SUMMARY: Second Annual Conference on CNS Clinical Trials and Brain Metastases, Co-Sponsored by SNO and ASCO

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The second annual conference on CNS clinical trials and brain metastases, organized by The Society for Neuro-Oncology and American Society of Clinical Oncology, took place from August 12th through 13th of 2022 in Toronto, Canada. The meeting served as a forum for enriching conversation, enlightening lectures, and other scholarly exchanges built upon the common goal of advancing CNS cancer treatments and promoting the highest quality of patient care. The following session summaries recap the breadth and depth of knowledge that was imparted regarding primary and secondary CNS malignancies, while serving as a launching point for clinical research that addresses the ultimate objective of prolonging survival for patients with these diagnoses of unmet clinical need.

Session 1: Metastasis, Metabolism, Microenvironment

Lisa Sevenich, PhD, kicked off session one with a captivating presentation on modulation of the tumor immune microenvironment (TIME) for brain metastasis (BM) control. Radiotherapy can sensitize BM towards immune checkpoint blockade (ICB). Additionally, given the critical role of the purine-adenosine axis in BM-associated inflammation, blockade of this axis demonstrated anti-tumor efficacy. In combination, radiotherapy with adenosinergic blockade provided a higher treatment benefit. Michael Pacold, MD, PhD, gave an enriching talk on PHGDH, a metabolic enzyme that is overexpressed in BM. Prophylactic suppression or inhibition of PHGDH has shown to decrease tumor growth in serine- and glycine-limiting environments, as well as reduce BM burden and improve overall survival in *in vivo* mouse models. Qing Chen, MD, PhD, concluded the discussion with an exciting presentation on the cross-talk between the brain environment and tumor cells. Astrocytes display pro-metastatic functions, including the activation of PPAR-gamma. PPAR-gamma is linked to increased cancer proliferation and is upregulated in BM. Thus, PPAR-gamma is a potential therapeutic target, and its inhibition has shown promising preclinical results.

For oral abstracts, Justin Low, MD, PhD found that Stimulator of interferon genes (STING) promoter methylation is anticorrelated with expression, and rescue of STING expression can be induced by reversing methylation with Deceitabine. Vincent Law found that HER2-/HER3-Dendritic cell vaccines are effective in HER2+ BM-Leptomeningeal disease (LMD) models with long-term protection against reinoculation of LMD. Josh Neman, PhD, showed that chemotherapy increases blood-cerebrospinal fluid-barrier (BCSFB) permeability and can worsen tumor infiltration, attributed to increased expression of matrix metalloproteinase 9 (MMP9) in breast cancer. Increased MMP9 expression results in cleavage of Tau released from tumor cells, leading to tumor-derived neurofibrillary tangles that can worsen the

integrity of the blood-CSF barrier. This loss of BCSFB function, hypothesized to also induce "Chemobrain," serves as the gateway to eventual seeding of brain metastases.

Session 2: Multi-Modality Approaches to Primary and Secondary Brain Tumors

Zeynep Eroglu, MD, gave an in-depth overview of multi-modality therapies in the treatment of melanoma brain metastases (MBM), including a review of published data from CheckMate 204, ABC, COMBI-MB, and TRICOTEL trials. Ongoing studies include: 1) the ABC-X trial which is investigating dual-immunotherapy in conjunction with stereotactic radiosurgery (SRS), and 2) the SWOG S2000 trial, which is comparing efficacy of encorafenib and binimetinib combination with ipilimumab and nivolumab combination in BRAF-V600 mutant BM. Mohammad Khan, MD, PhD, outlined the evidence for concurrent SRS with PD1-blockage (pembrolizumab) for treatment of MBM. Data demonstrates that SRS + PD1 blockade may provide an equal or better intracranial benefit compared to dual checkpoint inhibition in treatment naïve patients. Needed in future trials is the comparison of SRS and pembrolizumab combination with dual checkpoint inhibition for melanoma and NSCLC BM. Stephen Bagley, MD, MSCE, illustrated key observations from his ongoing Phase II trial investigating atezolizumab with or without tocilizumab, combined with fractionated SRS. He explained that determination of treatment efficacy can be difficult with confounding pseudoprogression and radiation necrosis. Jann Sarkaria, MD, discussed a paradigm for optimizing potent radiosensitizers, which includes: 1) defining optimal dosing regimens, 2) evaluating in multiple patient-derived xenograft models, and 3) identifying an enhanced therapeutic window. He also shared promising data on peposertib as a potential radiosensitizer for BM.

For oral abstracts, Alison Mercer-Smith, PhD found that cytotoxic tumor-homing human induced neural stem cell "spheres" therapy effectively migrate to non-small cell lung cancer (NSCLC) leptomeningeal disease (LMD) following focal radiation, and significantly improve survival in a leptomeningeal tumor mice model. Jonathan Yang, MD, PhD, shared results from a Phase I trial investigating safety and toxicity of Paxalisib, a small molecule inhibitor of PI3K/mTOR in patients with solid tumor BM. Safety was established with concurrent cranial radiotherapy and promising CNS control was observed in the early data.

Session 3: Enhancing Local and Compartmental Therapies

In session 3, Joshua Palmer, MD, shared his expertise on best practices for postoperative fractionated SRS for brain metastases. He concludes that post-op SRS for patients with resected brain metastases should be a standard of care, given the better cognitive preservation and quality of life compared to whole brain radiotherapy (WBRT). Contouring techniques need to be improved and standardized to accurately assess superiority of SRS to WBRT in trials. There may also be a benefit to preoperative SRS, with evidence supporting its association with lower rates of radiation necrosis and lower risk of LMD. Debra Nana Yeboa, MD, presented a Phase III randomized control trial design on preoperative vs. postoperative SRS for BM, with the primary endpoint of 1-year LMD-free rate. Jeffrey Weinberg, MD, shared evidence supporting brachytherapy using intraoperative GammaTile, which is designed to deliver local radiotherapy along walls of the resection cavity. Trial results show it reduces radiation-related

brain changes compared to traditional brachytherapy or repeat external beam radiation therapy. The trial is currently accruing patients, with 11 sites open to enrollment.

For oral abstracts, Nelson Moss, MD, shared data on brachytherapy for salvage treatment of previously irradiated brain metastases. He found that high local control with brachytherapy is superior to resection-only in this population. Preoperative predictors of seed requirements will be necessary given the significant cost of implants. Jonathan Yang, MD, PhD, shared promising phase I and II data showing proton craniospinal irradiation has a safety and survival benefit compared to standard of care. Isabella Olivia, MD, PhD shared the first ever clinical data on intrathecal anti-PD1 therapy in metastatic melanoma patients with LMD, demonstrating safety, feasibility, and preliminary evidence of clinical activity at 3 months. Andrew Brenner, MD, summarized ReSPECT-LM U.S. Phase I clinical trial design and data for the investigation of Rhenium-186 nanoliposomes delivered intraventricularly, which redistribute throughout the CSF, and are retained in the leptomeninges for a week, allowing for a longer therapeutic window. Emilie LeRhun, MD, PhD, augmented the discussion with her perspectives on LMD trial design.

Session 4: New Therapies on the Horizon

Invited speakers in session 4 shared data on novel therapeutics in the CNS tumor space. Carey Anders, MD, summarized the promising DESTINY-Breast03 trial data on antibody drug conjugate, trastuzumab deruxtecan (TDxD), which has demonstrated intracranial efficacy in breast cancer BM. This has also shown strong response in a HER2-mutant NSCLC trial. Since CNS surveillance was not systematically assessed in all patients, conclusions regarding its CNS tumor activity cannot be made. However, retrospective trial analyses have found that patients with BM had similar response rate to those without CNS lesions. Priscilla Brastianos, MD, shared a thorough summary of therapeutic targets in brain metastases. She discussed the phenomenon of BM harboring distinct clinically actionable genetic alterations compared to their primary tumor and extracranial sites as a result of branched evolution. She summarized the design and preliminary data of the Alliance A071701 national biomarker driven trial in BM. Evanthia Galanis, MD, discussed therapeutic horizons in glioma, including vorasidenib for the treatment of BRAF V600E mutations in glioma, MDM inhibitors, and TMZ sensitization with PARP-inhibitors, among several other novel treatments. She advocated for science-driven trials to avoid drug development mistakes of the past. For the oral abstract, Soma Sengupta, MD, PhD, shared Phase 3 Cancer Stem Cell-targeted vs. physician choice treatments in patients with recurrent high-grade gliomas. Patients who received selective chemotherapy from an assay-guided tool had an overall survival benefit of 3.5 months and progression free survival of 6.6 months compared to control patients.

Session 5: Supportive Care in Neuro-Oncology

To start session 5, Kim Edelstein, PhD, summarized data on neurocognitive outcomes in adult patients with brain tumors. Cognitive impairment in brain tumor patients is common even before RT, and patients experience a wide variability in domains of Health-related quality of life affected. Patients who receive SRS as part of their tumor-directed treatment tend to improve cognitively over time following SRS. She also discussed cognitive rehabilitation, strategy training, and patient education to provide

patients with cognitive support. Paula Sherwood, RN, PhD, synthesized existing data on caregiver support and quality of life in patients with brain tumors and outlined the challenges with research in this space. Caregivers continue to report high levels of unmet needs, with numerous areas of investigation to explore. Deborah Forst, MD, shared her perspectives on palliative and supportive care for patients with brain tumors. The landmark Temel study in 2010 showed that patients who received early palliative care had improved quality of life. Palliative care in Neuro-Oncology remains vastly understudied and underutilized in practice. Considerations for palliative interventions in trials include defining population-specific needs, intervention development, and endpoint selection and assessment.

For oral abstracts, Randa Higazy found that patients with advanced cancer have high rates of cognitive impairment, but number and volume of brain metastases are not associated with cognitive outcomes. Katherine Peters, MD, PhD, found that patients who received BMX-001 had improved cognitive performance during concurrent RT and TMZ treatment compared to controls in a Phase I study. Phase II investigations are currently active. Denise Correa, PhD, shared data on neurocognitive function in patients with LMD treated with proton craniospinal irradiation. Patients showed significant decline from baseline to three months post-irradiation in graphomotor speed and verbal memory learning and significant decline from baseline to 6 months post-irradiation in timed set-shifting/ cognitive flexibility. There were no significant changes in attention/ working memory.

Session 6: Innovations in Spinal Tumors

Honing in on the recent innovations in treatment of spinal tumors, session 6 began with a talk from Divya Yerramilli, MD, MBE, that emphasized the importance of aligning patients' goals of care with treatment intent. Specific to radiation therapy (RT), the benefits and risks vary based on prognosis, with risks including physical toxicity, financial strain, and decreased quality of life. Likewise, clinical trial endpoints should be framed in the context of patient values. As the discussion moved to spinal laser interstitial thermal therapy (LITT), Dr. Claudio Tatsui, MD, shared patient cases of spinal tumors to display the treatment benefit and promise of LITT. He then advocated for development of evidence-based practice and expansion of access to care, with suggested advances including a multidisciplinary medical team approach of radiation oncology and imaging, ubiquitous access to intraoperative MRI, and insurance coverage through CPT codes. Following Dr. Tatsui, Jason Levy, MD, FSIR, presented data on percutaneous interventional procedures for the management of bony metastatic disease. The goals of these treatments, including radiofrequency ablation (RFA) and cryotherapy, are rapid pain relief, improvement in quality of life, ability to maintain a systemic treatment protocol, reduction in skeletal related events, and disease stabilization. He presented data from a multicenter clinical trial evaluating RFA for palliation of painful bone metastases, which is the largest prospective publication of any percutaneous ablation therapy. Results of this clinical trial demonstrated that patients treated with RFA for bony metastases, 89% of which were involving the thoracolumbar spine, experienced significant improvement in pain and quality of life, as quickly as 3 days post RFA and sustained up to 12 months post RFA. Lastly, Arjun Sahgal, MD, shared level 1 evidence in support of stereotactic body radiotherapy (SBRT) from a phase 2/3 clinical trial of SBRT versus conventional external beam radiotherapy in patients with painful spinal metastases. Further randomized controlled trials and clinical trials should focus on optimizing the regimen and overall practice of spine SBRT.

Session 7: Current and Future Approaches for Integrating Neuroimaging into CNS Cancer Clinical Trials

Session 7 offered insight into the cutting-edge technology that is advancing the armamentarium of neuroimaging for primary brain tumors and brain metastases. Described through a compelling talk by Javier Villanueva-Meyer, MD, advocating for the inclusion of advanced neuroimaging in clinical trials, the versatility of techniques favors neuroimaging as a pivotal methodology for research studies designed to address various knowledge gaps. He recommended including mechanism-informed advanced imaging in clinical trial budgets, so that this is not "optional," but a well-powered analysis in the trial design. Raymond Huang, MD, PhD, shared how evolving techniques which include artificial intelligence and volumetric imaging offer complementary data to current mainstay diagnostic imaging, exhibiting potential to facilitate advanced detection and response assessment. Similarly, early results from a clinical trial studying adaptive radiotherapy which targets specific imaging-based phenotypes were shared by Michelle Kim, MD, demonstrating the applicability of advanced imaging biomarkers in identifying treatment-resistant regions of glioblastoma. Furthermore, other talks and abstracts detailed the utility of neuroimaging in determining a widely accepted standard of imaging endpoints for neuro-oncology clinical trials, distinguishing radiation necrosis from tumor or recurrent disease, and establishing diagnostic criteria for leptomeningeal disease. Further discussion highlighted that while neuroimaging classically represents "a snapshot in time," metabolic imaging is unique and utilizable for its insight on disease progression.

Session 8: Challenges in Pediatric Investigations

Duane Mitchell MD, PhD, of the University of Florida kicked off session 8 discussing innovation in vaccines for childhood brain tumors and explaining how therapeutic vaccines induce T-cell responses that localize to CNS tumors. Challenges in pediatric brain tumor immunotherapy; including overcoming the immunosuppressive tumor microenvironment (TME), identifying potent tumor rejection antigens, addressing tumor heterogeneity, and risking increased neurotoxicity; present distinct hurdles in the development of the aforementioned vaccines. Dr. Mitchell explained the mechanisms of action and clinical trials of peptide vaccines, dendritic cell vaccines, and mRNA-based vaccines, as well as the future directions utilizing precision immunotherapy with identified tumor targets. Next, Uri Tabori, MD, shared updates on immune approaches for hypermutant childhood cancers and his group's related research on tailoring immunotherapy for Replication-Repair Deficient glioblastoma. He explained how clinical trials investigating immune checkpoint inhibition (ICI) therapy with anti-PD1 therapy nivolumab appear effective for hypermutant pediatric tumors. Further prospective studies and clinical trials are investigating various combinatorial ICI therapies in this patient population. Following Dr. Tabori, Robert Wechsler-Reya, PhD, discussed novel therapeutic designs for MYC-driven medulloblastomas, which comprise 20-30% of human medulloblastomas and recur more frequently than other classes of medulloblastoma. Recognizing the benefit of a MYC-specific therapeutic given the activation of this proto-oncogene in more than 50% of all cancers, Dr. Wechsler-Reya's lab has developed a high content imaging- based assay for compounds that reduce MYC levels in medulloblastoma patient-derived xenografts; this assay has been used to identify compounds that accumulate in brain tissue and inhibit

MYC in intracranial tumors. Laura Donovan, PhD, later opened the discussion on the basic science of CAR-T cell therapy. In mouse group 3 medulloblastoma models, repeat administration of CAR-T cell therapy increases therapeutic efficacy, intraventricular CSF delivery allows direct CAR-T cell access to the tumor site, and combination of CAR-T cells with azacytidine leads to significant improvement in overall survival. A clinical trial studying intracranial CAR-T cell treatment is now underway, beginning to bridge promising results of murine studies to clinical translation. The discovery of this treatment is potentially paradigm shifting in the treatment of medulloblastoma and ependymoma, as Dr. Donovan explained this technology's ability to improve disease prognosis and resulting quality of life for surviving patients.

For oral abstracts, Mason Webb presented his group's research on the intratumoral delivery of adenovirus expressing CD40L, a potent immune costimulator. Delivery of these adenoviruses to mouse models of brainstem or frontal lobe gliomas has resulted in enhanced survival benefit. Using a conditionally replicative adenovirus for delivery maintained anti-tumor efficacy while reducing toxicity in murine models, so development of clinical trials investigating conditionally replicative adenoviruses expressing CD40L for treatment of recurrent pediatric high-grade gliomas is underway.

Session 9: How to Get a Therapy to Approval?

Session 9 closed out the conference forums with a discussion on the steps to progress novel therapeutics through rigorous experimentation, to clinical trials and assessments, to approval. Michael Weller, MD, began the session by contributing his insight on how to take a clinical trial from phase II to phase III. He advised that prerequisites for phase III trials include strong randomized phase II data or overwhelming uncontrolled phase II data if proceeding with caution. Next, Michael Davies, MD, PhD, and Howard Fine, MD, shared guidance for incorporating biologic assessments, including immune monitoring and biomarkers, as thresholds for taking drugs further into clinical development. Dr. Davies encouraged opportunities for non-invasive assessment of biomarkers, such as imaging, to overcome tumor heterogeneity and other common challenges of biomarker studies in drug development for CNS metastases. Dr. Fine shared his expertise from the angle of primary brain tumors, advising go/no go drug development decisions based on the drug's degree of engagement with target and mediation of toxicity, and closing with recommendations for the development of novel biomarkers to advance drug development in neuro-oncology. Susan Geyer, PhD, later discussed the importance of defining and balancing goals in early phase clinical trials of neuro-oncology research. She proposed that more complex trial design modeling might allow for information to be shared between phase 0 and phase I trials, highlighting opportunities for growth in this area of clinical trial design.

For oral abstracts, Mei-Yin Polley, PhD, raised the topic of using external control data for planning and supplementing randomized control (RCT) data in GBM trials, concluding that historical controls are not suitable for primary analysis of GBM confirmatory trials, but might be appropriate as primary analysis in early proof-of-concept trials. Omar Elghawy shared updates on the current state of clinical trials for patients with melanoma brain metastases. While most melanoma clinical trials excluded patients with active CNS or leptomeningeal disease, non-pharmaceutical sponsors and trials of non-immuno-oncology therapy were more likely to include active CNS disease compared to their respective counterparts.

Mustafa Khasraw, MD closed the session talks, preceding only a final panel discussion, by addressing future directions of clinical trials for patients with CNS cancers. He emphasized the importance of trials being guided by foundational science and reliable methods; utilizing new non-invasive technology; and involving collaboration with patient advocacy, academia, community oncology, and industry.