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: All HER2+ 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-