Neuro-Oncology Advances
7(1), vdaf049, 2025 | https://doi.org/10.1093/noajnl/vdaf049 | Advance Access date 4 March 2025

Consortium for Intracranial Metastasis Academic Research (CIMARa): Global interdisciplinary collaborations to improve outcomes of patient with brain metastases

Carey K. Anders*, Amanda E. D. Van Swearingen*, Josh Neman, Johanna A. Joyce, Diana M. Cittelly, Manuel Valiente, Alexandra S. Zimmer, Scott R. Floyd, Ajay Dhakal, Soma Sengupta, Manmeet S. Ahluwalia, Seema Nagpal, Priya U. Kumthekar, Sam Emerson, Reva Basho, Kathryn Beal, Nelson S. Moss, Evangelia D. Razis, Jonathan T. Yang, Sarah L. Sammons, Solmaz Sahebjam, Hussein A. Tawbi and , on behalf of CIMARa

All author affiliations are listed at the end of the article

Corresponding Authors: Carey K. Anders, MD, Duke Center for Brain and Spine Metastasis, DUMC #3381, Duke Cancer Institute, Seeley Mudd Building, Room 440, Durham, North Carolina, 27710, USA (carey.anders@duke.edu); Amanda E. D. Van Swearingen, PhD, Duke Center for Brain and Spine Metastasis, Duke Cancer Institute, Durham, NC, USA (amanda.vanswearingen@duke.edu)

*Authors contributed equally to the preparation of this manuscript.

Abstract

Brain metastases (BrM) arising from solid tumors is an ever-increasing and often devastating clinical challenge impacting hundreds of thousands of patients annually worldwide. As systemic anticancer therapies, and thus survival, improve, the risk for central nervous system (CNS) recurrence has increased. Historically, patients with BrM were excluded from clinical trials; however, there has been a shift toward increasing inclusion over the past decade. To most effectively design the next generation of clinical trials for patients with BrM, a multidisciplinary team spanning local and systemic therapies is imperative. CIMARa (Consortium for Intracranial Metastasis Academic Research), formalized in June 2021, is an inclusive group of multidisciplinary clinical investigators, research scientists, and advocates who share the collective goal of improving outcomes for patients with BrM. CIMARa aims to improve outcomes through the development, coordination, and awareness of multi-institutional clinical trials testing novel therapeutic agents for this unique patient population alongside the translation of preclinical research to the clinical setting.

Key Points

- CIMARa is focused on improving outcomes for patients with CNS metastases.
- CIMARa spans primary cancer types and includes collaboration with non-profit organizations and advocates.
- CIMARa includes global members across a spectrum of disciplines.

Brain metastases (BrM) arising from solid tumors is a growing clinical challenge that is impacting hundreds of thousands of patients annually worldwide. As systemic anticancer therapies and thus survival improve, the risk for central nervous system (CNS) metastases has been increasing. Historically, patients with BrM were excluded from clinical trials; yet there has been a shift in the tide over the past decade. To most effectively design the next generation of clinical trials for patients with BrM, including those with leptomeningeal disease (LMD), we recognized a growing need for a platform to bring together a

© The Author(s) 2025. Published by Oxford University Press, the Society for Neuro-Oncology and the European Association of Neuro-Oncology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (https://creativecommons.org/licenses/by-nc/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact reprints@oup.com for reprints and translation rights for reprints. All other permissions can be obtained through our RightsLink service via the Permissions link on the article page on our site—for further information please contact journals.permissions@oup.com.

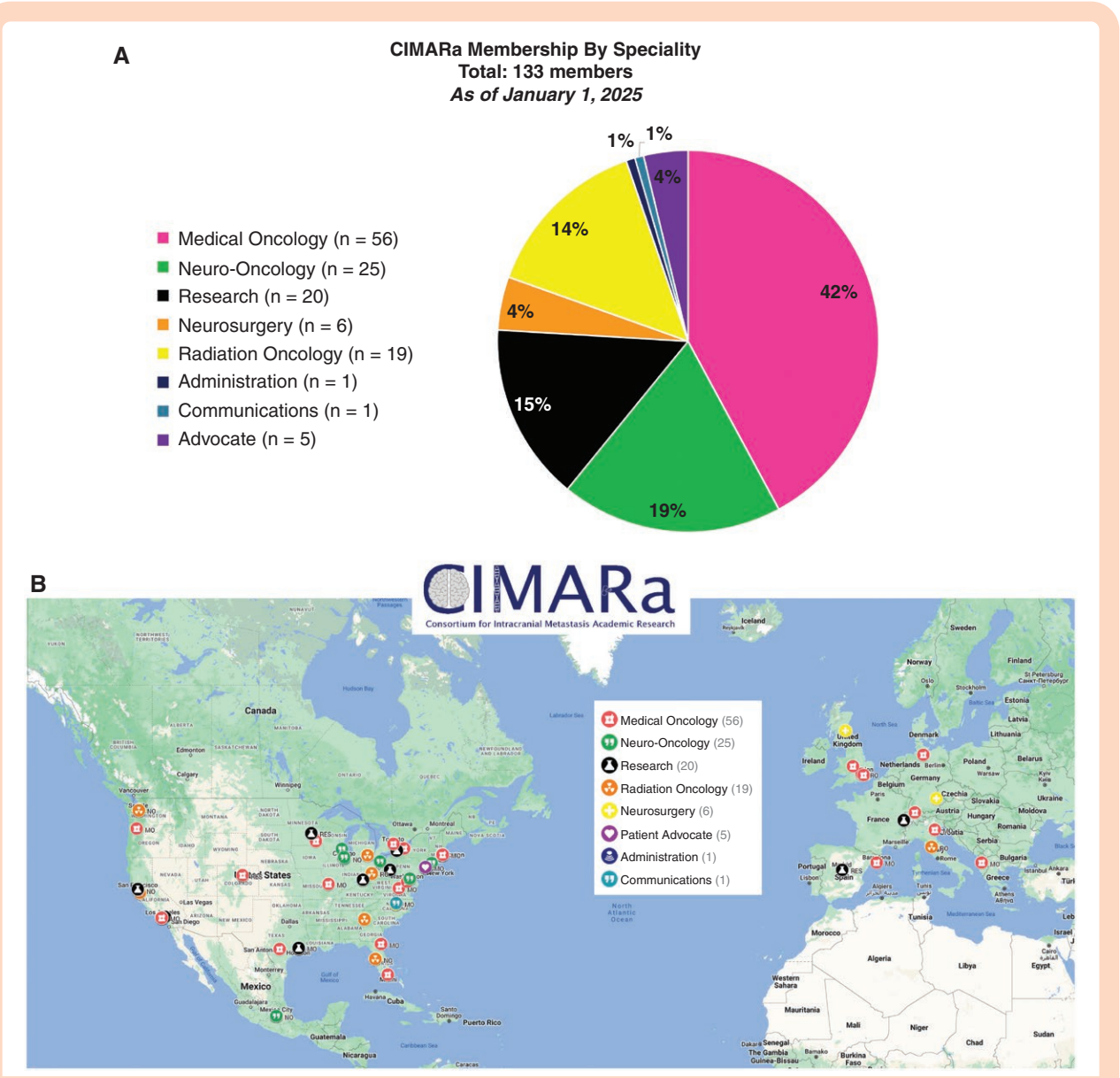

Figure 1. CIMARa membership. (A) Distribution of specialties within CIMARa membership. (B) Map of CIMARa members (n = 133) by institution (n = 62) and specialty, as of January 1, 2025.

multidisciplinary team of experts, spanning local and systemic therapies, basic and translational science, and clinical research to move the field forward.

CIMARa (Consortium for Intracranial Metastasis Academic Research) was formalized in June 2021 and is inclusive of a group of international, multidisciplinary clinical investigators, basic and translational research scientists, and advocates who share the collective goal of improving outcomes for patients with CNS metastases arising for any solid tumor type. CIMARa aims to improve outcomes through the development, coordination, and awareness of multi-institutional clinical studies, including those evaluating novel therapeutic agents for this unique patient population. Membership spans multiple specialties, including medical oncology, radiation oncology, neurosurgery, neuroradiology, neuropsychology, palliative care, non-profit and patient advocacy partners, and basic/translational research (**Figure 1a**). As of January 1, 2025, membership includes over 133 members from over 60 institutions and organizations across 9 countries (**Figure 1b**). Four non-profit organizations focused on patients with BrM are involved. While many of the CIMARa members and organizations have been focused on BrM research independently, CIMARa provides a unique platform to bring "like-minded" individuals together in a collaborative way to exchange ideas, collaborate on research initiatives, and raise awareness about the critical importance of research in this previously understudied disease state with the common goal of improving survival, and survivorship, for patients with CNS metastases.

To accomplish CIMARa's goals, the consortium has developed 4 main focus areas including (1) the establishment of a national and international infrastructure to enhance the discovery and development of CNS metastases therapies. This could include the graduation of preclinical agents to clinical trial evaluation, coordination of multi-institutional retrospective studies examining a defined question, and promotion of multi-institutional clinical trials driven by traditional outcomes, molecular and/or novel neuroimaging endpoints. Focus areas include molecularly targeted therapies and immunotherapies, as well as combination and sequencing strategies of local and systemic therapies. Importantly, this team focuses on the enhancement of the quality of life and mitigation of late-stage effects of therapies for patients with CNS metastases. Additional goals of CIMARa are to (2) provide a network of investigators who understand and are willing to advance and implement multicenter clinical trial opportunities for patients living with BrM and/or LMD, (3) develop opportunities to harmonize trial endpoints regarding CNS metastases across clinical trials, and (4) provide a common web-based forum for patients and providers to learn about clinical trial opportunities focused on patients with CNS metastases. In an effort to illustrate the work of CIMARa across the lifecycle of CNS metastases research, we will provide an overview of the manner in which CIMARa is promoting collaborative research from the basic to the translational and clinical trials perspective. In addition, we will outline our collective current and future efforts in patient education and outreach for patients living with BrM and LMD.

Focus on Basic Research Projects

As with many clinical discoveries in the field of oncology, the basis for initial investigation is rooted in sound preclinical rationale. This is no different in the field of CNS metastases. A unique feature of preclinical research in the setting of CNS metastases is the examination of the contribution of the brain microenvironment.[1] The brain's microenvironment, distinct from other organs, presents a formidable obstacle to invading tumor cells. At the forefront of this are 2 barriers: (A) the blood-brain barrier (BBB), a complex network of endothelial cells, pericytes, and astrocytes, and (B) the blood-cerebral-spinal fluid barrier (BCSFB) located at the choroid plexus within the brain's ventricles. Both the BBB and BCSFB exquisitely regulate the passage of molecules and cells into the brain parenchyma and leptomeningeal space. However, metastatic cells have evolved sophisticated strategies to breach these barriers, exploiting mechanisms such as the upregulation of adhesion molecules, secretion of proteolytic enzymes, and manipulation of endothelial cell junctions. Unraveling the interplay between cancer cells and the brain microenvironment lends itself to intervening therapeutically on these dependencies to prevent both the development and propagation of tumor cells in the CNS.[2]

Once within the brain, metastatic cells encounter neuroinflammatory mediators, including cytokines, chemokines, and growth factors, which foster a permissive environment for tumor growth and invasion. The neural niche contributes extensively to the establishment of metastases. Studies have demonstrated the significance of astrocytes as requisites for successful tumor colonization in the brain. As an example, estrogen-activated astrocytes were shown to promote metastatic colonization by triple negative breast cancer cells[3,4] yielding possible interventions focused on downregulation of estradiol. Recent work has also shown a pivotal role of the brain microenvironment, including microglia, neutrophils, astrocytes, and the tumor vasculature, in shaping the tumor microenvironment and modulating immune responses.[5–8] For example, astrocytes induce epigenetic silencing of the tumor suppressor PTEN in brain metastatic cells. This is accomplished by the release of astrocytic exosomes containing PTEN-targeting miRNA, after which tumor cells induce CCL2.[9] This recruits myeloid cells that promote the outgrowth of BrM, by increasing proliferation and limiting apoptosis.[9]

Preclinical studies have reported the acquisition of neuronal characteristics in BrM and enhanced expression of neurotransmitter receptors in aggressive breast cancers that prime them to successfully metastasize to the brain.[10,11] Specifically, breast to BrM cells display a GABAergic phenotype and show increased expression mediators of the GABA metabolic shunt resulting in increased proliferative capacity; similar phenomena have been observed in non-small-cell lung cancer BrM[12] and metastatic melanoma.[13–15] Moreover, within the neuronal niche, astrocytes secrete Reelin, an extracellular matrix molecule, which drives the proliferation of $HER2^{+}$ breast cancer cells.[16] A deeper understanding of the biology of CNS metastases as illustrated by representative preclinical discoveries outlined above provides the scientific rationale for clinical translation across the CIMARa team, inclusive of basic scientists and clinical translational researchers. The value and potential of basic research by members of CIMARa to generate clinical trials and interventions is highlighted by the fact that there are already examples of preclinical discoveries[17] being translated to interventional and therapeutic clinical trials (NCT05689619) for patients with BrM.

Focus on Translational and Retrospective, Real-World Projects

The framework of CIMARa provides a platform to catalyze collaborations globally, thereby facilitating the bench-to-bedside translation. One such integrative effort corresponds to the establishment of patient-centered networks in cancer research that are emerging in several countries.[18] If these national efforts are to be expanded and put forward to serve the broad scientific community under the FAIR (Findable, Accessible, Interoperable and Reproducible) principles, they will surely provide faster and more efficient bench-to-bedside transfer of novel findings.

The evaluation of new agents or novel strategies of treatment should be instigated utilizing the CIMARa structure, based on strong collaboration between preclinical and clinical researchers which is at the core of this consortium's goals.[19,20] In addition, the possibility to establish and study patient-derived organotypic cultures[21–24] from trials ongoing in different international teams will maximize the

Table 1. Real-World Data Retrospective Studies in Cohorts of Patients With CNS Metastasis

Authors	Tumor type	Description	Location (Continent)
Lee et al. 2019[27]	Non-small cell lung cancer	A retrospective nationwide (S. Korea) cohort study which compared incidence of BrM among patients with NSCLC who were treated with chemotherapy vs. targeted therapy.	Asia
Carron et al. 2020[28]	Melanoma	Provides a safety and efficacy analysis of stereotactic radiosurgery combined with anti-PD1 therapy for management of melanoma BrM.	Europe
Benna et al. 2018[29]	All tumor types	Provides an epidemiology of BrM in Tunisia.	Africa
Kabraji et al., 2023[25*]	Breast cancer	Reports data on efficacy of trastuzumab deruxtecan on parenchymal BrM disease preclinically and clinically from HER2+ breast cancer.	North America
Alder et al. 2023[26*]	Breast cancer	Reports data on efficacy of trastuzumab deruxtecan on LMD from HER2+ breast cancer.	North America

*CIMARa study. BrM = brain metastasis; LMD = leptomeningeal disease; NSCLC = non-small-cell lung cancer.

output of any clinical effort since ex vivo cultures will expand the value of the clinical trial beyond its specific scope (i.e., additional therapy combinations, toxicity, mechanisms of resistance). Furthermore, the academic nature of CIMARa should help promote data sharing including not only patient samples but also the information associated with them (i.e., omics) by creating data portals that are publicly available.

As one of the unique challenges to developing new therapeutics that are effective against BrM is the BBB, it is critical to determine whether a novel therapeutic can reach its intended target in the brain. Negative data from traditional early-phase trials focused on toxicity and efficacy may disqualify agents with potential for combination with other therapies or indications in different primary tumor types. Studies that harvest tissue following drug administration are critical, especially for BrM because demonstration of brain penetrance and on-target brain activity can justify "second-chance" strategies by combining with other potential synergistic therapies and/or expanded patient cohorts. Such trials can also validate biomarker strategies to identify ideal target patient populations. These "window of opportunity trials" are difficult owing to challenges to identify adequate numbers of appropriate patients, especially in the single-institution setting. By synergizing across institutions, CIMARa will catalyze window of opportunity trials (such as NCT03995706, NCT06058988, and NCT05620914) that can generate key early data regarding biomarkers of on-target activity for novel therapeutics.

In order to improve overall outcomes for patients with BrM, we must continue to generate novel hypotheses regarding approaches to patient care and therapy. Large patient cohorts with clearly annotated clinical outcomes are uncommon, as single-institution cohorts often lack the numbers of patients needed to adequately investigate a hypothesis. Furthermore, patients with CNS metastases are often excluded from many larger, multi-institution, prospective trials. CIMARa efforts have tackled this challenge by creating datasets of patients pooled across institutions with common outcome measures to identify rare patient subsets, resulting in important new hypotheses for BrM treatment.[25,26] Moreover, efforts are currently underway to develop even larger databases to collect data toward improved management of side effects of treatment, such as radiation necrosis (RN), a significant challenge for patients whose BrM are treated with stereotactic radiosurgery (SRS). Such coordinated and combined efforts across institutions will help generate robust datasets of larger cohorts of patients similar to those in **Table 1** and will enable more detailed investigations into clinical questions with more statistical rigor.

As CIMARa's platform spans different continents and includes CNS metastasis investigators from various disciplines, it is poised to develop and conduct extensive and meaningful retrospective projects for patients with BrM and LMD. Via CIMARa, multiple institutions from across the globe can share clinical data to generate large retrospective studies. Our consortium members have already published retrospective studies demonstrating the activity of antibody-drug conjugate trastuzumab deruxtecan against BrM and LMD from breast cancer.[25,26] A study of real-world experience with the antiangiogenic agent bevacizumab for RN, estimating involvement of 17 CIMARa sites and nearly 1700 patients, is ongoing with results anticipated within the next year. Other large-scale, multi-institutional projects evaluating clinically meaningful questions in the field of BrM and LMD are in development with impactful results anticipated in the coming years; CIMARa provides the perfect platform for this type of investigation.

Focus on Clinical Research Projects

As previously discussed, clinical trials testing new therapeutics and diagnostics have historically excluded all patients with BrM, both parenchymal and leptomeningeal. Fortunately, in the past decade, we have seen strong advocacy from multiple organizations, including the US National Cancer Institute (NCI) and the US Food and Drug Administration (FDA), to increase access to trials for patients with CNS metastases. Designing and running successful clinical trials of systemic therapy in patients with BrM and LMD requires attention to multiple considerations

unique to the CNS. Given the protective barriers that the CNS innately possesses (i.e., BBB, BCSFB, and efflux pumps), an understanding of the penetrability of a given therapeutic must be considered. This involves understanding size, lipophilicity, and whether or not the therapy is a substrate for glycoprotein efflux pumps. Ideally, CNS penetration should be established early in the development pathway, in preclinical models and phase 0/phase 1 clinical trials, ideally using cerebral spinal fluid and/or window of opportunity studies for biomarker development. In diseases with multiple agents competing in the same space (i.e., EGFR and ALK NSCLC, HER2+ breast cancer), including cohorts of CNS patients earlier may also confer an advantage to those who can present clearer evidence of CNS penetration and activity.

A successful study of systemic therapy in patients with BrM and/or LMD requires the use of clinically relevant endpoints and outcome measures. The RANO group has designed both BrM-specific and LMD-specific recommendations.[30–32] However, neither of these has yet been validated in prospective studies. A rationally designed study will need to address using (or not) separate criteria for BrM versus systemic metastases, clearly define an "active" BrM (e.g., has this been treated with SRS or systemic therapy before?), and define target lesions that are clinically relevant. For example, the 1 cm minimum for RECIST (or 1 × 1cm for RANO) is in opposition to how many clinicians practice, referring for SRS well before a lesion grows to this size. In addition, if a patient has multiple BrM and all but one stabilize on a therapy, does that define a treatment failure and require the patient to come off study? Predefined standard MRI brain and spine protocols should be included as part of the diagnostic imaging section.[33] Furthermore, with response rates previously low in the CNS prior to the advent of targeted agents and checkpoint inhibitors, and the high probability of discordant CNS versus systemic response, overall survival and CNS-specific progression-free survival (CNS-PFS) may be preferable endpoints. Overall survival as an endpoint also poses a challenge as it does not account for the cause of mortality, for instance, intracranial progression resulting in neurologic death versus extracranial progression or both. Therefore, consideration of the primary driver of mortality may help identify agents that are preferentially effective in the CNS. Standardizing and validating assessment and endpoint selection is crucial for the field to advance. The CIMARa consortium provides a platform for investigators to align on the selection of best endpoints, and hence, trial design, thereby enabling consistency in definitions and endpoints across trials.

As systemic therapies controlling extracranial disease improve, the incidence of CNS metastases is rising. Therefore, it is also increasingly critical to incorporate CNS recurrence endpoints across our trials of adjuvant, neoadjuvant, and metastatic therapies, even in the absence of active CNS disease. In operable HER2+ breast cancer, for example, a phase 3 trial of adjuvant T-DM1 versus continued trastuzumab in patients with residual disease after neoadjuvant chemotherapy and HER2-directed therapy including trastuzumab demonstrated improvement in invasive disease-free survival with T-DM1, but the incidence of CNS recurrence was similar across both arms.[34,35] This study highlighted the need to develop CNS-preventative therapies in patients with residual HER2+ breast cancer after neoadjuvant therapy. An ongoing trial, Compass-RD, is randomizing patients with residual HER2+ breast cancer after neoadjuvant therapy to adjuvant T-DM1 plus placebo vs the CNS-penetrant HER2 tyrosine kinase inhibitor tucatinib (NCT04457596), and BrM-free survival is a secondary endpoint. Several CIMARa investigators are participating.

Another important area of clinical need is secondary prevention in the CNS after the development of CNS metastases. In patients who develop low-volume CNS disease which is treated with locoregional therapies including resection and/or SRS, there is a need to optimize systemic therapy to prevent additional CNS lesions. Incorporation of secondary endpoints such as CNS lesion-free survival and time to the next CNS event is crucial to understanding the preventative abilities of our systemic therapies in such contexts. In addition, a number of such patients may have control of their systemic disease, and clinical trials focused on secondary prevention of CNS disease can optimize the clinical management of these patients with treatment-sensitive diseases. The ongoing BRIDGET trial (NCT05323955) will address this question in the HER2+ breast cancer space by investigating whether the addition of tucatinib to standard-of-care trastuzumab/pertuzumab or T-DMI improves intracranial PFS in patients with a first or second intracranial recurrence amidst stable extracranial disease. Again, several CIMARa sites and investigators are participating.

In addition, treatment timing and sequencing is emerging as a critical element in these patients who nearly always require multimodal therapy: most often a combination of systemic cancer-directed therapy and radiotherapy, at times also surgical resection, and in rare cases edema- or necrosis-mitigating therapies. As new anticancer agents emerge, understanding CNS-relevant interactions will become increasingly important. For example, some systemic therapies,[36] including antibody-drug conjugates,[37,38] appear to increase the risk of RN when given concurrently with SRS, and steroids, which are often prescribed to counter cerebral edema, are postulated to interfere with immunotherapy.[39,40] Furthermore, adjuvant radiation in combination with neurosurgical resection of BrM appears to be best delivered within a narrow window postoperatively,[41] with radiation delivered beyond 30 days postoperatively increasing the risk of local recurrence. CNS radiation delivered too early may increase the risk of adverse radiation effects, although with non-definitive clinical validation.[42] The safety and efficacy of preoperative SRS as an alternative to postoperative SRS is also a topic of great interest,[43] and is being prospectively investigated in enrolling clinical trials (NRG BN012, NCT05438212). Prospectively pooling complex multiparametric datasets is necessary to account for the histologic/biologic, CNS-anatomic, treatment-related (including timing/sequencing), and other patient-specific confounding features at play.

Finally, long-term evaluation and management of any BrM treated with SRS (or WBRT) needs careful and consistent management and follow-up even in the absence of recurrent or active disease. RN is a common toxicity typically occurring 6–18 months following SRS that is well

recognized. There are also reports of cystic degeneration that can occur many years after SRS.[44] CIMARa has a subgroup studying the different long-term effects of radiation in the modern era but the risks associated with radiation therapy must be incorporated in clinical trial design as well.

Focus on Education and Outreach

*The treating providers.*CIMARa will lead not only in research but also in the teaching of the unique biology of CNS metastases and their microenvironment to the scientific and medical community. Improved education of clinicians managing CNS metastatic disease may lead to informed decision-making and improved patient outcomes. The educational efforts of CIMARa will be directed both at basic science advances and at clinical aspects of optimal management of our patients with CNS metastases.

At a clinical level, a key focus is the importance of the multidisciplinary approach to CNS metastases. The need for discussion of all such patients in specialty tumor boards cannot be reinforced enough. Fortunately, recent guidelines[45–47] have been developed and need to be communicated to all clinicians. Nevertheless, there is still a lack of consensus regarding the optimal sequencing of different treatment modalities, as modern systemic therapy is increasingly effective in the CNS, and there is more awareness of the potential interaction of systemic therapy and radiation therapy leading to increased toxicity. Furthermore, given the particularities of follow-up and response assessment in the CNS, the treating community should become aware of the special RANO criteria for BrM and LMD, as well as the eventuality of pseudoprogression, especially in the setting of immunotherapy (iRANO),[48] and the potential association with RN.[30–32] Mitigation and management of the latter will be an additional educational goal. Last, but not least, particular awareness needs to be increased and education focused on LMD, which is rare, but severe and increasing in incidence. Education regarding the recognition of LMD symptoms, appropriate diagnostic procedures, and potential therapeutic options, as well as the dire need for clinical trials is paramount.

Cancer survivorship and trials addressing the needs of BrM patients are critical in the palliative care arena. Staff in training must be educated particularly on the unique neurologic complications of CNS metastatic disease and their management, including the optimal use of antiepileptics and steroids, as well as anticoagulant treatment for thrombosis. In addition, patients with BrM are often drawn to integrative medicine to improve their quality of life.[49] An area of foremost importance is the identification of optimal study design for new treatment approaches to CNS metastasis and consistent use of optimal outcome measures. The diligent follow-up of the CNS in other studies also would contribute to accumulating data regarding screening and prevention which lags behind in breast cancer, for instance, compared to lung cancer and melanoma.

*The patients.*CIMARa is committed to raising awareness in patients, caregivers, and healthcare professionals on the landscape of CNS metastasis and the research being conducted in the field. Central to this goal is the objective of increasing recognition of ongoing clinical trials across institutions. CIMARa aims to ensure potential participants and providers are well-informed by compiling and disseminating key information on available clinical trials. Recognizing the importance of collaborative efforts, CIMARa also aims to actively engage with patient advocates and non-profit organizations such as the American Brain Tumor Association (ABTA) and the National Brain Tumor Society (NBTS) to elevate awareness and education specifically related to CNS metastasis. We strive to work synergistically to amplify the impact of their initiatives, such as the Metastatic Brain Tumor Collaborative and Workshop on CNS Metastases, driving a collective effort toward improving medical knowledge and clinical outcomes.

CIMARa is also committed to creating and promoting websites that offer patient-friendly information on clinical trials and care options. These online platforms serve as valuable tools by providing easily accessible and meaningful information for patients, caregivers, and healthcare professionals, promoting inclusivity and facilitating informed decision-making. In addition, they play an important role in demystifying complex medical research and fostering a sense of community. In summary, CIMARa works to increase clinical trials awareness, collaborate with organizations, and key stakeholders including patient advocates to promote education and awareness, and create and publicize user-friendly online resources. Through these objectives, CIMARa aims to bring the community together to advance CNS metastasis research and to enhance the overall inclusiveness and quality of patient care.

Summary

Multidisciplinary research spanning basic, translational, and clinical studies is essential to make meaningful impacts on outcomes, including quality of life, for patients with CNS metastases,[50] both BrM and LMD. The complexity of the biology of CNS metastases, including in part the unique microenvironment of the brain and the processes involved in reaching this organ from elsewhere in the body, necessitates collaborative studies from a diverse team with complementary expertise across cancer biology, neurobiology, immunology, and other specialties. The treatment of CNS metastases also requires a multidisciplinary approach involving specialists in medical oncology, radiation oncology, neurosurgery, neuroradiology, supportive care, and patient advocacy.[50–52] CIMARa provides a central location for individuals across all backgrounds and expertise to work on a common goal of improving outcomes for patients with BrM and LMD by providing opportunities for collaboration, awareness, and dissemination of information and ideas to a wider audience.

CIMARa can be followed on Bluesky through @cimaragroup.bsky.social or in the future online at our website (currently https://sites.google.com/view/cimaraduke/home). For information, please contact CIMARa by email at cimarainfo@gmail.com.

Keywords

brain metastases | central nervous system metastases | clinical trials | consortium | research

Funding

C.K.A. is a Translating Duke Health Scholar. S.R.F. receives salary support from National Institutes of Health (NIH) grants (5U01-TR003715-02, 5R44-CA228694-05/4R44-CA228694-05, 5R01-NS100866-05, and R21-AG077075-01). J.A.J. receives funding from the Swiss National Science Foundation Advanced Grant (TMAG-3_209224), Ludwig Institute for Cancer Research, Breast Cancer Research Foundation, and The Mark Foundation. D.M.C. receives funding from NIH (R37CA227984) and the US Department of Defense (DOD) (W81XWH-22-1-0042). M.V. receives funding through the European Research Council (ERC) (ID: 864759), Fundación AECC (PRYCO234528VALI), and Fundación La Caixa (HR23-00051). Investigators at Memorial Sloan Kettering are supported in part by NIH/National Cancer Institute (NCI) P30 CA008748.

Conflict of interest statement. C.K.A. reports research funding (grants or contracts) from PUMA, Lilly, Merck, Seattle Genetics, Nektar, Tesaro, G1-Therapeutics, ZION, Novartis, Pfizer, AstraZeneca, Elucida, Incyclix, Beigene; receipt of consulting fees from Genentech, Eisai, IPSEN, Seattle Genetics; Astra Zeneca, Novartis, Immunomedics, Elucida, Athenex, and Roche; and receipt of royalties from UpToDate and Jones and Bartlett outside the submitted work. J.A.J. has received research support for her laboratory from the Ludwig Institute for Cancer Research, the University of Lausanne, the Swiss National Science Foundation Advanced Grant (TMAG-3_209224), Breast Cancer Research Foundation, Carigest Foundation, and Fondation SIREC; consulting fees from t-Kinfe Therapeutics and Pionyr Therapeutics; honoraria for speaking at symposia organized by Bristol Meyer Squibb; and an unpaid role on the European Association for Cancer Research Board. D.M.C. has received research funding from the NIH (1R01CA290813-01, R37 CA227984-01) and DoD (BCRP BC210460); and honoraria from the University of Southern California, West Virginia University, and San Antonio Breast Cancer Symposium (SABCS); as well as support for attending a meeting from SABCS. M.V. reports receiving research funds from an AstraZeneca research grant; honoraria from MEDSIR; and a leadership/fiduciary role on the EANO Board and Metastasis Research Society Board. S.R.F. reports support from the American Cancer Society (grant MBGI-1252459) and the NIH (R21CA286097, U01TR003715). A.D. reports funding for a trial paid to the institution from Celcuity and Puma; service on the advisory board of Eli Lilly, Gilead Science, and AstraZeneca; honoraria from OncLive/MJH Life Sciences, WebMD, and Empire State Hematology/Oncology Society. S. Sengupta reports consulting fees from Mayfield Scholar Award (to institution) and Imvax; meeting attendance support from the Society of Neuro-Oncology, provisional patents (no royalties), and participation on a Data Safety Monitoring Committee/Advisory Board for Bexion. M.S.A. receives research funding (to institution) from NIH (1R01CA277728-01A1, 1R01CA264017-01A1), consulting fees from Bayer, Xoft, Apollomics, Viewray, Cairn Threrapeutics, Anheart Therapeutics, Theraguix, Menarini Ricerche, Sumitomo Pharma Oncology, Autem Therapeutics, GT Medical Technologies, Allovir, EquilliumBio, QV Bioelectronics, Servier Pharmaceuticals, Incyte, and Recordati; participates on a Data Safety Monitoring Board/Advisory Board for VBI Vaccines, Modifibioscience, and Bugworks; has stock/stock options in Mimivax, Cytodyn, MedimmovateAdvisors LLC, and Trisalus Lifesciences. S.N. reports consulting fees from Daiichi Sankyo, Novartis, Telix, Enclear, and Plus Therapeutics. P.U.K. reports receipt of grants/contracts from Genentech and Novocure; consulting fees from Belay Diagnostics, FYR Diagnostics, Plus Therapeutics, Enclear Therapeutics, Affinia Therapeutics, Biocept, Janssen, Bioclinica, Mirati, Novocure, Servier, Telix Pharmaceuticals, and Biodexa; honoraria from Seagen; a provisional patent (WO2016/205367) with no financial incentive or gain; and participation on a Data Safety Monitoring/Advisory Board for BPGBio and In8bio. R.B. reports receipt of grants/contracts (to institution) from Metavivor Foundation, Genentech, and AstraZeneca; consulting fees from AstraZeneca, Seattle Genetics, Genentech, Gilead, Pfizer, Novartis, and Eli Lilly; honoraria from MJH Healthcare, Medscape, Curio Science, MD Outlook, and Aptitude Health; meeting/travel support from MJH Healthcare; leadership/fiduciary role on a board/committee with NCI (ComboMATCH National PI), Roche (INAVO 122 and 123 Steering Committees), and AstraZeneca (DB-RESPOND Steering Committee), and employment with the Ellison Medical Institute. N.S.M. receives research funding (to institution) from AstraZeneca, GT Medical Technologies, and Amgen; consulting fees from AstraZeneca; and honoraria from Varian. E.D.R. reports receiving support for meeting attendance/travel from Gilead, Servier, Integris, AstraZeneca, BMS, Roch, Genesis Pharma, and Pfizer; and participation on a Data Safety Monitoring/Advisory Board with honoraria from AstraZeneca, Servier, and Novartis. S. Sammons reports consulting fees from Foundation Medicine, AstraZeneca, Daiichi Sankyo, Eli Lilly, Pfizer, Incyclix, Relay, Gilead, Sermonix, and Novartis; and research funding (to institution) from AstraZeneca, Eli Lilly, Relay, Seagen, Sermonix, and Novartis. S. Sahebjam reports receipt of honoraria from the National Cancer Institute and PDQ Editorial Board; has served on advisory board committees (with consulting compensation) for Pliant Therapeutics and Telix Pharmaceuticals; and has served in a leadership or fiduciary role for the Society for Neuro-Oncology (Co-Chair, Public Policy Committee). H.A.T. has received research funding from Bristol Myers-Squibb, Novartis, Merck, Genentech, Eisai, Dragonfly Therapeutics, GlaxoSmithKline, Regeneron, and Syntrix; and consulting fees from Bristol Myers-Squibb, Genentech, Merck, Novartis, Regeneron, Medicenna, Iovance, Eisai, Pfizer, Io Biotech, Krystal Biotech, T-Knife Therapeutics, Corcept Therapeutics, and Strand Therapeutics. The other authors (A.E.D.V., J.N., A.S.Z., S.E., K.B., J.T.Y.) have nothing to disclose.

Authorship Statement

Manuscript writing: C.K.A., A.E.D.V., J.N., J.A.J., M.V., A.S.Z., S.R.F., A.D., S.S., M.S.A., S.N., P.U.K., S.E., R.B., K.B., N.S.M., E.D.R., J.T.Y., S.L.S., H.A.T. Final version approval: C.K.A., A.E.D.V., J.N., J.A.J., D.C., M.V., A.S.Z., S.R.F., A.D., S.S., M.S.A., S.N., P.U.K., S.E., R.B., N.S.M., E.D.R., J.T.Y., S.L.S., H.A.T.

Affiliations

Duke Center for Brain and Spine Metastasis, Duke Cancer Institute, Durham, North Carolina, USA (C.K.A., A.E.D.V, S.R.F.); University of Southern California, Los Angeles, California, USA (J.N.); University of Lausanne, Ludwig Institute for Cancer Research, Lausanne, Switzerland (J.A.J.); University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA (D.M.C.); Brain Metastasis Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain (M.V.); Oregon Health

State University, Portland, Oregon, USA (A.S.Z.); Department of Radiation Oncology, Duke University, Durham, North Carolina, USA (S.R.F.); Department of Medicine, University of Rochester, Rochester, New York, USA (A.D.); Department of Neurology & Neurosurgery, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA (S.Sengupta); Miami Cancer Institute, Miami, Florida, USA (M.S.A.); Division of Neuro-oncology, Stanford University, Palo Alto, California, USA (S.N.); Northwester Medicine, Chicago, Illinois, USA (P.U.K.); Neurological Surgery, University of Washington, Seattle, Washington, USA (S.E.); Ellison Medical Institute, Los Angeles, California, USA (R.B.); Weill Cornell Medicine, New York, New York, USA (K.B.); Memorial Sloan Kettering Cancer Center, New York City, New York, USA (N.S.M.); Hygeia Hospital, Athens, Greece (E.R.); New York University, New York City, New York, USA (J.T.Y.); Dana Farber Cancer Institute, Boston, Massachusetts, USA (S.L.S.); Johns Hopkins School of Medicine, Baltimore, Maryland, USA (S.Sahebjam); Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Sibley Memorial Hospital, Washington, District of Columbia, USA (S.Sahebjam); Andrew M. McDougall Brain Metastasis Clinic and Research Program, University of Texas MD Anderson Cancer Center, Houston, Texas, USA (H.A.T.)

References

1. Quail DF, Joyce JA. The microenvironmental landscape of brain tumors. *Cancer Cell* 2017;31(3):326–341.
2. Saatian B, Deshpande K, Herrera R, et al. Breast-to-brain metastasis is exacerbated with chemotherapy through blood-cerebrospinal fluid barrier and induces Alzheimer's-like pathology. *J Neurosci Res.* 2023;101(12):1900–1913.
3. Sartorius CA, Hanna CT, Gril B, et al. Estrogen promotes the brain metastatic colonization of triple negative breast cancer cells via an astrocyte-mediated paracrine mechanism. *Oncogene.* 2016;35(22):2881–2892.
4. Contreras-Zarate MJ, Day NL, Ormond DR, et al. Estradiol induces BDNF/TrkB signaling in triple-negative breast cancer to promote brain metastases. *Oncogene.* 2019;38(24):4685–4699.
5. Klemm F, Maas RR, Bowman RL, et al. Interrogation of the microenvironmental landscape in brain tumors reveals disease-specific alterations of immune cells. *Cell.* 2020;181(7):1643–1660.e17.
6. Maas RR, Soukup K, Fournier N, et al. The local microenvironment drives activation of neutrophils in human brain tumors. *Cell.* 2023;186(21):4546–4566.e27.
7. Wischnewski V, Maas RR, Aruffo PG, et al. Phenotypic diversity of T cells in human primary and metastatic brain tumors revealed by multiomic interrogation. *Nat Cancer* 2023;4(6):908–924.
8. Bejarano L, Kauzlaric A, Lamprou E, et al. Interrogation of endothelial and mural cells in brain metastasis reveals key immune-regulatory mechanisms. *Cancer Cell* 2024;42(3):378–395.e10.
9. Zhang L, Zhang S, Yao J, et al. Microenvironment-induced PTEN loss by exosomal microRNA primes brain metastasis outgrowth. *Nature.* 2015;527(7576):100–104.
10. Neman J, Termini J, Wilczynski S, et al. Human breast cancer metastases to the brain display GABAergic properties in the neural niche. *Proc Natl Acad Sci U S A.* 2014;111(3):984–989.
11. Zeng Q, Michael IP, Zhang P, et al. Synaptic proximity enables NMDAR signalling to promote brain metastasis. *Nature.* 2019;573(7775):526–531.
12. Bhattacharya D, Barille R, Toukam DK, et al. GABA(A) receptor activation drives GABARAP-Nix mediated autophagy to radiation-sensitize primary and brain-metastatic lung adenocarcinoma tumors. bioRxiv 2023; 2023.11.29.569295.
13. Deshpande K, Martirosian V, Nakamura BN, et al. Neuronal exposure induces neurotransmitter signaling and synaptic mediators in tumors early in brain metastasis. *Neuro Oncol* 2022;24(6):914–924.
14. Pomeranz Krummel DA, Nasti TH, Kaluzova M, et al. Melanoma cell intrinsic GABA(A) receptor enhancement potentiates radiation and immune checkpoint inhibitor response by promoting direct and T cell-mediated antitumor activity. *Int J Radiat Oncol Biol Phys.* 2021;109(4):1040–1053.
15. Tagore M, Hergenreder E, Perlee SC, et al. GABA regulates electrical activity and tumor initiation in melanoma. *Cancer Discov* 2023;13(10):2270–2291.
16. Jandial R, Choy C, Levy DM, Chen MY, Ansari KI. Astrocyte-induced Reelin expression drives proliferation of Her2(+) breast cancer metastases. *Clin Exp Metastasis.* 2017;34(2):185–196.
17. Priego N, Zhu L, Monteiro C, et al. STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis. *Nat Med.* 2018;24(7):1024–1035.
18. Valiente M and Ortega-Paino E. Updating cancer research with patient-focused networks. *Trends Cancer* 2024;10(1):1–4.
19. Zimmer AS, Steinberg SM, Smart DD, et al. Temozolomide in secondary prevention of HER2-positive breast cancer brain metastases. *Future Oncol.* 2020;16(14):899–909.
20. Jenkins S, Zhang W, Steinberg SM, et al. Phase I study and cell-free DNA analysis of T-DM1 and metronomic temozolomide for secondary prevention of HER2-positive breast cancer brain metastases. *Clin Cancer Res.* 2023;29(8):1450–1459.
21. Zhu L, Miarka L, Baena P, Perea-Garcia M, Valiente M. Protocol to generate murine organotypic brain cultures for drug screening and evaluation of anti-metastatic efficacy. *STAR Protoc* 2023;4(2):102194.
22. Monteiro C, Miarka L, Perea-Garcia M, et al; RENACER. Stratification of radiosensitive brain metastases based on an actionable S100A9/RAGE resistance mechanism. *Nat Med.* 2022;28(4):752–765.
23. Zhu L, Retana D, Garcia-Gomez P, et al; RENACER. A clinically compatible drug-screening platform based on organotypic cultures identifies vulnerabilities to prevent and treat brain metastasis. *EMBO Mol Med.* 2022;14(3):e14552.
24. Mann B, Zhang X, Bell N, et al. A living ex vivo platform for functional, personalized brain cancer diagnosis. *Cell Rep Med* 2023;4(6):101042.
25. Kabraji S, Ni J, Sammons S, et al. Preclinical and clinical efficacy of trastuzumab deruxtecan in breast cancer brain metastases. *Clin Cancer Res.* 2023;29(1):174–182.
26. Alder L, Trapani D, Bradbury C, et al. Durable responses in patients with HER2+ breast cancer and leptomeningeal metastases treated with trastuzumab deruxtecan. *npj Breast Cancer.* 2023;9(1):19.
27. Lee JS, Hong JH, Sun DS, et al. The impact of systemic treatment on brain metastasis in patients with non-small-cell lung cancer: A retrospective nationwide population-based cohort study. *Sci Rep.* 2019;9(1).
28. Carron R, Gaudy-Marqueste C, Amatore F, et al. Stereotactic radiosurgery combined with anti-PD1 for the management of melanoma brain metastases: A retrospective study of safety and efficacy. *Eur J Cancer* 2020;135:52–61.
29. Benna M, Mejri N, Mabrouk M, et al. Brain metastases epidemiology in a Tunisian population: trends and outcome. *CNS Oncol* 2018;7(1):35–39.
30. Chamberlain M, Junck L, Brandsma D, et al. Leptomeningeal metastases: a RANO proposal for response criteria. *Neuro Oncol* 2017;19(4):484–492.
31. Lin NU, Lee EQ, Aoyama H, et al; Response Assessment in Neuro-Oncology (RANO) group. Response assessment criteria for brain

metastases: proposal from the RANO group. *Lancet Oncol.* 2015;16(6):e270–e278.

32. Le Rhun E, Devos P, Boulanger T, et al; European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor Group (BTG) Central Nervous System (CNS) Metastases Committee and the EORTC BTG Imaging Committee. The RANO Leptomeningeal Metastasis Group proposal to assess response to treatment: lack of feasibility and clinical utility and a revised proposal. *Neuro Oncol* 2019;21(5):648–658.
33. Kaufmann TJ, Smits M, Boxerman J, et al. Consensus recommendations for a standardized brain tumor imaging protocol for clinical trials in brain metastases. *Neuro Oncol* 2020;22(6):757–772.
34. Mamounas EP, Untch M, Mano MS, et al. Adjuvant T-DM1 versus trastuzumab in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: subgroup analyses from KATHERINE. *Ann Oncol.* 2021;32(8):1005–1014.
35. von Minckwitz G, Huang CS, Mano MS, et al; KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. *N Engl J Med.* 2019;380(7):617–628.
36. Park C, Buckley ED, Van Swearingen AED, et al. Systemic therapy type and timing effects on radiation necrosis risk in HER2+ breast cancer brain metastases patients treated with stereotactic radiosurgery. *Front Oncol.* 2022;12:854364.
37. Lebow ES, Pike LRG, Seidman AD, et al. Symptomatic necrosis with antibody-drug conjugates and concurrent stereotactic radiotherapy for brain metastases. *JAMA Oncol* 2023;9(12):1729–1733.
38. Stumpf PK, Cittelly DM, Robin TP, et al. Combination of trastuzumab emtansine and stereotactic radiosurgery results in high rates of clinically significant radionecrosis and dysregulation of aquaporin-4. *Clin Cancer Res.* 2019;25(13):3946–3953.
39. Tawbi HA, Forsyth PA, Hodi FS, 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):1961–1973.
40. Tringale KR, Reiner AS, Sehgal RR, et al. Efficacy of immunotherapy for melanoma brain metastases in patients with concurrent corticosteroid exposure. *CNS Oncol* 2023;12(1):CNS93.
41. Bander ED, El Ahmadieh TY, Chen J, et al. Outcomes following early postoperative adjuvant radiosurgery for brain metastases. *JAMA Netw Open* 2023;6(10):e2340654.
42. Jessurun CAC, Hulsbergen AFC, de Wit AE, et al. The combined use of steroids and immune checkpoint inhibitors in brain metastasis patients: a systematic review and meta-analysis. *Neuro Oncol* 2021;23(8):1261–1272.
43. Prabhu RS, Akinyelu T, Vaslow ZK, et al. Risk factors for progression and toxic effects after preoperative stereotactic radiosurgery for patients with resected brain metastases. *JAMA Oncol* 2023;9(8):1066–1073.
44. Giantini-Larsen A, Abou-Mrad Z, Goldberg JL, et al. Postradiosurgery cystic degeneration in brain metastases causing delayed and potentially severe sequelae: systematic review and illustrative cases. *J Neurosurg Case Lessons* 2023;5(6):CASE22462.
45. Ramakrishna N, Anders CK, Lin NU, et al. Management of advanced human epidermal growth factor receptor 2-positive breast cancer and brain metastases: ASCO guideline update. *J Clin Oncol.* 2022;40(23):2636–2655.
46. Le Rhun E, Guckenberger M, Smits M, et al; EANO Executive Board and ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. EANO-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up of patients with brain metastasis from solid tumours. *Ann Oncol.* 2021;32(11):1332–1347.
47. Vogelbaum MA, Brown PD, Messersmith H, et al. Treatment for brain metastases: ASCO-SNO-ASTRO guideline. *J Clin Oncol.* 2022;40(5):492–516.
48. Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol.* 2015;16(15):e534–e542.
49. Lin WF, Zhong MF, Zhou QH, et al. Efficacy of complementary and integrative medicine on health-related quality of life in cancer patients: a systematic review and meta-analysis. *Cancer Manag Res* 2019;11:6663–6680.
50. Moss NS, El Ahmadieh TY, Brown S, et al. Integrated multidisciplinary brain metastasis care reduces patient visits and shortens time to adjuvant irradiation. *JCO Oncol Pract* 2022;18(11):e1732–e1738.
51. Fecci PE, Champion CD, Hoj J, et al. The evolving modern management of brain metastasis. *Clin Cancer Res.* 2019;25(22):6570–6580.
52. Moravan MJ, Fecci PE, Anders CK, et al. Current multidisciplinary management of brain metastases. *Cancer.* 2020;126(7):1390–1406.