Narita Y, et al. Effects of Surgery with salvage stereotactic radiosurgery versus surgery with whole-brain radiation therapy in patients with one to four brain metastases (JC0G504): a phase III, noninferiority, randomized controlled trial. J Clin Oncol. 2018;Jo2018786186.
54. Parsa S, Miller JA, Juloori A, Chao ST, Kotecha R, Mohammadi AM, et al. Stereotactic radiosurgery with concurrent laptatinib is associated with improved local control for HER2-positive breast cancer brain metastases. J Neurosurg. 2019;132(2):503–11.
55. Kotecha R, Kim JM, Miller JA, Juloori A, Chao ST, Murphy ES, et al. The impact of sequencing PD-1/PD-L1 inhibitors and stereotactic radiosurgery for patients with brain metastasis. Neuro Oncol. 2019;21(8):1060–8.
56. Kotecha R, Miller JA, Venur VA, Mohammadi AM, Chao ST, Suh JH, et al. Melanoma brain metastasis: the impact of stereotactic radiosurgery, BRAF mutational status, and targeted and/or immune-based therapies on treatment outcome. J Neurosurg. 2018;129(1):50–9.
57. Chiu AL, Li G, Gephart MH, Sandhu N, Nagpal S, Soltys SG, et al. Stereotactic radiosurgery after resection of brain metastases: changing patterns of care in the United States. World Neurosurg. 2020;144:e797–806.
58. Prabhu RS, Press RH, Patel KR, Boselli DM, Symanowski JT, Lankford SP, et al. Single-fraction stereotactic radiosurgery (SRS) alone versus surgical resection and SRS for large brain metastases: a multi-institutional analysis. Int J Radiat Oncol Biol Phys. 2017;99(2):459–67.
59. Patel KR, Burri SH, Asher AL, Crocker IR, Fraser RW, Zhang C, et al. Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: a multi-institutional analysis. Neurosurgery. 2016;79(2):279–85.
60. Brown PD, Ballman KV, Cerhan JH, Anderson SK, Carrero XW, Whitton AC, et al. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. Lancet Oncol. 2017;18(8):1049–60.
61. Kotecha R, Tonse R, Menendez MAR, Williams A, Diaz Z, Tom MC, et al. Evaluation of the impact of pre-operative stereotactic radiotherapy on the acute changes in histopathologic and immune marker profiles of brain metastases. Sci Rep. 2022;12(1):4567.
62. Suh JH, Barnett GH. Brachytherapy for brain tumor. Hematol Oncol Clin North Am. 1999;13(3):635–50, viii-ix.
63. Ruge MI, Kickingereder P, Grau S, Hoevels M, Teuver H, Sturm V. Stereotactic biopsy combined with stereotactic (125)iode brachytherapy for diagnosis and treatment of locally recurrent single brain metastases. J Neurooncol. 2011;105(1):109–18.
64. Chitti B, Goyal S, Sherman JH, Caputy A, Sarfaraz M, Cifter G, et al. The role of brachytherapy in the management of brain metastases: a systematic review. J Contemp Brachytherapy. 2020;12(1):67–83.
65. Gadgeel SM, Gandhi L, Riely GJ, Chiappori AA, West HL, Azada MC, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002iG): results from the dose-finding portion of a phase 1/2 study. Lancet Oncol. 2014;15(10):1119–28.
66. Shaw AT, Felip E, Bauer TM, Besse B, Navarro A, Postel-Vinay S, et al. Lorlatinib in non-small-cell lung cancer with brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. Lancet Oncol. 2020;21(5):655–63.
67. Bearz A, Garassino I, Tiseo M, Caffo O, Soto-Parrà H, Boccalon M, et al. Activity of Pemetrexed on brain metastases from non-small cell lung cancer. Lung Cancer. 2010;68(2):264–8.
68. He Q, Bi X, Ren C, Wang Y, Zou P, Zhang H, et al. Phase II study of the efficacy and safety of high-dose Pemetrexed in combination with Cisplatin versus Temozolomide for the treatment of non-small cell lung cancer with brain metastases. Anticancer Res. 2017;37(8):4711–6.
69. Yun I, Lee SH, Kim SY, Jeong SY, Kim JH, Pyo KH, et al. Antitumor activity of amivantamab (JNJ-61186372), an EGFR-MET bispecific antibody, in diverse models of EGFR Exon 20 insertion-driven NSCLC. Cancer Discov. 2020;10(8):1194–209.
70. Jänne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015;372(18):1689–99.
a single-arm, open-label, phase 1/2 trial. Lancet Oncol. 2016;17(12):1683–96.
87. Kim DW, Tiseo M, Ahn MJ, Reckamp KL, Hansen KH, Kim SW, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. J Clin Oncol. 2017;35(22):2490–8.
88. Solomon BJ, Besse B, Bauer TM, Felip E, Soo RA, Camidge DR, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. Lancet Oncol. 2018;19(12):1654–67.
89. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Hochmair MJ, et al. Brigatinib versus Crizotinib in advanced ALK inhibitor-naive ALK-positive non-small cell lung cancer: second interim analysis of the phase III ALTA-1L trial. J Clin Oncol. 2020;38(31):3592–603.
90. Camidge DR, Kim HR, Ahn MJ, Yang JC, Han JY, Lee JS, et al. Brigatinib versus Crizotinib in ALK-Positive non-small-cell lung cancer. N Engl J Med. 2018;379(21):2027–39.
91. Novello S, Maiorelli J, Oh JI, de Castro J, Migliorini MR, Helland A, et al. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. Ann Oncol. 2018;29(6):1409–16.
92. Camidge DR. Lorlatinib should not be considered as the preferred first-line option in patients with advanced ALK rearranged NSCLC. J Thorac Oncol. 2021;16(4):528–31.
93. Pacheco JM, Gao D, Smith D, Purcell T, Hancock M, Bunn P, et al. Natural history and factors associated with overall survival in stage IV ALK-rearranged non–small cell lung cancer. J Thorac Oncol. 2019;14(4):691–700.
94. Magnuson WJ, Lester-Coll NH, Wu AJ, Yang TJ, Lockney NA, Gerber NK, et al. Management of brain metastases in tyrosine inhibitor-naive epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. J Clin Oncol. 2017;35(10):1070–7.
95. Subbiah V, Gainor JF, Oxnard GR, Tan DSW, Owen DH, Cho BC, et al. Intracranial efficacy of selpercatinib in RET fusion-positive non-small cell lung cancers on the LIBRETTO-001 trial. Clin Cancer Res. 2021;27(15):4160–7.
96. Paz-Ares LG, Ciuleanu T-E, Lee J-S, Urban L, Bernabe Caro R, Park K, et al. Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line treatment for advanced non-small-cell lung cancer (NSCLC): 4-year update from CheckMate 227. Wolters Kluwer Health; 2021.
97. Kunte S, Abraham J, Montero AJ. Novel HER2-targeted therapies for HER2-positive metastatic breast cancer. Cancer. 2020;120(19):4278–88.
98. Bachelot T, Romieu G, Campone M, Diéras V, Croset C, Dalenc F, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. Lancet Oncol. 2013;14(1):64–71.
99. Montemurro F, Delagle S, Barrios CH, Wuehrsteine R, Anton A, Brain E, et al. Trastuzumab emtansine (T-DM1) versus capecitabine for patients with HER2-positive metastatic breast cancer and brain metastases: exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIib clinical trial. Ann Oncol. 2020;31(10):1350–8.
100. Yan M, Ouyang Q, Sun T, Niu L, Yang J, Li L, et al. Pyrotinib plus capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases (PERMEATE): a multicentre, single-arm, two-cohort, phase 2 trial. Lancet Oncol. 2022;23(3):353–61.
factor receptor 2-positive breast cancer and brain metastases. J Clin Oncol. 2019;37(13):1081–9.
102. Lin NU, Borges V, Anders C, Murthy RK, Pampilata E, Hamilton E, et al. Intracranial efficacy and survival with tucatinib plus trastuzumab and capcitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB Trial. J Clin Oncol. 2020;38(23):2610–9.
103. Jerusalim GHM, Park YH, Yamashita T, Hurvitz SA, Modi S, Andre F, et al. Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: a subgroup analysis of the DESTINY-Breast01 trial. Wolters Kluwer Health; 2021.
104. Diers V, Werner R, Tolaney SM, Bardia A, Punie K, Brufsky A, et al. Subgroup analysis of patients with brain metastases from the phase 3 ASCENT study of sunitinib/govitecan versus chemotherapy in metastatic triple-negative breast cancer. Cancer Res. 2021;81(4).
105. Batalini F, Moulder SL, Winer EP, Rugo HS, Lin NU, Wulf GM. Response of brain metastases from PIK3CA-mutant breast cancer to alpelisib. JCO Precis Oncol. 2020;4.
106. Tolaney SM, Sahebjam S, Le Rhun E, Bachelot T, Kabos P, Awada A, et al. Phase II study of Abemaciclib in patients with breast metastases secondary to hormone receptor-positive breast cancer. Clin Cancer Res. 2020;26(20):5310–9.
107. Exman P, Mallery RM, Lin NU, Parsons HA. Response to Olaparib in a patient with germline BRCA2 mutation and breast cancer leptomeningeal carcinomatosis. NPJ Breast Cancer. 2019;5:46.
108. Leone JP, Embile KE, Weitz M, Gelman RS, Schneider BP, Freedman RA, et al. Phase II trial of carboplatin and bevacizumab in patients with breast cancer brain metastases. Breast Cancer Res. 2020;22(1):131.
109. Fabi A, Terrenato I, Vidiri A, Villani V, T anzilli A, Airoldi M, et al. Eribulin in metastases of breast cancer: outcomes of the EBRAIM prospective observational trial. Future Oncol. 2021;17(26):3445–56.
110. Ekenel M, Hormigo AM, Peak S, Deangelis LM, Abrey LE. Capecitabine therapy of central nervous system metastases from breast cancer. J Neurooncol. 2007;85(2):223–7.
111. Anders C, Deal AM, Abramson V, Liu MC, Storniolo AM, Carpenter JT, et al. TBCRC 018: phase II study of iniparib in combination with irinotecan to treat progressive triple negative breast cancer brain metastases. Breast Cancer Res Treat. 2014;146(3):557–66.
112. Schmid P, Rugo HS, Adams S, Schneeweiss A, Barrios CH, Iwata H, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol. 2020;21(1):44–59.
113. Rivera E, Meyers C, Groves M, Valero V, Francis D, Arun B, et al. Phase I study of capecitabine in combination with temozolomide in the treatment of patients with brain metastases from breast carcinoma. Cancer. 2006;107(6):1348–54.
114. Christodoulou C, Bafaloukos D, L inardou H, Aravantinos G, Bamias A, Carina M, et al. Temozolomide (TMZ) combined with cisplatin (CDDP) in patients with brain metastases from solid tumors: a Hellenic Cooperative Oncology Group (HeCOG) Phase II study. J Neurooncol. 2005;71(1):61–5.
115. Davies MA, Saag P, Robert C, Grob JJ, Flaherty KT, Arance A, et al. Dabrafenib plus trametinib in patients with BRAF(V600)-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017;18(7):863–73.
116. Roberts C, Grob JJ, Stroyakovsky D, Karaszewska B, Hauschild A, Levecenko E, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med. 2019;381(7):626–36.
117. Drago JZ, Lawrence D, Livingstone E, Zimmer L, Chen T, Giobbie-Hurder A, et al. Clinical experience with combination BRAF/MEK inhibitors for melanoma with brain metastases: a real-life multicenter study. Melanoma Res. 2019;29(1):65–9.
118. Holbrook K, Lutzyj I, Davies MA, Davis JM, Glitza JC, Amaria RN, et al. Intracranial antitumor activity with encorafenib plus binimetinib in patients with melanoma brain metastases: a case series. Cancer. 2020;126(3):523–30.
119. Goldberg SB, Gettigner SN, Mahajan A, Chiang AC, Herbst RS, Szol M, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. Lancet Oncol. 2016;17(7):976–83.
120. Long GV, Atkinson V, Lo S, Guminiski AD, Sandhu SK, Brown MP, et al. Five-year overall survival from the anti-PD1 brain collaboration (ABC Study): randomized phase 2 study of nivolumab (nivo) or nivo+ ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets). Wolters Kluwer Health; 2021.
121. Tawbi HA, Forisyth PA, Hodi FS, Lao CD, Moschos SJ, Hamid O, et al. Safety and efficacy of the combination of nivolumab plus ipilimumab in patients with melanoma and asymptomatic or symptomatic brain metastases (CheckMate 204). Neuro Oncol. 2021;23(11):1961–73.
122. Long GV, Atkinson V, Lo S, Sandhu S, Guminiski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncol. 2018;19(5):672–81.
123. Qian JM, Martin AM, Martin K, Hammoudel L, Catalano PJ, Hodi FS, et al. Response rate and local recurrence after concurrent immune checkpoint therapy and radiotherapy for non-small cell lung cancer and melanoma brain metastases. Cancer. 2020;126(24):5274–82.
124. Reungwetwattana T, Nakagawa K, Cho BC, Cobo M, Cho EK, Bertolini A, et al. CNS response to Osimertinib Versus standard epidermal growth factor receptor tyrosine kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer. J Clin Oncol. 2018;Jc2018783118.
125. Long GV, Trefzer U, Davies MA, Kefford RF, Ascieto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol. 2012;13(11):1087–95.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.