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Intracranial metastases from solid tumors: Call to Action and Consensus from the Society for Neuro-Oncology and American Society of Clinical Oncology Collaborative

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Abstract

Intracranial metastases (ICM), specifically parenchymal brain metastases, remain a major clinical challenge in solid tumor oncology, despite recent advances in cancer therapies which have led to improvements in survival for these patients. Improving outcomes even further in this patient population will require a multi-disciplinary approach, including pre-clinical and translational studies, clinical trials, and studies of patient reported outcomes and quality of life. At the 2023 and 2024 joint Society for Neuro-Oncology (SNO) and American Society of Clinical Oncology (ASCO) CNS Metastases Conferences, two ICM collaborative group think tanks convened, composed of diverse, multi-disciplinary stakeholders, including basic and translational researchers, clinical trialists, and clinicians from academia and the community setting. Here we summarize the key knowledge gaps and consensus recommendations put forth by these two think tanks. Advances in ICM research and improvements in patient outcomes will require close inter-specialty and inter-institutional collaboration between stakeholders, including pre-clinical and translational researchers, clinical investigators, industry, and regulatory bodies.

Key words

Intracranial metastases, brain metastases, clinical trials, tumor microenvironment, consensus

Key points

- Current ICM therapies lead to considerable toxicity and only modest benefit.
- Critical needs in ICM include improving toxicity, survivorship, and neurocognitive outcomes.
- Multidisciplinary, international collaboration and clinical trials will improve outcomes.

Introduction

Intracranial metastases (ICM) are a notable cause of morbidity and mortality among patients with advanced solid malignancies.[1, 2] Recent advances in cancer systemic therapies have improved survival across a range of tumor types, but these gains are modest, and the brain remains a common site of failure. The functional and cognitive consequences of ICM are highly deleterious for most patients and many of our current therapies produce modest benefit with considerable long-term sequela. Survivorship considerations and toxicity mitigation are essential domains requiring major improvement. Patients with untreated or progressive ICM have historically been excluded from many of the landmark legacy clinical trials; therefore, limited data describing the intracranial efficacy of modern systemic therapies exist. Our understanding of how to interdigitate systemic and local therapies for patients remains poor, which could represent a lost opportunity if we fail to capitalize on sequence-dependent synergies or recognize sequence-dependent toxicities of these therapies.

At the 2023 and 2024 joint Society for Neuro-Oncology (SNO) and American Society of Clinical Oncology (ASCO) annual CNS Metastases Conferences in San Francisco, CA, and Denver, CO, a unique collaborative group ICM think tank convened (**Table 1**). In parallel, a think tank on leptomeningeal metastases from solid tumors convened at each conference, resulting in a separate consensus review.[6] The ICM think tank brought together diverse, multidisciplinary stakeholders, including basic and translational researchers, leading clinical trialists, and clinicians. Multiple scientific and clinical specialties were represented, including cancer biology, medical oncology, radiation oncology, neuro-oncology, and neurosurgery. These timely events dissected critical issues impeding progress in the field of ICM research aiming to (1) define knowledge gaps and discover areas of needed consensus in pre-clinical and clinical domains, (2) highlight model systems and their utility for future research, particularly in key areas of

unmet need in the ICM space, (3) identify challenges unique to research in the field of ICM, (4) chart a clear path towards increasing opportunities and impact of investigator-initiated and industry-sponsored clinical trials, and (5) identify essential features for patient-centric care that will improve patient outcomes. This manuscript delves into the key points raised during the think tanks to provide a roadmap for advancing research and improving outcomes for these patients.

Pre-clinical models of ICM: First the Right Question, then the Right Model

The "Right" Questions

What is unique about the brain metastases tumor microenvironment that impact the translational potential of preclinical studies?

The brain metastasis tumor microenvironment (TME), which consists of unique cell types, anatomic structures, and metabolic features, poses distinct challenges to cancer cells during the metastatic cascade (**Figure 1**). To establish ICM, circulating tumor cells (CTCs) must penetrate the BBB. Once disrupted by cancer cells, the BBB is known as the blood-tumor barrier (BTB), characterized by its highly heterogeneous permeability and biological changes.[7] Brain metastases grow in close proximity to endothelial cells, and many depend on vessel-co-option.[8, 9] The blood-cerebrospinal fluid barrier (BCSFB) is another unique barrier that protects the brain from cancer cells. Understanding the mechanisms by which CTCs cross these barriers is essential to identifying novel targets and improving ICM prevention and treatment strategies. *In vivo* studies using multiphoton laser-scanning microscopy demonstrated that extravasation of CTCs into the brain occurs at sites of micro clot formation associated with platelet recruitment and expression of von Willebrand factor.[10] The BBB, BTB, and BCSFB are dynamic barriers, and their permeability to cancer cells or systemic therapies is potentially modifiable. For instance, in *in-vitro* BBB and BCSFB models, hydrocortisone increased the transmigration of breast cancer cells across the BCSFB.[11] Better understanding of the BBB, BCSFB, and BTB will

lead to the development of more effective systemic therapies for ICM and uniform delivery of systemic therapies across the highly heterogeneous BTB.

Once cancer cells have crossed the BBB or BCSFB, the brain parenchyma itself is a unique and highly specialized microenvironment, consisting of cell types not found in any other organ system, including astrocytes, microglia, oligodendrocytes, and neurons (**Figure 1**). The interaction between tumor cells and the brain TME can lead to the development of synaptic connections between neurons and cancer cells, indicating integration of cancer cells into the specialized synaptic network in the brain TME.[12, 13]

What are the types and impact of heterogeneity in brain metastases?

Understanding the different microenvironments within the brain and longitudinally throughout the disease process remains a critical knowledge gap. Patients may have solitary or multifocal ICM, and may have prior or concurrent extracranial disease with prior exposure to several lines of systemic and radiation therapy which would have impacted the cellular makeup of the ICM. ICM patients have been shown to have compromised immune systems, which are likely to affect both the progression and treatment of the disease.[14-16]

Longitudinal CSF monitoring of ctDNA and/or CTCs using intraventricular reservoirs may be performed to gather information about the evolution of ICM over time, but this is currently considered invasive even by those invested in ICM management and thus remains a significantly underutilized method, with limitations to knowledge of concordance with heterogeneity of ICM. Inter-institutional, inter-specialty and inter-disease centric collaboration is essential to gather larger biorepositories and maximize progress in this field. Additionally, implementation of rapid autopsy programs that enable collection of patient specimens are vital

to identifying alterations in cancer cells, the brain TME, and to create models that reflect modern clinical practice.

The "Right" Models

What are the strengths and weaknesses of current models?

One key focus of the discussion around pre-clinical research was determining the right question for the right model. The "right" question often involves elucidating a specific component of the pathogenesis of ICM[17] (**Figure 2**). Most preclinical studies in ICM are performed in mice, which allows mimicking multiple steps in the metastatic cascade, although no single model can recapitulate the complexity of brain metastases. The choice of pre-clinical model must be closely aligned with the specific research question, particularly when aiming to replicate distinct steps in the metastatic cascade (Figure 1). Current strategies for modeling ICM *in vivo* include: (1) spontaneous from a primary tumor, (2) intravenous (i.e. tail vein) injection, (3) intracarotid or intracardiac injection, and (4) intracranial (heterotopic) injection models of ICM. Spontaneous models include both orthotopic injection models, in which cells are implanted in the primary site matching the injected cancer (e.g. mammary fat pad for breast cancer cells), and genetically engineered mouse models (GEMMs), in which tumors are spontaneously created. Spontaneous models allow the study of mechanisms that dictate early tumor dissemination and can be valuable to test therapies with potential to prevent metastatic colonization; however, these often result in extensive extracranial disease requiring resection for survival, limiting spontaneous brain metastasis formation.[18-20] Intravenous, intracarotid, and intracardiac injections model hematogenous dissemination, BBB traversal, and brain colonization, serving as useful models for testing strategies to prevent early colonization and to delay progression of multifocal brain metastases. These models have the advantage of maintaining the BBB structure that is critical to brain metastatic colonization, can evolve with brain metastatic progression, and serve well when testing the ability of drugs to penetrate the BTB. However, the multifocal nature of these

models makes them less suited for imaging studies or preclinical modeling of SRS. Intracranial injections allow for evaluation of tumor growth within the brain, tumor–microenvironment interactions, and in some cases, responses to therapy, particularly if the mechanisms at play do not involve key interactions with the BTB. These models only allow for the study of specific steps in the ICM cascade and often do not take into account the impact of a co-existing primary tumor on the establishment of the brain metastatic niche.[21, 22]All these models can utilize human tumor cells in patient-derived xenografts (PDX) or cell-line derived xenografts (CDX), or mouse tumor cells derived from syngeneic implanted models, or GEMMs.[17] Patient-derived xenograft (PDX) models more faithfully reflect the genetic diversity, intratumor heterogeneity, and prior therapy exposures of human metastases compared to traditional cell lines.[21] However, since PDXs typically require immunocompromised mice, they are less suitable for studies involving immune-based therapies. Organoid and brain slice models can be used as a platform to model heavily pre-treated ICM[23], which is relevant given the limitations of treatment-naïve models, but it is often difficult to mirror the heterogeneity of the ICM environment in these models. Additional *ex vivo* and device-based models, such as brain slices, organoids, and microfluidic cell-containing chips have their merits and have been shown to recapitulate tumors in patients and provide prognostic insights, but do not capture the complexity of BTB or BBB.[24-26]

How does the BBB impact the design of pre-clinical (and clinical) studies of ICM?

The structure of the BBB regulates the passage of circulating molecules, including cancer systemic therapies, from the systemic circulation into the brain.[7] Although the BBB is frequently disrupted in ICM, residual barrier function in the BTB leads to heterogeneous drug permeability and suboptimal drug delivery to ICM[27], which correlates with lower responses of ICM to systemic therapies. When evaluating the impact of the BBB on study design, it is important to consider what is known about the BBB penetration and intracranial efficacy of the selected agent. For instance, the BRAF inhibitor dabrafenib demonstrates limited brain delivery in an

intact BBB model[28]; dabrafenib monotherapy demonstrates an approximately 40% intracranial response rate in patients with asymptomatic melanoma ICM harboring the BRAF V600 mutation.[29] However, the brain is a common site of disease progression in patients with melanoma who receive dabrafenib for extracranial disease but have not yet developed ICM. Osimertinib, an epidermal growth factor receptor (EGFR) inhibitor, demonstrates high BBB penetrance and CNS concentrations in pre-clinical models[30] and high intracranial response rates in clinical trials.[4] Similarly, anaplastic lymphoma kinase (ALK) inhibitors exhibit high intracranial response rates in patients with non-small cell lung cancer (NSCLC) with ALK rearrangements.[5] These data suggest that there is an important difference between penetration of the intact BBB to *prevent* ICM versus penetration of the disrupted BTB to *treat* patients with established ICM.

Although tyrosine kinase inhibitors (TKIs) are hypothesized to penetrate the BBB more easily than larger molecules based on size and BBB permeability, larger molecules such as antibody drug conjugates (ADCs) or monoclonal antibodies seem to achieve efficacy in treating ICM by taking advantage of focal BBB disruption as well as mechanisms such as tumor cell targeting and bystander cell killing. For instance, trastuzumab deruxtecan (T-DXd) demonstrates high intracranial activity in patients with HER2+ breast cancer ICM, and intracranial activity has also been reported with other ADCs, such as ado-trastuzumab emtansine (T-DM1) and sacituzumab govitecan.[31-33] Immune therapy with ipilimumab-nivolumab demonstrates >50% intracranial response rate in patients with asymptomatic melanoma ICM[3, 34], which may be related to T-cell trafficking into the CNS rather than direct drug penetration. The high intracranial activity of these agents highlights the importance of including patients with untreated or progressive ICM in all clinical trials of novel systemic therapies. As new classes of cancer systemic therapies become available, key questions in modern clinical trial design include whether the BBB or BTB has a rate-limiting impact on the intracranial efficacy of the drug of choice, whether or what degree of

BBB penetration is necessary for intracranial efficacy, and how the BBB/BTB function should be accounted for in drug development and clinical trial design.

Bringing Research to and from the Clinic: What are the needs and obstacles?

What are the obstacles in translation of concepts from the lab to the clinic?

Identified obstacles to translation of research from the lab to the clinic coalesced around 3 main themes: 1) lack of sufficient funding, 2) complexity of ICM studies due to their often multidisciplinary and cross-cancer nature, and 3) inconsistencies in trial designs and outcomes (**Figure 3**). Funding remains a critical challenge for clinical trials, particularly in ICM research. Securing financial support at the federal level requires concerted efforts to highlight the importance of research in ICM separate from pre-existing funding for the primary tumor type and advocate for increased investment in and prioritization of ICM research. In most cases, ICM trials require the cooperation of multiple sites to complete accrual in a timely fashion, and the multicenter coordination and monitoring requires additional financial resources. Further, trials can be cost prohibitive to run and recruit, potentially leading to premature failure. Careful consideration of the budget and coverage analysis should be done early during trial design to assess real-life feasibility and cost effectiveness. Trialists and sponsors must consider that if a treatment is cost-prohibitive, logistically difficult, or may not fall under the *"standard of care"* guidelines that insurance carriers use (usually based on Medicare), it will not only fail but only contribute further to the dramatic inequity in care already existing in this space.

Another identified obstacle, which is somewhat unique to ICM in the field of oncology, is their particularly complex and multifaceted nature. ICM trials are by necessity usually multidisciplinary in nature, which requires inter-specialty collaboration in clinical trial design and

conduct. With rapidly evolving systemic therapy options both within and across different primary cancers, even with promising brain penetrance, it is unclear how to best design trials and build the most effective trial team with expertise representing both effective systemic therapies and local treatment modalities. In contrast to a model in which different tumor types or different types of intervention are "siloed," effective clinical trials in the ICM space are becoming increasingly pan-cancer and may allow inclusion of patients with multiple different primary tumor types and/or may allow patients to receive multiple different types of therapy (for example, both systemic and local therapy). Some oncology cooperative groups, such as the National Research Group in Oncology (NRG Oncology), already run multidisciplinary and multi-cancer trials, but additional "homes" for ICM studies are sorely needed. There are recent efforts in the field to centralize and operationalize funding and research collaboration in the ICM space. The Consortium for Intracranial Metastasis Academic Research (CIMARa), established in 2021, is a collaborative group that has grown to include over 130 members spanning multiple disciplines, including patient advocates and research organizations, from over 60 institutions in 9 countries.[35] Additionally, the American Brain Tumor Association (ABTA) has expanded its interest and support beyond primary brain tumors to ICM, and has developed an active Metastatic Brain Tumor Collaborative (https://www.abta.org/metastatic-brain-tumor-collaborative/), which includes multiple research foundations and organizations across primary cancer specialties. The NIH/NCI Brain Metastases Interest Group[36, 37] aims to facilitate high-impact brain metastases research through coordination of multidisciplinary stakeholders around collaborative research opportunities, and infrastructural facilitation of preclinical research translated to next-generation clinical trials. Such shared initiatives involving researchers, advocacy groups, and policymakers will be essential for garnering attention and resources for advancing clinical trials in ICM.

What are the challenges to successful execution of clinical trials in ICM?

One of the identified obstacles in ICM trials was restricted eligibility (**Figure 3**). Early inclusion of ICM patients in trials not only allows for the evaluation of novel therapeutic agents but also provides valuable insights into drug penetration, efficacy and safety profiles specific to ICM.[38] Industry and sponsor concerns stem from fears of increased toxicity and poor performance status. Alleviating these concerns through comprehensive risk assessment, robust multidisciplinary patient selection criteria, multidisciplinary team involvement,[39, 40] and clear communication regarding the benefits of including this patient population is essential.[41] Including separate cohorts for patients with active (untreated and/or progressive) ICM can be a successful strategy for evaluating the activity of systemic therapies in early-phase trials, while maintaining the standard evaluation of safety and efficacy in other cohorts. Apart from the inclusion of patients with ICM in trials, there should also be increased consideration of pre-specified CNS endpoints in trials of novel agents. In cancers with high ICM risk, such as melanoma or HER2+ breast cancer, CNS endpoints such as incidence of new CNS metastases or time to onset of CNS metastases can be very important and useful. Endpoints that quantify intracranial tumor response and progression such as CNS objective response rate, CNS disease control rate, and time to CNS progression should also be included when appropriate.

Another gap is the limited access to innovative drugs, both those with BBB penetration and those with even *potential* BTB penetration, for investigation in investigator-initiated clinical trials. Often, drugs with significant potential may be shelved or research programs suspended due to a perceived lack of financial benefit for a small patient population. Additionally, drugs that may not cross the intact BBB should not automatically be excluded from ICM trials as they may display efficacy in the setting of the compromised BTB often seen in ICM, as demonstrated by ADCs and discussed above. We should consider encouraging the development of such medications

via a national subsidy program or other innovative funding strategies to increase the options available for our patients.

A second theme to obstacles in ICM trials was inconsistencies in outcomes. While FDA guidance plays a crucial role in ensuring drug safety and efficacy, industry trials for ICM may encounter challenges with regulatory requirements that impact trial design and implementation. In addition, outcomes beyond overall survival – including functional independence, neurocognitive function, and the composite of neurological symptoms plus imaging response - are valuable clinical data points and merit inclusion in trial design. By aligning priorities, engaging in strategic advocacy efforts, and fostering a culture of collaboration, the field can enhance its credibility, influence policy decisions, and secure the necessary resources to drive impactful research initiatives forward.

How do we obtain and track consistent data and biospecimens?

Standardizing the types of data collected, such as clinical outcomes and treatment regimens, imaging data, and ctDNA levels, enables researchers to aggregate and compare data from multiple studies. This can enhance the statistical power of analyses and accelerate the discovery of meaningful associations. Collecting as much contextual data as possible, including factors like dosage times, steroid doses and tapers, etc. enriches the dataset and provides a more comprehensive understanding of patient responses and disease dynamics.

Serial sampling during treatment is another critical aspect of biospecimen collection. Liquid biopsies, which involve the analysis of blood or CSF samples to detect ctDNA and/or CTCs, offer a less invasive alternative to traditional tissue biopsies. Regular serial sampling during treatment also provides a dynamic view of tumor evolution and treatment response, facilitating more personalized and adaptive treatment strategies.[42, 43] Tissue correlation studies are needed

to establish the concordance between different types of liquid (plasma versus CSF) and tissue biopsies, ensuring that liquid biopsy data can be used to inform clinical decisions. Standardized protocols for ctDNA collection (including site of CSF collection), processing, and analysis are essential to ensure that data are consistent and comparable across different studies and clinical settings. This standardization facilitates large-scale data pooling and meta-analyses, which are critical for documenting the safety of acquiring these samples, validating ctDNA as a reliable biomarker and for advancing our understanding of its role in cancer progression and treatment response. Establishing uniform guidelines and protocols will also streamline the implementation of ctDNA monitoring in routine clinical practice.

One promising approach to standardized ctDNA tracking is the phase 0 window of opportunity model. This model involves obtaining biospecimens before, during, and after a short period of treatment to assess biological responses at an early stage. Replicating this model in more centers could provide valuable insights into drug efficacy and mechanisms of action. Different clinical settings and institutions have unique workflows, resources, and patient populations, which impacts the feasibility and effectiveness of standardization efforts. We can start by identifying best practices and potential barriers, thus informing the development of adaptable and scalable protocols.

Harmonizing the data collected across clinical trials is vital, and this harmonization is enabled through more consistent and comprehensive capture of the contextual details in metadata. The integration of these extensive data into artificial intelligence (AI) models presents a significant opportunity in cancer research and clinical practice. AI models can analyze large, complex datasets to identify patterns and predict outcomes; however, the capabilities of AI are often limited to the availability, quality and relevant usability of the data. By feeding standardized and contextualized data into these models, researchers can uncover insights that inform future trial

designs and clinical guidelines. A recent publication by the Federation of American Scientists[44] called out the importance of consistency in medical imaging in enabling AI, which is of particular relevance when using MR imaging to detect and measure small tumors in many cases of ICM. Moreover, AI-driven analyses may help identify potential biomarkers, optimize treatment strategies, and enhance the precision of personalized medicine. These analyses can be strengthened by the inclusion of real-world data from registries or retrospective analyses. Real world data provides important and valuable information on the experience of patients outside of trials and in diverse practice settings – being able to pool this data together in a secure manner would provide the ability to glean meaningful insights and practical information for patient care and future research.

How do we overcome these obstacles?

Several action items and solutions emerged from the discussions (**Table 2**). First and foremost, significant multi-center and multi-disciplinary collaboration is imperative to overcoming many of these obstacles. Collective research efforts will also enable the pooling of resources, expertise, and patient populations across institutions, facilitating larger-scale studies, improving generalizability of results, and accelerating the pace of scientific discovery. Additionally, collaborative groups can increase the visibility of the unmet need of ICM at all levels – across institutions and at the national to international levels.

Such collaborations will also help address the challenge of insufficient funding. These groups can improve the quality of trials by developing and refining study concepts and designs through multi-disciplinary and multi-institutional discussions, and earlier incorporation of patient advocates. Sharing trial experiences will also help educate investigators new to clinical trial conduct and can provide roadmaps to navigate clinical research. Investigators can balance financial considerations by developing smaller studies to assess initial efficacy and safety

signals. Utilization of more creative study designs, such as umbrella and octopus platform trial models, can also help but will require extensive collaboration not just between academic investigators and institutions, but also research organizations and industry.

Clinical Research and Care: What are the highest needs, and how can we address them?

How can we predict and prevent ICM?

Prevention of ICM is a critical area of unmet need in clinical practice. Specific patient subsets at high risk of developing ICM are not clearly defined, and current guidelines for ICM screening in asymptomatic patients do not provide tailored recommendations based on clinical or molecular risk factors.[45, 46] In patients who underwent resection of melanoma ICM as the first site of visceral disease, whole-exome sequencing identified enrichment in *KRAS* mutations compared to The Cancer Genome Atlas (TCGA) database.[47] This finding was concordant with enrichment of *KRAS* mutations in extracranial metastases in the same patients and was associated with reduced survival. Identification of molecular alterations in primary tumors which are associated with increased CNS tropism will help identify patients at high risk of ICM, which can then lead to personalized screening algorithms and earlier detection.

Another key knowledge gap in the treatment and prevention of ICM is the optimization of longitudinal monitoring, including (1) screening of patients at high risk of ICM, (2) longitudinal monitoring of patients with a history of ICM, (3) selection and interpretation of monitoring techniques, and most importantly, (4) establishing that this is a worthwhile pursuit by demonstrating that early intervention made possible by earlier detection produces meaningful clinical benefit. Serial surveillance MR imaging, while available for some diseases, remains difficult to obtain in other cancer types since NCCN guidelines do not recommend imaging unless the patient is symptomatic and therefore inhibit insurance approval. Data on the most

common timepoints at which ICMs occur could help with standardizing timing of imaging and limit cost. Most published data are retrospective, consisting of small and heterogeneous cohorts, and prospective studies are needed to define the optimal use of these assays in routine clinical practice[42].

Few clinical trials have been performed with the endpoint of primary or secondary prevention of ICM. In a phase I trial of prophylactic T-DM1 and temozolomide as secondary prevention for ICM in patients with HER2+ breast cancer, only 2 of 12 patients had developed additional ICM at 9.6 month follow up.[48] Factors which have limited the conduct of these trials include lack of data to guide eligibility criteria and patient selection in addition to the cost and time required [36]. Further, the available systemic therapies are limited to drugs with proven intracranial or extracranial efficacy, for which there are little to no data demonstrating preventive capabilities. Studies to identify cohorts of patients who are at high risk of developing ICM will not only help personalize screening algorithms but will also facilitate the rational design of clinical trials for this patient population.

Clinical Trial Design, Eligibility and Comparability

How do we define symptomatic vs asymptomatic ICM in clinical studies?

In clinical studies, the distinction between symptomatic and asymptomatic ICM is crucial for accurate trial outcomes and patient management. However, there are inherent challenges in this process, such as subjectivity in symptom reporting and variability in symptom presentation, as well as the challenge of distinguishing if clinical changes are occurring from progression or pseudoprogression (necrosis). By standardizing these criteria, we can ensure that clinical trials are more comparable and that patient selection is more consistent. Criteria may include ECOG/KPS, steroid use, focal neurological signs with an objective exam or score, cognitive testing, and the presence, absence or worsening of seizures. Le Rhun et al recently discussed

this issue as it pertains to ICM in melanoma and included a recommendation of standardized and validated tools that should be considered in standard practice.[49] Other key eligibility criteria which could be standardized include minimal size criteria for enrollment in ICM trials and permitted time interval from baseline CNS imaging to trial enrollment.

How can we optimize endpoints and comparability across studies?

Results of trials in the intracranial metastases (ICM) space are often difficult to interpret and compare due to a lack of standardized language and harmonized endpoints. Traditional measures such as overall survival do not adequately capture the patient experience or the nuanced significance of disease control in the CNS, which can yield meaningful functional and cognitive benefits independent of survival. Neurocognitive outcomes, while valuable, must be interpreted in the context of an individual patient's acceptable level of cognitive change and may not fully reflect functional status or quality of life. Furthermore, it is challenging to isolate CNS-specific benefit given the interplay with systemic disease—extracranial tumor burden, treatment adjustments in light of extracranial disease, and disability from non-CNS disease all influence outcomes. Addressing these challenges requires clear, consensus-driven definitions for key concepts such as symptomatic versus asymptomatic disease, steroid dependence, neurological disability, and clinical benefit, supported by standardized methods of measurement and reporting. Uniform adoption of CNS-specific endpoints - including time to CNS progression or incidence, CNS disease control rate, and CNS overall response rate - would enable more accurate assessment of therapeutic benefit and facilitate cross-trial comparison. Achieving this will require coordinated collaboration across research networks to align definitions, measures, and reporting standards, ensuring that future trials truly reflect the impact of treatment on both survival and quality of life for patients with ICM.

How to Improve Care and Outcomes for Patients

What are the biggest areas of unmet need in clinical management of ICM?

One critical area that requires exploration is the delicate balance between treatment efficacy and toxicity. While advancements in oncological therapies have shown promise in combating cancer, treatments may still have a high risk-to-benefit ratio. An example is whole-brain radiation therapy (WBRT) – WBRT improves intracranial disease control and neurologic death rates in patients with a high burden of ICM who may otherwise rapidly deteriorate and die, but this benefit often comes at the cost of significant neurotoxicity.[51] As we strive to enhance interventions for these patients, it is imperative to evaluate the impact of treatments on quality of life and consider validated patient-reported outcome measures in clinical trials.[52] For example, a phase 3 trial comparing stereotactic radiation (SRS) versus WBRT in patients with > 4 brain metastases used a primary endpoint of average of patient-reported symptom severity and interference with life, and reported improvement in these domains with SRS compared to WBRT.[53] Inconsistency in the acquisition of QoL metrics included across studies poses a significant challenge, hindering the comparability of data across studies. More consistency and coordination across investigators in the choice and meaningful change thresholds for patient-reported outcomes, functional activity measures, QoL tools and for evaluation of neurocognitive function in this population is much needed.[52, 54]

There is a pressing need for updated guidelines on screening and surveillance tailored to various cancer subtypes that commonly give rise to ICM. We also strive for more inclusive and equitable access to clinical trials so they more appropriately represent our diverse populations.[38] Poor enrollment has plagued neuro-oncology clinical trials, encouraging a significant effort over the last decade to evaluate contributing factors. The result has been numerous consensus papers that provide practical guidance to address barriers to trial recruitment and enrollment.

The expansion of eligibility criteria approved and encouraged by ASCO/FoCR/FDA is an important step in providing regulatory guidance for trials in this space.[55] Despite this guidance, in an evaluation of NCI-sponsored trials between 2018 and 2020, the percentage allowing for active ICM in the inclusion criteria remained low at 15%.[56] There are also numerous other factors at play that may either be patient, community or institution centered, or are inherent issues with clinical trial design and organization. Several excellent articles in recent years include an in-depth discussion of these issues and provide practical suggestions and guidance that should be carefully considered and integrated into future trials.[57, 58]

The optimal integration of radiation therapy into the therapeutic strategy remains a complex issue that requires further investigation and standardization. While systemic therapies have demonstrated efficacy in managing ICM in certain cancer types, the decision to defer or forego radiation therapy in asymptomatic ICM lacks definitive evidence to guide clinical practice and is dependent on interdisciplinary discussion and expertise due to the high variability in risk associated with lesional location within the brain.[59] Variability in treatment approaches underscores the need for standardization of risk assessment and acceptability, early involvement of neuro-oncology consultation and robust trial and real-world data that evaluate different therapeutic strategies and sequences in order to help non-neurological clinicians make informed decisions based on evidence-based practices rather than individual preferences. ICM occurs with systematic disease; the timing, modality, and intensity of CNS-directed interventions should be aligned with systemic disease status, patient performance, and overall goals of care, recognizing that outcomes in the CNS are closely intertwined with extracranial disease control. We must continue to keep our focus on the broader treatment strategy and overall picture in a multidisciplinary fashion, instead of on the ICM alone, recognizing that treatment adjustments for systemic disease will affect the CNS and vice versa.

Additionally, the challenge of distinguishing radiation necrosis from disease progression on imaging poses a significant clinical dilemma in patient subsets, highlighting the need for non-invasive diagnostic tools, such as AI models,[60] that can accurately differentiate between these entities. Advances in imaging modalities such as perfusion scans and amino acid PET scans hold promise in addressing this challenge, but further research is needed to validate their efficacy and cost-effectiveness for routine clinical use.[61]

How do we ensure our clinical care and research is more patient-centric?

Patients with ICM require the expertise of specialists from diverse specialties (medical oncology, neurology or neuro-oncology, neurosurgery, radiation oncology, palliative care, rehabilitation medicine, social work, financial counseling, nurse navigation etc.) as they traverse the journey with ICM (**Figure 4**). It is challenging to find centers where all specialties are easily accessible to the patient in one place, especially in a non-academic, community hospital setting, where most patients with cancer are seen. Successful programs bring together the multiple required specialists to ensure that patients receive optimal care. This may be done in the format of a multidisciplinary tumor board and/or clinic. These efforts require significant time and financial commitments in addition to assurance from all involved specialists to communicate, collaborate, and coordinate patient care. Patients and their families are increasingly becoming aware that this type of care is advantageous; however, there remains significant inequity in access to as well as delivery across the country. The ability to provide telemedicine during the COVID-19 pandemic had improved access to care and expert opinion for patients even in rural pockets of the country; rolling back of telehealth laws has reduced these advantages and again isolated patients who are not in communities with a comprehensive, multidisciplinary ICM program.

Patient-centered research focuses on outcomes that are meaningful for patients and their families. This starts with understanding and exploring what endpoints (apart from survival) are

important to patients and the patient's experience by incorporating patients and advocates early and often in study development. Patient-reported outcomes are increasingly and rightfully gaining more space in research and clinical trials and are important to capture. This includes the consideration of symptoms that are CNS-focused, but also domains that are crucial to patients such as quality of life, psychological wellbeing, financial and time toxicity, burden of care. The challenge has been that these outcomes, while important to patients and families, are generally more difficult to objectify and standardize and therefore have frequently been included only as exploratory endpoints, rather than as primary or key secondary endpoints with clear, pre-specified benchmarks to evaluate whether therapeutic strategies provide meaningful benefit. Additional work is needed to standardize which outcomes should routinely and systematically be captured in trials, and to reach a consensus on which tools and measures should be used to collect these outcomes.

It is critically important to include the patient and care partner voice as we develop our research protocols and clinical trials. We need to consider the realistic burden that we place on patients and families when designing a clinical trial; this is only possible when we keep their perspective on the table throughout development and implementation. Patients bring critical considerations to aspects such as lab testing, appointment burden, infusion or imaging times, financial and time costs of travel, etc. Patients and families will also be able to provide valuable insights on what might help them be more open to enrolling on a clinical trial, whether educational materials, handouts or specific features of a trial that might make it more appealing and less intimidating.

Conclusion

The 2023 and 2024 Think Tanks at the annual SNO/ASCO CNS Metastasis Conference convened multidisciplinary experts to confront some of the most pressing challenges in the field.

Through these dynamic discussions, key themes emerged across preclinical research, clinical care and investigation, and the critical bridge between them. A consistent thread throughout was the essential role of collaboration—across disciplines, institutions, and research stages—as both a solution and a foundation for progress. Table 2 presents a Call to Action, outlining priority areas and proposed strategies in each domain. Moving forward, our collective ability to meet these challenges depends on sustained, unified collaboration and a shared dedication to innovation and patient-centered care. Together, we can chart a path toward meaningful and transformative advances in ICM research and treatment.

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Figure Captions

Figure 1: Interactions of ICM with the normal brain. ICM present in the brain disrupt the blood-brain barrier, leading to a compromised barrier called the blood-tumor barrier (BTB). ICM are embedded within the normal brain microenvironment, and develop interactions with cells such as neurons, astrocytes, microglia and macrophages. Additional research into these two processes is needed to better understand their impact on ICM cell growth and survival, as well as potential interventions targeting these processes that may improve patient outcomes.

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Figure 2: The "Right" Model for the right question. Preclinical animal models of ICM can utilize multiple different methods to generate intracranial lesions from solid tumors. Each model has strengths and weaknesses which require careful consideration when designing experiments. The main point to emerge from the ICM think tank was that investigators must first determine the "right" question about the metastatic process, and then select the "right" model(s) which match the associated metastatic cascade step(s). (**Top**) The stages of the metastatic cascade from a primary tumor site to (brain) metastatic site, from (1) invasion of surrounding tissue, (2) intravasation into the blood, (3) circulation, (4) colonization of the brain, including (a) extravasation through the BBB, (b) survival and dormancy of disseminated tumor cells, and growth of (c) micrometastasis into (d) macrometastasis. (**Bottom**) Multiple methods of tumor generation in animal models of ICM, though the specific model utilized must be selected based on which is best suited to investigate the specific metastatic stage. Some models, specifically orthotopic injection models in the lung, mammary fat pad, or subcutaneously as appropriate to the model (lung cancer, breast cancer, or melanoma, respectively), can recapitulate the entire cascade (stages 1-4d), whereas others, such as intracranial (heterotopic) implantation are only

appropriate for studying outgrowth of macrometastasis (4d). Created in BioRender. Van Swearingen, A. (2025) https://BioRender.com/os0tebc~~Created in https://BioRender.com~~.

Figure 3: Obstacles in ICM Clinical Trials. Several obstacles in ICM clinical trials were identified by the collaborative group, falling largely into 3 categories: trial design, harmonization, and study conduct. Specific trial design gaps that were highlighted included the complexity of ICM trials given their often multi-disciplinary and pan-cancer scope, insufficient availability of novel agents, and insufficient inclusion of patients with ICM early in clinical development for therapies. Issues with harmonization in clinical trials were highlighted as being due to limited adoption of standardized outcomes, particularly those of interest and meaningful to patients and caregivers. Recurrent themes for obstacles in the conduct of ICM trials included difficulties in recruiting diverse patient populations common to oncology trials, but more specifically unique to ICM trials was insufficient dedicated funding and insufficient available multi-disciplinary and pan-cancer “homes” for such trials in cooperative groups and organizations. Created in BioRender. Van Swearingen, A. (2025) https://BioRender.com/qnsrdt5~~Created in https://BioRender.com~~.

Figure 4: Optimal clinical care for patients with ICM involves multiple specialties with a patient-centric approach. Patients with ICM require multi-disciplinary care for their disease, including interventional treatment specialists from medical oncology, neurosurgery, radiation oncology, and neuro-oncolgy/neurology. Palliative care involvement early and often is also essential to ensure care plans align with patient goals and needs. To help manage logistics and provide a central point of contact for communication among team members and the patient, nurse navigators are central to care. Additional specialists, including financial counselors, physical medicine/rehabilitation specialists, and social workers may be required for some patients to manage financial, physical, and social burdens due to their disease and/or care plan.

Table 1: **Members of the SNO/ASCO CNS Metastases Conference 2023 and 2024 Think Tanks on Brain Metastases**. The participants below contributed to indicated collaborative Think Tank(s) which resulted in this consensus. * denotes Think Tank co-chairs and organizers. Affiliations reflect institutions at the time of Think Tank participation.

Name	Affiliation	Year(s)
Sarah Goldberg*	Yale School of Medicine	2023, 2024
Mustafa Khasraw*	Duke University	2023
Manmeet Ahluwalia	Miami Cancer Institute	2023, 2024
Stephen Bagley	University of Pennsylvania	2023, 2024
Tracy Batchelor	Brigham and Women's Hospital	2023
Lucy Boyce Kennedy	Cleveland Clinic	2023, 2024
Caroline Chung	U of Texas MD Anderson Cancer Center	2023
Mariza Daras	University of California, San Francisco	2023, 2024
Michael Davies	U of Texas MD Anderson Cancer Center	2023, 2024
Peter Fecci	Duke University	2023
Jona Hattangadi-Gluth	University of California, San Diego	2023, 2024
Kelly Hotchkiss	Duke University	2023
Michelle Kim	University of Michigan	2023, 2024
Nancy Lin	Dana-Farber Cancer Institute	2023, 2024
Rachna Malani	U of Utah/Huntsman Cancer Institute	2023
Minesh Mehta	Miami Cancer Institute	2023, 2024
Josh Neman	University of Southern California	2023, 2024
Don Nguyen	Yale School of Medicine	2023
Saul Priceman	City of Hope	2023
Akanksha Sharma	Pacific Neuroscience Institute	2023, 2024
Helen Shih	Massachusetts General Hospital	2023, 2024
Riccardo Soffietti	Candiolo Cancer Institute, FPO-IRCCS, Candiolo, Turin, Italy	2023
Vivek Subbiah	Sarah Cannon Cancer Institute	2023
Hussein Tawbi	U of Texas MD Anderson Cancer Center	2023, 2024
Amanda Van Swearingen	Duke University	2023, 2024
Jessica Waibl Palonia	Duke University	2023
Alexandra Zimmer	OHSU, Knight Cancer Institute	2023, 2024
Carey Anders*	Duke University	2024
Veronica Chiang	Yale School of Medicine	2024
Diana Cittelly	University of Colorado, Denver	2024
Daphne Haas-Kogan	Mass General Brigham	2024
Katarzyna Jerzak	Sunnybrook Odette Cancer Centre	2024
Nelson Moss	Memorial Sloan Kettering Cancer Center	2024
Solmaz Sahebjam	Johns Hopkins University	2024
Sarah Sammons	Dana-Farber Cancer Institute	2024
Nancy Wang	Massachusetts General Hospital	2024

Table 2: Critical areas identified by the Think Tanks where strategic action can accelerate progress for patients with ICM. These coordinated efforts will not only improve outcomes but also ensure that future breakthroughs benefit the populations most in need.

Topic Area	Action Item
Preclinical Obstacles	
Preclinical Models	• Invest in better models • Support consortia and collaborations • Share fit-for-purpose ICM models • Create a centralized repository with validation standards • Reduce redundancy across institutions
Translation Obstacles	
Biospecimens	• Build infrastructure for a national network for rapid autopsy and longitudinal sampling • Embed CSF and plasma ctDNA collection into ICM trials • Standardize protocols for collection and create shared data frameworks
Clinical Trial Design and Eligibility	• Enforce standardization • Harmonize eligibility criteria • Define and develop consensus on symptomatic versus asymptomatic • Harmonize outcome measures for intracranial response, neurocognitive impact, steroid use, and quality of life • Add CNS endpoints in non-ICM trials
Industry-Investigator Collaboration	• Incentivize CNS drug development • Work with regulators to define acceptable endpoints • Offer development incentives for companies that are willing to test agents with CNS activity • Educate around the real-world constraints of pricing and costs with the current healthcare and insurance system, and develop more practical, balanced budgets for trials
Clinical Trial Funding and Operationalization	• Align incentives and infrastructure between funders, industry partners, regulatory agencies, investigators, researchers and clinicians. • Diversify funding opportunities for researchers • Collaborate to identify areas of excess or redundancy to cut costs and create more amenable budgets • Identify or create multi-disciplinary and pan-cancer “homes” for ICM trials
Clinical Trial Recruitment	• Open all trials of systemic therapy to ICM patients, including untreated patients • Increase use and variety of agents, ~~both~~ whether brain-penetrant and not in preclinical work, in trials • Incentive launch of low-burden, early-phase studies that are tailored to ICM patients
Technology Integration	• Leverage real-world data by supporting secure, interoperable platforms

	• Maximize the use of clinical data across centers • Design trials to be amenable for analysis via high resolution, time stamped metadata
Clinical Obstacles	
Earlier intervention	• Develop studies specifically focused on prevention of ICM, both primary and secondary • Prospectively investigate utility of longitudinal monitoring and increased screening for ICM
Care Delivery	• Expand access to specialized care, for example by deploying hub and spoke regional care models (linking centers of excellence with community sites) • Secure permanent telehealth coverage • Reduce barriers to trial participation through patient navigation and logistical support

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