cnio.es/app/BrainMetastasis/CellLines) represents the first of its class and includes information about each cell line, how tropism to the brain was established, and the behavior of each model *in vivo*. The BrMPanel is composed of 60 cell lines, derived from patients (32 cell lines, 53%), mouse (27, 45%) or rat (1, 2%), and represent the three main cancer types that result in brain metastasis: breast cancer (38 cell lines, 63%), lung cancer (8, 13%) and melanoma (14, 23%). This resource is intended to assist investigators in choosing the most suitable model for research on brain metastasis, and is available to the entire scientific community. The ultimate goal of this effort is to facilitate research on this unmet clinical need, to improve models through a collaborative environment, and to promote the exchange of information on these valuable resources. We invite other collaborators to contribute their models to the BrMPanel to grow this resource.

### 53. TUCATINIB VS PLACEBO ADDED TO TRASTUZUMAB AND CAPECITABINE FOR PATIENTS WITH PREVIOUSLY TREATED HER2+ METASTATIC BREAST CANCER (MBC) WITH BRAIN METASTASES (BM) (HER2CLIMB)

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BACKGROUND: HER2CLIMB (NCT02614794) primary results have been reported previously (Murthy, NEJM 2019). We report results of exploratory efficacy analyses in pts with brain metastases (BM). METHODS: MBC pts enrolled had a baseline brain MRI. Pts with BM were eligible and randomized 2:1 to receive tucatinib (TUC) or placebo, in combination with trastuzumab and capecitabine. Efficacy analyses were performed by applying RECIST 1.1 to the brain based on investigator evaluation. CNS-PFS and OS were evaluated in BM pts overall. Intracranial (IC) confirmed ORR-IC and DOR-IC were evaluated in BM pts with measurable IC disease. After isolated brain progression, pts could continue study therapy until second progression, and time from randomization to second progression or death was evaluated. RESULTS: Overall, 291 pts (48%) had BM at baseline: 198 (48%) in the TUC arm and 93 (46%) in the control arm. There was a 68% reduction in risk of CNS-PFS in the TUC arm (HR: 0.32; P<0.0001). Median CNS-PFS was 9.9 mo in the TUC arm vs 4.2 mo in the control arm. Risk of overall death was reduced by 42% in the TUC arm (OS HR: 0.58; P=0.005). Median OS was 18.1 mo vs 12.0 mo. ORR-IC was higher in the TUC arm (47.3%) vs the control arm (20.0%). Median DOR-IC was 6.8 mo vs 3.0 mo. In pts with isolated brain progression who continued study therapy after local treatment (n=30), risk of second progression or death was reduced by 71% (HR: 0.29), and median time from randomization to second progression or death was 15.9 mo vs 9.7 mo, favoring the TUC arm. CONCLUSIONS: In pts with previously treated HER2+ MBC with BM, TUC in combination with trastuzumab and capecitabine doubled the ORR-IC, reduced risk of IC progression or death by two-thirds and reduced risk of death by nearly half.

### 54. TGLI1 IS AN ACTIONABLE THERAPEUTIC TARGET IN BREAST CANCER BRAIN METASTASES

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Breast cancer is the second leading cause of brain metastases in women; patients with breast cancer brain metastasis (BCBM) survive an average of 6–18 months following diagnosis. Cancer stem cells are thought to be one of the driving forces behind distant metastasis, treatment resistance, and late-stage recurrence. The hedgehog-smoothened pathway has been identified as an important mediator of breast cancer stem cells (BCSC); however, FDA-approved therapies targeting smoothened have demonstrated limited clinical efficacy in breast cancer. Despite advances made in understanding BCSC, it is still challenging to effectively target BCSC underscoring the need to identify and inhibit novel mediators of BCSC for treating BCBM patients. Our laboratory recently reported that truncated glioma-associated oncogene homolog 1 (tGLI1) promotes preferential metastasis to the brain in breast cancer by activating BCSC and astrocytes in the tumor microenvironment (Oncogene 39:64–78, 2020). tGLI1 was discovered in our laboratory as an alternatively spliced GLI1 that functions as a tumor-specific gain-of-function transcription factor and terminal effector of the hedgehog pathway. We found that tGLI1 knockdown abrogated BCBM, providing the rationale to therapeutically target tGLI1. Cell-based chemical screens followed by validations demonstrated that ketoconazole, an FDA-approved azole antifungal, specifically inhibits tGLI1 leading to suppression of BCSC in vitro and BCBM in vivo. Based on these data, we opened a window-of-opportunity study in patients with BCBM to determine if ketoconazole penetrates the blood-brain barrier (BBB) and alters tGLI1 signaling in humans (NCT03796273). Preliminary sample analysis has confirmed tGLI1 expression in collected BCBM samples. To help identify more effective tGLI1 inhibitors, we screened 63 azole compounds for tGLI1-selectivity and identified four additional compounds as potential tGLI1 inhibitors. Animal studies were performed to compare the efficacy of these four compounds with ketoconazole in suppressing BCBM. Collectively, these data establish tGLI1 as an actionable target for BCBM.

### 55. A RANDOMIZED, MULTICENTER PHASE III TRIAL OF SURGERY PLUS STEREOTACTIC RADIOSURGERY (SRS) COMPARED WITH SURGERY PLUS PERMANENTLY IMPLANTED COLLAGEN TILE BRACHYTHERAPY (CTBT) FOR RESECTABLE METASTATIC BRAIN TUMORS-PROTOCOL IN PROGRESS

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BACKGROUND: Resection (R) followed by single or multi-fraction stereotactic radiosurgery (SRS) lowers resection bed recurrence compared to R alone. Nevertheless for larger brain metastasis (>2.5 cm) 12-month recurrence rates after R+SRS can exceed 20–30%. Aiming to improve outcomes, a permanently implanted collagen tile brachytherapy (CTBT) device (GammaTile, GT Medical Technologies, Tempe AZ) utilizing Cs-131 was developed, hypothesizing that immediate adjuvant radiotherapy (RT) and/or RT dose intensification could improve outcomes. The device received FDA clearance for this indication, based on a single-arm pre-commercial study and in early commercial use due to the excellent safety and local control of R+CTBT. It is hypothesized that R+CTBT will increase the time to post-resection-recurrence, while prolonging survival and reducing the impact on functional and neurocognitive status compared to R+SRS. STUDY DESIGN: Multicenter, randomized, comparison trial. Patients with resectable, previously untreated "index" brain metastases measuring >2.5–5 cm and 0–3 other tumors will be preoperatively randomized 1:1 to undergo either R+ SRS or R+CTBT to the index lesion; unresected tumors in both groups will receive SRS. Planned sample size is 160 from ~5 sites; accrual to start in Q3-2020. Primary endpoint is surgical bed-recurrence free survival. Secondary endpoints include overall survival, quality of life (Functional Assessment of Cancer Therapy-Brain, Linear Analog Self-Assessment), neurocognition (Hopkins Verbal Learning Test, Trail Making Tests, Mini-Mental Status Exam, Controlled Oral Word Association), functional decline (Karnofsky Performance Scale, Barthel-ADL), and adverse events. Follow-up will be at 1,3,6,9, and 12 months, then q 6 months through 5 years. CONCLUSIONS: This will be the first randomized trial comparing R+SRS versus R+CTBT delivered by Cs-131 sources in permanently implanted resorbable collagen tile carriers. Primary and secondary outcome measures will be captured to elucidate the potential risks and benefits of these two differing approaches for patients with metastatic brain tumors.

### 56. TUMOR-HOMING STEM CELL THERAPY INHIBITS THE PROGRESSION OF BREAST CANCER LEPTOMENINGEAL CARCINOMATOSIS

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INTRODUCTION: Leptomeningeal carcinomatosis remains one of the most lethal forms of central nervous system metastasis, with a median survival of only 4 months. Effective new therapies are urgently needed to treat this highly aggressive cancer. In this study, we used models of both prophy-

lactic and established leptomeningeal disease to investigate the efficacy of engineered tumor-homing neural stem cells (NSCs) therapy for breast cancer leptomeningeal carcinomatosis. METHODS: Personalized NSC carriers were created using Sox2 overexpression to transdifferentiate human fibroblasts into induced NSCs (iNSCs) that home to cancer cells and carry therapeutic agents to induce tumor kill. Leptomeningeal models were created by engineering MDA-MB231-Br human breast cancer cells with fluorescent and bioluminescent reporters, then using intracisternal injection to inoculate Nude mice with the tumor cells. iNSC therapy was evaluated by infusing iNSCs releasing the pro-apoptotic agent TRAIL into the lateral ventricle of mice either 1 week prior to or 3 days after tumor inoculation for prophylactic or established tumor treatment respectively. Tumor progression in the brain and spinal cord was monitored by serial bioluminescence imaging (BLI). RESULTS: Serial BLI showed that intracerebroventricular (ICV) iNSC-TRAIL therapy reduced the volume of metastatic tumor burden 99.49% in the brain and 99.80% in the spine within 2 weeks post-infusion and extended survival from 24 to 42 days. Additionally, prophylactic iNSC-TRAIL therapy delivered ICV markedly delayed tumor development, with tumors in the brain remaining >1000-fold smaller than control through 1-month post-treatment, below the limit of detection in the spinal cord through 1 month, and eliminating mortality through 50 days post-therapy. CONCLUSION: These data suggest that iNSC therapy could be a promising treatment option for breast cancer patients with leptomeningeal carcinomatosis.

## 57. CIRCULATING TUMOR CELLS (CTC) IN CEREBROSPINAL FLUID (CSF) AS A PREDICTOR OF SURVIVAL IN CNS METASTASES

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BACKGROUND: CSF-CTC testing using the CellSearch® platform is a validated diagnostic tool for leptomeningeal metastases (LM) from solid tumors. CSF-CTCs can also be detected in patients with brain metastases (BM), but their significance is unclear. Our objective was to evaluate the utility of CSF-CTC measurement in predicting outcomes in CNS metastases. METHODS: We conducted a retrospective single-institution review of patients who underwent CSF-CTC testing from 2016–2019. Information on neuroaxis imaging, CSF results, systemic cancer status, tumor molecular profile and survival was collected. LM was diagnosed by unequivocal MRI findings and/or positive or suspicious CSF cytology. Survival analyses were performed using Cox proportional hazards modeling, and CSF-CTC splits associated with survival were identified through recursive partitioning analysis. RESULTS: A total of 407 patients (38% lung primary, 34% breast, 28% other tumor types) were included; of these, 144 had LM and 233 had BM diagnosed before or around the time of CSF analysis (97 had both). We identified a subgroup of newly diagnosed CNS metastases, comprising 144 patients with LM, BM, or both diagnosed within 30 days of CSF sampling: 70 patients with LM, 43 with BM, and 31 with both. For 101 patients with newly diagnosed LM, mean and median CSF-CTCs were 127.3 and 200, respectively, compared to 44.6 and 0 in the overall cohort; 73/101 had positive (66) or suspicious (7) cytology. CSF-CTCs predicted survival in patients with newly diagnosed LM, with optimal cutoff identified at 61 CSF-CTCs, above which the risk of death doubled (HR=2.09, 95% CI: 1.13–3.87, p=0.02). For this group, positive/suspicious cytology was also associated with higher risk of death, but this result was not statistically significant (HR=1.79, 95% CI: 0.95–3.35, p=0.07). CONCLUSION: In newly diagnosed LM, quantification of CSF-CTCs predicts survival. CSF-CTC measurement can be used as a prognostic tool in patients with CNS metastases.

## 58. CLINICAL PRESENTATION AND IMAGING CHARACTERISTICS OF LEPTOMENINGEAL CARCINOMATOSIS (LC) IN PATIENTS WITH EGFR MUTATED NON-SMALL CELL LUNG CANCER (NSCLC)

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BACKGROUND: LC is a late and often fatal manifestation of advanced EGFR mutated NSCLC with up to 9% of patients developing LC. Given the higher incidence of LC in EGFR mutated tumors, we hypothesized it may have unique imaging and clinical characteristics. METHODS: We identified 23 patients with EGFR mutated NSCLC and LC treated at a large academic institution between 2016 and 2019. Clinical and treatment characteristics were obtained from the electronic medical record. Radiographic subtype of LC and presence of ventriculomegaly were determined by independent review of available brain and spine MRI imaging. RESULTS: Among 23 eligible patients, mean age was 57 years, 96% had advanced NSCLC at diagnosis and 61% had EGFR exon 19 deletion. Median time from NSCLC diagnosis to LC

development was 23 months (95% CI:13–33), with only 17% of patients presenting with LC in the absence of parenchymal brain metastases. Of the 91% of patients with radiographic evidence of LC, equal numbers had nodular or linear LC (22% each) and 39% had a mixed presentation. Additionally, 30% of patients had evidence of spinal LC. Ventriculomegaly was present in 52% of patients, with 48% developing clinical symptoms of hydrocephalus and 13% receiving shunt placement. Median overall survival (OS) from time of LC diagnosis was 3.9 months (95% CI:2.7–10.0), which is lower than in prior published studies. Patients with nodular LC and absence of ventriculomegaly fared better with a median OS of 6.5 months and 5.7 months respectively. CONCLUSIONS: OS is poor in patients with LC associated with EGFR mutated NSCLC, although appears better in patients with nodular LC. The high incidence of hydrocephalus emphasizes the need for its early recognition and treatment. Further studies are needed to identify promising treatment strategies and to determine factors associated with improved OS in this population.

## 59. A RADIOMICS-BASED MACHINE LEARNING MODEL FOR DISTINGUISHING RADIATION NECROSIS FROM PROGRESSION OF BRAIN METASTASES TREATED WITH STEREOTACTIC RADIOSURGERY (SRS)

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PURPOSE: This study aims to test whether MRI radiomic signatures can distinguish radiation necrosis (RN) from tumor progression (TP) in a multi-institution dataset using machine learning. METHODS: Brain metastases treated with SRS were followed by serial MRI, and those showing evidence of RN or TP underwent pathologic confirmation. Radiomic features were extracted from T1 post-contrast (T1c) and T2 fluid attenuated inversion recovery (T2 FLAIR) MRI. High dimensional radiomic feature space was visualized in a two-dimensional space using t-distributed stochastic neighbor embedding (t-SNE). Cases from 2 institutions were combined and randomly assigned to training (2/3) and testing (1/3) cohorts. Backward elimination was used for feature selection, followed by random forest algorithm for predictive modeling. RESULTS: A total of 135 individual lesions (37 RN and 98 TP) were included. The majority (72.6%) received single-fraction SRS to a median dose of 18Gy. Clear clustering of cases around the institutional origin was observed on t-SNE analysis. 21 T1c and 4 FLAIR features were excluded from subsequent modeling due to significant correlation with the institutional origin. Backward elimination yielded 6 T1c and 6 FLAIR features used for model construction. A random forest model based on the 6 FLAIR features (cluster shade, neighborhood gray tone difference matrix (NGTDM) coarseness, NGTDM texture strength, run length nonuniformity, run percentage, and short run high gray-level emphasis) achieved sensitivity of 76% and specificity of 70% on the training cohort (AUC 0.74, 95% CI 0.60–0.88), and sensitivity of 67% and specificity of 83% on the testing cohort (AUC 0.75, 95% CI 0.59–0.93). Addition of the T1c features resulted in overfitting of the training cohort (AUC 1.00), but did not improve model performance on the testing cohort (AUC 0.69, 95% CI 0.51–0.87). CONCLUSION: MRI radiomics based machine learning can distinguish RN from TP after brain SRS in a heterogeneous image dataset.

## 60. IDEAL TREATMENT REGIMEN FOR PATIENTS WITH ≥1 BRAIN METASTASIS FROM PRIMARY NON-SMALL-CELL LUNG CANCER – A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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BACKGROUND: Brain metastases (BM) are common in non-small cell lung cancer (NSCLC). The aim of this study was to assess the comparative effectiveness of treatments for BM from NSCLC. METHODS: We searched MEDLINE, EMBASE, Web of Science, ClinicalTrials.gov, CENTRAL and references of key studies for randomized controlled trials (RCTs) published