About the Authors

Jie Wei Zhu, MD

Dr. Zhu is an incoming Medical Oncology Resident at the University of Toronto and will be completing her Internal Medicine training starting in July 2025 also at the University of Toronto. Her professional interests include breast, gynecologic, and gastrointestinal malignancies, and she hopes to pursue further research training in clinical research methodology or molecular genetics.

Affiliations: Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Ines B. Menjak, MD

Dr. Ines Menjak is a staff medical oncologist at Sunnybrook Health Sciences Centre. She completed her medical training at the University of Toronto and has a Master's of Science in Health Research Methodology, Clinical Epidemiology Stream from McMaster University. She specializes in skin cancer and thoracic cancer. She is the founder and lead of the Geriatric Oncology Clinic at Sunnybrook. She is also the head of the Lung Clinical Trials Group. Her research focuses on improving the care of older patients with cancer, as well as immunotherapy toxicity.

Affiliations: Department of Medicine, Division of Medical Oncology and Hematology, University of Toronto, Toronto, Ontario, Canada
Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Arjun Sahgal, BSc, MD, FRCPC

Dr. Arjun Sahgal is an international clinical and research leader in the field of high precision stereotactic radiation to the brain and spine for both metastases and primary tumors. He currently serves as the Chief of the Department of Radiation Oncology at the University of Toronto affiliated Sunnybrook Odette Cancer Centre. Since his radiation oncology training at the University of Toronto and fellowship at the University of California San Francisco, he has published over 600 peer reviewed papers in high impact journals like the Journal of Clinical Oncology, Lancet Oncology and New England Journal of Medicine, and 40 international guidelines specific to SRS and SBRT. He has given over 200 lectures as an invited international speaker. He invented the 24 Gy in 2 SBRT fractions regimen for spinal metastases which was tested in his landmark international CCTG SC24 randomized trial, proving superiority over conventional palliative radiation with respect to complete pain response. He has been instrumental in raising ~$50M in grant and philanthropic funding to support central nervous system research at Sunnybrook. In addition to leading several international research consortia, he has served as co-Chairperson of the AOSpine Tumour Knowledge Forum, and is currently the President of the International Stereotactic Radiosurgery Society (ISRS). His next phase of research is in the development of advanced MR in CNS radiation therapy, MR Linac adaptive RT for GBM, CT-adaptive radiotherapy, and automated vertebral fracture risk prediction. In addition, he leads the Canadian randomized trial of SBRT vs. conventional radiation for non-spine bone metastases (CCTG SC-29).

Affiliations: Department of Radiation Oncology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada
Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

doi.org/10.58931/cot.2025.2132

Katarzyna J. Jerzak, MD, MSc, FRCPC

Dr. Katarzyna Jerzak is a Medical Oncologist and Clinician Investigator at the Sunnybrook Odette Cancer Center and Assistant Professor at the University of Toronto. She is also an Associate Scientist at the Sunnybrook Research Institute and Lead of breast oncology clinical trials at her Centre. Dr. Jerzak's research focus is related to clinical trials and brain metastases. She is a member of international clinical trials organizations, including the breast committee within NRG Oncology and the Breast International Group (BIG) Brain Metastases Task Force. She is also actively participating in the National Cancer Institute's National Clinical Trials Network (NCTN)-BIG Core Working Group regarding brain metastases and is a core member of the Canadian "REAL" Breast Cancer Alliance. Dr. Jerzak has over 100 publications, including publications in high impact journals such as Lancet Oncology, JAMA Oncology, and Clinical Cancer Research.

Affiliations: Department of Medicine, Division of Medical Oncology and Hematology, University of Toronto, Toronto, Ontario, Canada
Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

Current Approaches and Future Directions for the Treatment of Solid Tumour Brain Metastases

Jie Wei Zhu, MD
Ines B. Menjak, MD
Arjun Sahgal, BSc, MD, FRCPC
Katarzyna J. Jerzak, MD, MSc, FRCPC

Introduction

Brain metastases (BrM) are most common among patients with metastatic lung cancer, breast cancer, and melanoma.[1] Historically, management of BrM consisted of local treatments with surgical resection and/or radiation therapy, with either whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS). Current guidelines recommend SRS as the initial therapy for patients who have up to four BrM,[2] but several studies have demonstrated that upfront SRS may be considered for some patients who have more than four BrM given additional clinical benefits of improved memory function and quality of life compared to WBRT.[3-5]

Systemic therapies are increasingly understood to cross the blood-brain barrier (BBB) following disruption of its integrity upon BrM development. Disseminated tumour cells intravasate into the circulation and spread hematogenously with a "seed and soil" tropism for the brain that provides a suitable tumour microenvironment.[6,7] Tumour cells extravasate and increase the permeability of the BBB by decreasing tight junction protein expression, decreasing astrocyte pedicles, reducing pericyte coverage, and increasing neoangiogenesis.[8] The altered integrity of the BBB allows penetration of large drug molecules, such as antibody-drug conjugates (ADCs), which exert their therapeutic effects by binding to tumour cell-specific epitopes and releasing a cytotoxic payload, even in the absence

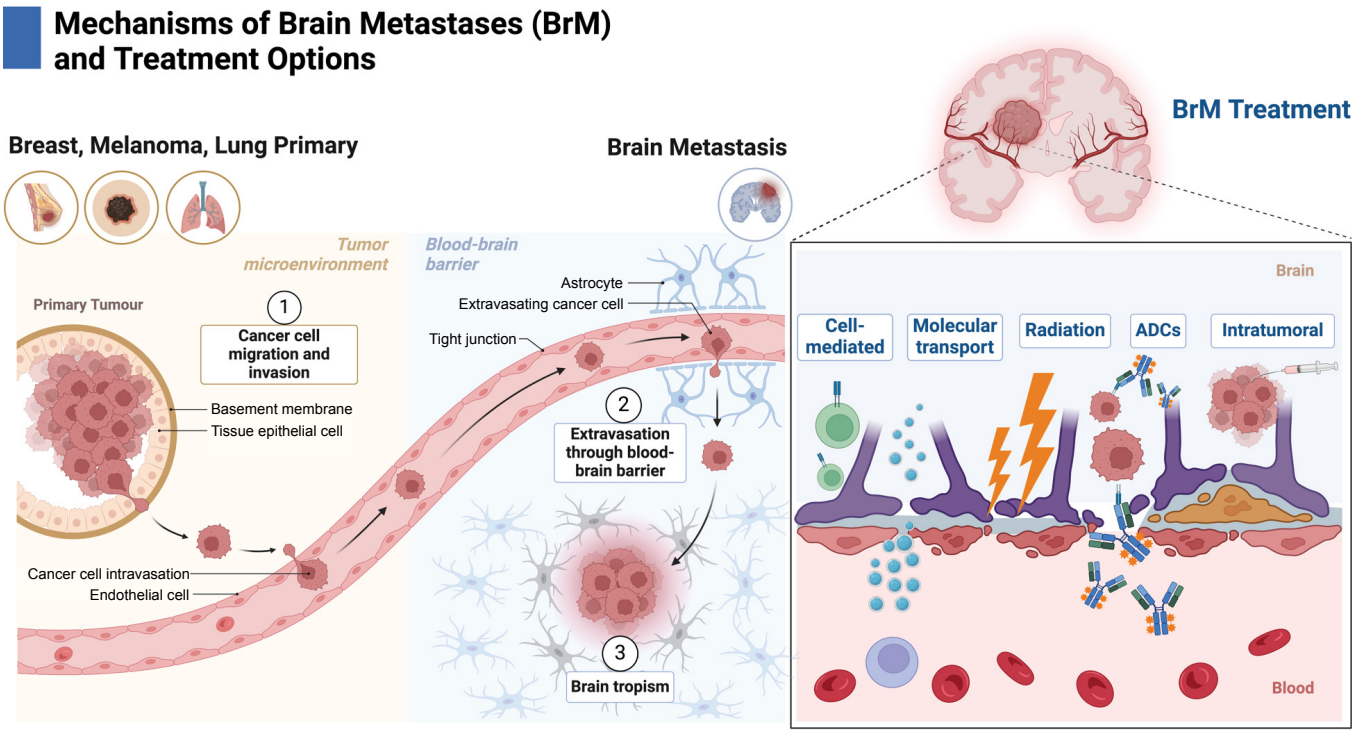

Figure 1. Schematic illustrating the mechanisms by which primary tumours metastasize to the brain and mechanism of action for various therapies, including cell-mediated transport, molecular transport, physical disruption (i.e., radiation), antibody-drug conjugate epitope recognition, and intratumoral drug delivery; *created with Biorender.com.*

Abbreviations: BrM: brain metastases, **ADCs:** antibody-drug conjugates

of radiation.[9] Other therapeutic mechanisms of action include molecular (passive or receptor-mediated transport), physical (radiation or focused ultrasound), direct delivery to the brain (intrathecal or intratumoral), and cell-mediated (immune cell extravasation) (**Figure 1**).[8,9]

Several novel small-molecule tyrosine kinase inhibitors (TKIs) have been developed for the treatment of driver mutation-positive lung cancer, which is associated with the highest risk of BrM. Novel anaplastic lymphoma kinase (ALK) inhibitors, including crizotinib, alectinib, brigatinib, and lorlatinib, have led to a breakthrough in the treatment of patients with ALK-mutant non-small cell lung cancer (NSCLC) and BrM.[10-13] The phase III CROWN trial compared lorlatinib to crizotinib in advanced ALK-positive NSCLC and included 78 (26.4%) patients with active BrM, among whom 30 patients (10.1%) had measurable disease.[13] This study found that patients treated with lorlatinib had a significantly higher intracranial objective response rate (IC-ORR) compared to those receiving crizotinib (66% vs. 20%); the complete intracranial response rate was much higher among patients receiving lorlatnib as well (61% vs. 15%). In addition, only 4 out of the 114 patients (3%) without BrM at baseline in the lorlatinib group later developed BrM; this is much lower than 33% of patients who developed BrM in the crizotinib arm of this trial.[13] Altogether, the evidence suggests that lorlatinib not only controls existing BrM but may also prevent the development of new BrM.

Similarly, there is evidence supporting the use of osimertinib for the treatment of BrM among patients with epidermal growth factor receptor (EGFR)-mutant metastatic NSCLC. A systematic review and meta-analysis that included 15 studies with 324 patients reported an IC-ORR rate of 64% (95% confidence interval [CI] = 53–76%; n = 195) and complete intracranial response rates of 7% to 23%.[14] The median duration of central nervous system (CNS) response among included studies ranged from 8.9 to 15.2 months. A recent multi-centre retrospective study examining

317 TKI-naïve patients with EGFR- and ALK-mutant NSCLC with BrM found that the addition of upfront SRS to TKI treatment prolonged time to CNS progression versus TKI treatment alone. Local CNS control was significantly improved with the use of both TKI and SRS (hazard ratio [HR] = 0.30, 95% CI = 0.16–0.55, P <.001) versus TKI alone, and the cumulative incidence of CNS progression at 24 months was 9% vs. 25%, respectively.[15] However, there was no significant difference in overall survival (OS).[15] This lack of survival detriment with omission of brain radiotherapy has motivated a phase II Canadian-led trial that is currently underway to determine the impact of SRS plus osimeritnib versus osimeritnib alone for patients with treatment-naïve EGFR-mutant metastatic NSCLC with BrM (NCT03769103). These results are eagerly anticipated to better understand which patients with EGFR-mutant metastatic NSCLC can safely avoid upfront brain radiation (and its associated toxicities) for newly diagnosed BrM. For locally advanced disease, the LAURA trial that randomized 216 patients with Stage III EGFR-mutated NSCLC to osimertinib versus placebo following chemoradiation and found that the incidence of new brain lesions was much lower at 8% in the osimertinib group compared to 29% with placebo.[16]

Another important setting where TKIs have demonstrated significant benefit among patients with BrM is HER2⁺ metastatic breast cancer (MBC).[17,18] The strongest data come from the randomized HER2CLIMB trial that demonstrated a survival benefit associated with the addition of tucatinib to capecitabine/trastuzumab among patients with active or treated stable BrM compared to those receiving capecitabine and trastuzumab alone.[19] This study included 291 patients (48%) with HER2⁺ MBC and BrM, among whom 60% had active BrM, defined as previously untreated or treated but progressing BrM at time of enrolment. Patients with BrM who received tucatinib also had a longer median OS than those who did not (22 vs. 13 months; HR = 0.60, 95% CI = 0.44–0.81), which was similar to the overall study population. Furthermore, the median new brain lesion-free survival was 11.1 months longer among tucatinib-treated patients (24.9 vs. 13.8 months, respectively, p = 0.006). This study reflects an emerging shift in the design of clinical trials to include patients with active BrM, with the safety of this approach to date allowing for major advancements in the treatment of patients with HER2⁺ MBC.

For patients with HER2⁺ MBC and BrM, treatment with HER2-directed ADCs may also be an option. The first available ADC for patients with HER2⁺ MBC was trastuzumab emtansine (T-DM1), which showed intracranial efficacy in the KAMILLA phase IIIB clinical trial.[20] Among 2,002 patients with HER2⁺ MBC, 398 (19.9%) had BrM at baseline.[20] A ≥30% reduction in the "sum of the major diameters" of BrM was observed for ~43% of the overall cohort and for ~49% of those (n=67, 16.8%) who did not receive prior brain radiotherapy. Since then, trastuzumab deruxtecan (T-DXd) has demonstrated a 73.3% IC-ORR in patients with HER2⁺ MBC and active BrM (n= 15 patients in the intention-to-treat population),[21] as well as an impressive IC-ORR of 45% in a pooled analysis of the DESTINY-Breast-01, -02, and -03 clinical trials.[22] More recently, the DESTINY-Breast-12 trial that included 263 patients with MBC and stable or active BrM and previously treated with anti-HER2 therapy reported a CNS PFS of 58.9% and CNS ORR of 71.7%.[23]

Additional systemic therapies with demonstrated efficacy for treating BrM include immune checkpoint inhibitors and BRAF/MEK inhibitors that are frequently used to treat patients with metastatic melanoma. Approximately 25% of patients have BrM at the time of melanoma diagnosis, and up to 75% of patients will eventually develop BrM during their lifetime.[19] Clinical trials examining the combination of ipilimumab and nivolumab for patients with metastatic melanoma and asymptomatic BrM established this combination to be a valuable treatment with intracranial response rates over 50%.[24,25] The CheckMate-204 trial reported an IC-ORR of 55% among 101 patients with melanoma and asymptomatic BrM, and 17% among 18 patients with symptomatic BrM.[24] BRAF V600E-mutated melanoma is associated with a higher risk of BrM; for this population, therapies targeting BRAF and MEK (i.e. dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib) have been approved as the standard of care usually after disease progression on immunotherapy.[26] BRAF/MEK inhibitor combinations cross the BBB, and are associated with intracranial response rates of up to 59% for oral dabrafenib plus trametinib among patients with BRAFV600E-positive metastatic melanoma and asymptomatic BrM.[27] A recent randomized trial examining the combination of relatlimab, a lymphocyte activation gene-3 (LAG-3)-blocking antibody, and nivolumab in patients with treatment-naïve unresectable Stage III or IV melanoma reported a 4% decrease

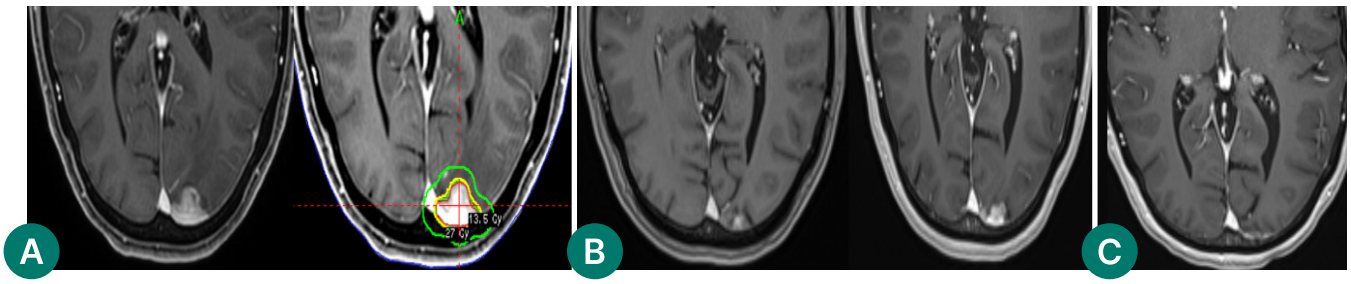

Figure 2. (A) Patient with HER2⁺ (IHC 3+) breast cancer with a brain metastasis treated with SRS (27 Gy in 3 fractions) with good response. **(B)** Two years later while continuing trastuzumab/pertuzumab had evidence of growth with perfusion imaging suggesting recurrence. **(C)** Following 3 cycles of trastuzumab deruxtecan a dramatic response is observed; *courtesy of Jie Wei Zhu, MD, Ines B. Menjak, MD, Arjun Sahgal, BSc, MD, FRCPC, and Katarzyna J. Jerzak, MD, MSc, FRCPC*.

Abbreviations: IHC: immunohistochemistry, **SRS:** stereotactic radiosurgery

in the frequency of new CNS metastases with relatlimab and nivolumab compared to nivolumab alone (5% vs. 9%, respectively).[27] Further, this study found that relatlimab and nivolumab extended the median time to development of CNS metastases from 6.6. months to 11.1 months.[28]

While there is optimism for the use of systemic therapies for BrM, it is prudent to be cautious and adopt a multi-disciplinary approach to treatment with review by neurosurgeons, CNS radiation oncologists, and medical oncologists. There are several factors to consider when selecting the best treatment approach, including patient factors (i.e., number and location of BrM, patients' neurological symptoms and functional status), tumour biology (biomarker status and likelihood of IC-ORR), and prior treatment history. In some cases, multimodal treatment may be an option; however, in cases where radiation has already been maximized, systemic therapy may be a more attractive option, but has been poorly studied in this setting (**Figure 2**). The use of systemic therapies first is attractive as this is a strategy that can potentially avoid radiation-associated toxicities, such as radiation necrosis. This may be of particular concern with the advent of ADCs, which are associated with an increased risk of symptomatic radiation necrosis with a 2-year risk of 42% for patients with HER2⁺ MBC receiving trastuzumab deruxtecan or sacituzumab govitecan concurrently with SRS; in contrast, the risk of radiation necrosis is much lower (only 9%) when ADCs and radiation therapy are used sequentially.[29] Another retrospective study including 67 patients with HER2⁺ breast cancer with BrM also reported a significantly higher risk of radiation necrosis associated with T-DM1 exposure following SRS (p =0.02), with an overall probability of post-SRS radiation necrosis of 21.6%.[30] As such, caution should be taken to mitigate the risk of radiation necrosis with the increasingly widespread usage of ADCs for other disease sites.

Future efforts should be directed towards encouraging enrolment of patients with BrM in clinical trials, especially when CNS efficacy of investigational agents is expected. This has been reviewed by Corbett et al.; while 56% of phase III clinical trials evaluating the efficacy of systemic therapies in metastatic lung cancer, breast cancer, and melanoma enroled patients with BrM, there is still room for progress.[31] Further, including patients with BrM in clinical trials may accelerate the investigation into biomarkers to enable a better understanding of the biology of BrM, predictive markers of response, and mechanisms of resistance to evaluated therapies, as well as novel therapeutic targets.[32]

Future trials should also determine whether therapies effective in the metastatic setting may have utility in the prevention of BrM. The HER2CLIMB-05 trial (NCT05132582), which is evaluating the efficacy of first-line maintenance tucatinib, will also investigate whether this small molecule TKI can reduce the incidence of BrM among patients with newly diagnosed HER2⁺ MBC. In the early-stage setting, the CompassHER2-RD trial (NCT04457596) is evaluating the addition of tucatinib to T-DM1 for patients with residual HER2⁺ breast cancer following neoadjuvant HER2-directed therapy. Therapies that can prevent the development of BrM are of significant interest and represent an important unmet need; a nomogram to predict development of BrM among

patients with various solid tumours would be of value and could help inform inclusion criteria for future prevention trials.

Another area of unmet need is the evaluation of CNS-active systemic therapies among patients with leptomeningeal disease (LMD), which are associated with a particularly short survival. A recent systematic review demonstrated that none of the 244 phase III trials reported LMD-specific outcomes and only 5.3% of studies included CNS-specific outcomes.[33] Brastianos et al. identified that single agent immune checkpoint inhibitor is an effective treatment option among patents with breast, lung, and ovarian cancer and LMD; evaluation of future combination therapies, ideally in randomized trials, would be of high interest.[34] Therapies for patients with LMD originating from breast, melanoma, and NSCLC have been recently reviewed.[35-37] The recent BLOSSOM phase II trial examining the efficacy of osimertinib among 73 patients with EGFR-mutated NSCLC who developed LMD following prior TKI therapy reported an objective response rate for LMD of 52%, although larger studies are required to validate these findings.[38] Several novel therapeutic approaches are also being investigated; examples include the use of intrathecal treatment with nivolumab and ipilimumab (NCT055988530), as well as liposomal-rhenium-186, a novel radioligand therapy that is encapsulated in nanoliposomes (NCT05034497).

Increasing attention to solid tumours that are less likely to metastasize to the brain is required. For example, patients with gastrointestinal and gynecological malignancies are living longer and may experience metastases to the brain, with an emerging need for tumour-agnostic BrM trials, particularly when systemic therapies with a high likelihood of CNS efficacy are available across different primary tumour subtypes.

Conclusion

In conclusion, BrM represent a significant challenge in the treatment of patients with solid tumours. Recent advancements in systemic therapies for BrM including TKIs, ADCs and immune checkpoint inhibitors have improved patients' outcomes. Future efforts should be directed towards understanding the molecular drivers of BrM and therapies to prevent their development.

Correspondence

Katarzyna Joanna Jerzak, MD
Email: katarzyna.jerzak@sunnybrook.ca

Financial Disclosures

J.W.Z.: None declared.
I.B.M.: None declared.
A.S.: None declared.
K.J.J.: Speaker/advisor board/consultant for: Amgen, AstraZeneca, Apo Biologix, Daiichy Sankyo, Eli Lilly, Esai, Genomic Health, Gilead Sciences, Knight Therapeutics, Merck, Myriad Genetics Inc, Pfizer, Roche, Seagen, Novartis, Organon, Viatris;
Research funding: AstraZeneca, Eli Lilly, Seagen

References

1. 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): 2865–2872. doi: 10.1200/JCO.2004.12.149.
2. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO Guideline. J Clin Oncol 2022;40(05):492–516. doi: 10.1200/JCO.21.02314.
3. Yamamoto M, Serizawa T, Sato Y, Higuchi Y, Kasuya H. Stereotactic radiosurgery results for patients with 5-10 versus 11-20 brain metastases: a retrospective cohort study combining 2 databases totaling 2319 patients. World Neurosurg 2021;146: e479–e491. doi: 10.1016/j.wneu.2020.10.124.
4. Balasubramanian SK, Sharma M, Venur VA, et al. Impact of EGFR mutation and ALK rearrangement on the outcomes of non-small cell lung cancer patients with brain metastasis. Neuro-oncol 2020;22(02):267–277. doi: 10.1093/neuonc/noz155.
5. Sahgal A, Ruschin M, Ma L, Verbakel W, Larson D, Brown PD. Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues. Neuro Oncol. 2017;19(suppl_2):ii2-ii15. doi:10.1093/neuonc/nox001.
6. Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Primers. 2019;5(1):66. doi:10.1038/s41572-019-0111-2.
7. Gwak HS. Molecular biology of brain metastases. Brain Tumor Res Treat. 2023 Jan;11(1):8-15. doi: 10.14791/btrt.2022.0045.
8. Arvanitis, C. D., Ferraro, G. B. & Jain, R. K. The blood–brain barrier and blood–tumour barrier in brain tumours and metastases. Nat Rev Cancer 20, 26–41 (2020). doi: 10.1038/s41568-019-0205-x.

9. Mair MJ, Bartsch R, Le Rhun E, et al. Understanding the activity of antibody-drug conjugates in primary and secondary brain tumours. Nat Rev Clin Oncol. 2023;20(6):372-389. doi:10.1038/s41571-023-00756-z.
10. Solomon BJ, Cappuzzo F, Felip E, et al. Intracranial efficacy of crizotinib versus chemotherapy in patients with advanced ALK-positive non-small-cell lung cancer: results from PROFILE 1014. J Clin Oncol 2016;34(24):2858–2865. doi: 10.1200/JCO.2015.63.5888.
11. Peters S, Camidge DR, Shaw AT, et al; ALEX Trial Investigators. Alectinib versus crizotinib in untreated ALK-positive non-small cell lung cancer. N Engl J Med 2017;377(09):829–838. doi: 10.1056/NEJMoa1704795.
12. Soria JC, Tan DSW, Chiari R, et al. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open label, phase 3 study. Lancet 2017;389(10072):917–929. doi: 10.1016/S0140-6736(17)30123-X.
13. Shaw AT, Bauer TM, de Marinis F, et al; CROWN Trial Investigators. First-line lorlatinib or crizotinib in advanced ALK-positive lung cancer. N Engl J Med 2020;383(21):2018–2029. doi: 10.1056/NEJMoa2027187.
14. Erickson AW, Brastianos PK, Das S. Assessment of effectiveness and safety of osimertinib for patients with intracranial metastatic disease: A systematic review and meta-analysis. JAMA Netw Open. 2020;3(3):e201617. doi:10.1001/jamanetworkopen.2020.1617.
15. Pike LRG, Miao E, Boe LA, et al. Tyrosine Kinase Inhibitors with and Without Up-Front Stereotactic Radiosurgery for Brain Metastases From EGFR and ALK Oncogene-Driven Non-Small Cell Lung Cancer (TURBO-NSCLC). J Clin Oncol. Published online July 24, 2024. doi:10.1200/JCO.23.02668.
16. Lu S, Kato T, Dong X, et al. Osimertinib after Chemoradiotherapy in Stage III EGFR-Mutated NSCLC. N Engl J Med. 2024;391(7):585-597. doi:10.1056/NEJMoa2402614.
17. Saura C, Garcia-Saenz JA, Xu B, et al. Safety and efficacy of neratinib in combination with capecitabine in patients with metastatic human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2014;32(32):3626–33. doi: 10.1200/JCO.2014.56.3809.
18. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs placebo, both in combination with trastuzumab and capecitabine, for previously treated ERBB2 (HER2)-positive metastatic breast cancer in patients with brain metastases: updated exploratory analysis of the HER2CLIMB. doi: 10.1001/jamaoncol.2022.5610.
19. Cagney DN, et al. Incidence and prognosis of patients with brain metastases at diagnosis of systemic malignancy: a population-based study. Neuro Oncol. 2017;19(11):1511–21. https://doi. org/10.1093/neuonc/nox077.
20. Montemurro F, Delaloge S, Barrios CH, et al. Trastuzumab emtansine (T-DM1) in 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):1350-1358. doi:10.1016/j.annonc.2020.06.020.
21. Bartsch R, Berghoff AS, Furtner J, et al. Trastuzumab deruxtecan in HER2-positive breast cancer with brain metastases: a single-arm, phase 2 trial. Nat Med. 2022;28(9):1840-1847. doi:10.1038/s41591-022-01935-8.
22. Hurvitz SA, Modi S, Li W, et al. 377O A pooled analysis of trastuzumab deruxtecan (T-DXd) in patients (pts) with HER2-positive (HER2+) metastatic breast cancer (mBC) with brain metastases (BMs) from DESTINY-Breast (DB) -01, -02, and -03. Ann Oncology. 2023;34(2):335-336. doi: 10.1016/j.annonc.2023.09.554
23. Harbeck N, Ciruelos E, Jerusalem G, et al. Trastuzumab deruxtecan in HER2-positive advanced breast cancer with or without brain metastases: a phase 3b/4 trial. Nat Med. Published online September 13, 2024. doi:10.1038/s41591-024-03261-7.
24. Tawbi HA, Forsyth PA, Hodi FS, et al. Long-term outcomes of patients with active melanoma brain metastases treated with combination nivolumab plus ipilimumab (CheckMate 204): final results of an open-label, multicentre, phase 2 study. Lancet Oncol. 2021;22(12):1692-1704. doi:10.1016/S1470-2045(21)00545-3.
25. Long GV, 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. doi: 10.1016/S1470-2045(18)30139-6.
26. Eroglu Z, Ribas A. Combination therapy with BRAF and MEK inhibitors for melanoma: latest evidence and place in therapy. Ther Adv Med Oncol. 2016;8(1):48–56. doi: 10.1177/ 1758834015616934.
27. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. Lancet Oncol. 2017;18(7):863-873. doi:10.1016/S1470-2045(17)30429-1.
28. Tawbi HA, Schadendorf D, Lipson EJ; RELATIVITY-047 Investigators. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N Engl J Med. 2022;386(1):24-34. doi: 10.1056/NEJMoa2109970.
29. Lebow ES, Pike LRG, Seidman AD, Moss N, Beal K, Yu Y. Symptomatic necrosis with antibody-drug conjugates and concurrent stereotactic radiotherapy for brain metastases. JAMA Oncol. 2023;9(12):1729-1733. doi:10.1001/jamaoncol.2023.4492.
30. Id Said B, Chen H, Jerzak KJ, et al. Trastuzumab emtansine increases the risk of stereotactic radiosurgery-induced radionecrosis in HER2 + breast cancer. J Neurooncol. 2022;159(1):177-183. doi:10.1007/s11060-022-04055-y.

31. Corbett K, Sharma A, Pond GR, et al. Central nervous system-specific outcomes of phase 3 randomized clinical trials in patients with advanced breast cancer, lung cancer, and melanoma. JAMA Oncol. 2021;7(7):1062-1064. doi:10.1001/jamaoncol.2021.1359.
32. Lazaratos AM, Petrecca K, Guiot MC, Jerzak KJ, Dankner M. CNS activity of trastuzumab deruxtecan in HER2-expressing non-small-cell lung cancer. Lancet Oncol. 2024;25(7):e282. doi:10.1016/S1470-2045(24)00261-4.
33. Sharma, A. E., Corbett, K., Soliman, H., Sahgal, A., Das, S., Lim-Fat, M. J., & Jerzak, K. J. (2023). Assessment of phase 3 randomized clinical trials including patients with leptomeningeal disease: A systematic review. JAMA oncol, 9(4), 566–567. doi: 10.1001/jamaoncol.2022.7364
34. Brastianos PK, Lee EQ, Cohen JV, et al. Single-arm, open-label phase 2 trial of pembrolizumab in patients with leptomeningeal carcinomatosis [published correction appears in Nat Med. 2020 Aug;26(8):1309. doi: 10.1038/s41591-020-0978-1]. Nat Med. 2020;26(8):1280-1284. doi:10.1038/s41591-020-0918-0.
35. Bartsch R, Jerzak KJ, Larrouquere L, Müller V, Le Rhun E. Pharmacotherapy for leptomeningeal disease in breast cancer. Cancer Treat Rev. 2024;122:102653. doi:10.1016/j.ctrv.2023.102653.
36. Khaled ML, Tarhini AA, Forsyth PA, Smalley I, Piña Y. Leptomeningeal disease (LMD) in patients with melanoma metastases. Cancers (Basel). 2023;15(6):1884. doi:10.3390/cancers15061884.
37. Wang Y, Yang X, Li NJ, Xue JX. Leptomeningeal metastases in non-small cell lung cancer: Diagnosis and treatment. Lung Cancer. 2022;174:1-13. doi:10.1016/j.lungcan.2022.09.013.
38. Park S, Baldry R, Jung HA, et al. Phase II Efficacy and Safety of 80 mg Osimertinib in Patients With Leptomeningeal Metastases Associated With Epidermal Growth Factor Receptor Mutation-Positive Non-Small Cell Lung Cancer (BLOSSOM). J Clin Oncol. 2024;42(23):2747-2756. doi:10.1200/JCO.24.00708.