sequencing and PDX modeling. CONCLUSION: We propose a trial using clinical microdialysis, placed in diffuse midline glioma tissue post biopsy, as an experimental research tool, to assess CNS drug entry and targeted inhibition with abemaciclib. These studies will be the first of their kind focused on the dynamic nature of CNS drug delivery with the overall intent to inform future clinical therapies.

**CLRM-06**

**PROSPECTIVE CLINICAL STUDY OF CONVENTIONALLY FRACTIONATED CONCURRENT CHEMORADIOTHERAPY AND HYPOFRACTIONATED CONCURRENT CHEMORADIOTHERAPY AFTER THE SURGERY OF HIGH-GRADE GLIOMAS**

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PURPOSE: To observe and evaluate the efficacy and safety of conventional fractionated concurrent chemoradiotherapy and hypofractionated concurrent chemoradiotherapy for adjuvant treatment of newly treated high-grade glioma. METHOD: For newly treated patients with high-grade gliomas with WHO grade III-IV, all patients started concurrent chemoradiotherapy within 1 month after surgery, and received concurrent temozolomide 75 mg/m2 during radiotherapy until the end of radiotherapy. Sequential temozolomide chemotherapy at 200 mg/m2 for at least 6 cycles. All patients were randomly divided into groups, one group was given conventional fractional irradiation, 60Gy/30f in high-risk areas, 46Gy/23f in low-risk areas, and the other group was given low-fractionated irradiation, 53Gy/15f in high-risk areas, and 53Gy/15f in low-risk areas 43Gy/15f. The overall survival (OS), progression-free survival (PFS), radiation-induced cerebral edema and radiation-induced brain necrosis were evaluated. RESULT: As of December 31, 2022, a total of 60 patients were enrolled, including 30 in the conventional fractionation treatment group and 30 in the hypofractionated treatment group. At present, 58 patients survived and 2 died, 2 in the conventional fractionation group, one due to tumor recurrence and one due to cardiac accident; 7 patients recurred, including 4 in the conventional fractionation group and 3 in the low fractionation group. Radiation cerebral edema occurred in 9 cases, 6 cases in the hypofractionated group and 3 cases in the conventional fractionation group, all of which were completely relieved after dehydration with mannitol, which did not affect the progress of radiotherapy. No radiation necrosis occurred during follow-up. CONCLUSION: Compared with the standard stupp regimen, using 53Gy/15f in the high-risk area and 43Gy/15f in the low-risk area as an adjuvant therapy with concurrent temozolomide and sequential temozolomide, there was no increased risk of disease recurrence, no increased risk of death, and no increased risk of death.

**CLRM-07**

**A MULTIVARIATE RETROSPECTIVE ANALYSIS OF 159 PATIENTS WITH HIGH-GRADE GLIOMAS: OVERALL SURVIVAL, PROGRESSION-FREE SURVIVAL, AND PROGNOSTIC FACTORS**

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BACKGROUND AND PURPOSE: High-grade gliomas are highly malignant, aggressive, high incidence rate, and mortality. The purpose of this study was to analyze retrospectively and identify prognostic factors of patients with high-grade gliomas diagnosed by biopsy or postoperative pathological examination. METHODS: In this retrospective study, we analyzed the patient's demographic data, tumor characteristics, treatment approaches, immunocytochemistry results, the overall survival (OS) time, and the progression-free survival (PFS) time in a series of 159 histologically proven high-grade gliomas recruited from January 2011 to December 2019. OS time and PFS time were analyzed by Kaplan-Meier survival analysis with log-rank test and found the independent factors by using Cox regression analysis. RESULTS: Survival analysis showed that an OS of 84.90%, 55.35% and 13.20% was observed at 1, 2 and 5 years, respectively. And a PFS of 56.6%, 25.26% and 3.14% was observed at 1, 2 and 5 years, respectively. The mean OS was 52.73 months and mOS was 35 months. Univariate analysis showed that postoperative pathological classification and grade and age were statistically significant for patient outcome ($P < 0.01$). 147 patients underwent concurrent chemoradiotherapy and 80 of them died; 12 patients did not undergo concurrent chemoradiotherapy and 10 died ($P = 0.03$); There were statistically significant differences in the prognostic impact of Ki-67 expression, MGMT, IDH1R132H and p53 mutations by immunohistochemistry ($P = 0.001$; $P = 0.016$; $P = 0.003$; and $P = 0.021$, respectively). Similarly, we concluded that different grades, age, pathological classification, Ki-67 and IDH1R132H expression by immunohistochemistry were statistically significantly associated with PFS ($P < 0.01$; $P = 0.004$; $P = 0.003$; $P = 0.001$; $P = 0.028$). CONCLUSIONS: Tumor grade and concurrent chemoradiotherapy after surgery were independent prognostic factors affecting patients' survival, and grade was also an independent factor affecting PFS.

**CLRM-08**

**TARGETING IMMUNE-PAYLOAD TO THE GLIOBLASTOMA TUMOR MICROENVIRONMENT USING A MACROPHAGE-BASED TREATMENT RELYING ON AUTOLOGOUS, GENETICALLY MODIFIED, HEMATOPOIETIC STEM CELL-BASED THERAPY: THE TEM-GBM STUDY (NCT03866109)**

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We developed an autologous hematopoietic stem cell-based platform designed to deliver IFNa, by a transcriptional and post-transcriptional control mechanism mediated by miRNA target sequences, specifically into the tumor microenvironment (TME) via Tie-2 expressing monocytes (Temferon). As of Feb 2022, 3 escalating doses of Temferon (0.5-2.0x106/kg) were tested across 15 newly diagnosed, unmethylated MGMT GBM patients assigned to 5 cohorts. Follow-up from surgery is 6–28mo (2–25mo after Temferon). To date, no DLTs have been identified. As expected, 1mo after the administration of the highest tested dose, the hematopoietic system of Temferon-treated patients was composed of up to 30% of CD14+ modified cells. Temferon-derived progeny persisted, albeit at lower levels, up to 18mo (longest time of analysis). Despite the substantial proportion of engineered cells, very low concentrations of IFNα were detected in the plasma and in the CSF, indicating tight regulation of transgene expression. SAEs were mostly attributed to conditioning chemotherapy (infections) or disease progression (seizures). 1SUSAR (persistent GGT elevation) occurred. Median OS is 15mo from surgery. Homing of transduced cells to the tumor was demonstrated by the presence of gene-marked cells in the 2nd surgery specimens of 3 out 4 pts belonging to low dose cohorts. Single-cell RNA seq of the TME highlighted a Temferon signature associated with the induction IFNa responsive genes and macrophage repolarization. Potential long-term benefit with Temferon was identified in a patient from cohort 3, who had PD at D+120 with two distant enhancing lesions, and increased tumor necrosis. 1y following Temferon, with no 2nd-line therapy added, there was approximately 40% reduction in enhancing tumor volume compared to D+180 with a stable clinical and imaging picture thereafter. The results provide initial evidence of Temferon's potential to modulate the TME of GBM patients, and anecdotal evidence for long lasting effects of Temferon in prevention of disease progression.

**CLRM-09**

**FIRST-LINE TUMOR TREATING FIELDS (200 KHZ) THERAPY FOR NEWLY-DIAGNOSED GLIOBLASTOMA: THE PHASE 3 TRIDENT TRIAL (EF-32)**

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BACKGROUND: Tumor Treating Fields therapy (TTFields; 200 kHz) comprise alternating electric fields that disrupt cancer cell division, and is approved for newly diagnosed glioblastoma (ndGBM), recurrent GBM and mesothelioma. In the phase 3 EF-14 trial, TTFields/temozolomide

(TMZ) significantly increased overall survival (OS) and progression-free survival (PFS) vs TMZ alone in patients with ndGBM. TTFields-related adverse events (AEs) were mainly dermatological with no increases in systemic toxicity. In preclinical models, the addition of TTFields to radiotherapy (RT) increased the therapeutic effect. Additionally, TTFields added to RT/TMZ was reported as feasible and well-tolerated in 2 clinical pilot phase 2 studies. MATERIALS AND METHODS: TRIDENT (EF-32; NCT04471844) is an international, phase 3 randomized trial comparing TTFields (200 KHz, ≥18 h/day)/RT/TMZ vs RT/TMZ alone. Adult patients (N=950; ≥18 years of age [≥22 years of age; US]) with histologically confirmed ndGBM, Karnofsky Performance Status ≥70, life expectancy ≥3 months, adequate organ function and eligible for RT/TMZ will be enrolled. Patients will be stratified by extent-of-resection and MGMT promoter methylation status and randomized 1:1 to receive continuous TTFields/RT/TMZ or RT/TMZ during the investigational period. Subsequently, all patients will receive TTFields/6 cycles of maintenance TTFields/TMZ; TTFields will continue for 24 months or until second disease progression per Response Assessment in Neuro-Oncology (RANO). The primary endpoint is median OS. Secondary endpoints include median PFS (RANO), 1- and 2-year survival rates, overall radiological response (RANO), PFS6, PFS12, severity and frequency of AEs and quality-of-life, OS per TTFields duration-of-usage. The study is powered at 80% to detect a hazard ratio of <0.8 (5% type I error). The study is currently open to enrolment in Austria, Belgium, Czech Republic, France, Germany, Israel, Switzerland, and across the US.

## CLRM-10

### METIS (EF-25): A PIVOTAL, RANDOMIZED CONTROLLED STUDY OF TUMOR TREATING FIELDS IN PATIENTS WITH 1–10 BRAIN METASTASES FROM NON-SMALL CELL LUNG CANCER

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BACKGROUND: Tumor Treating Fields (TTFields) are electric fields that disrupt cancer cell division. TTFields treatment showed efficacy in preclinical non-small cell lung cancer (NSCLC) models. Furthermore, TTFields therapy improved survival with a tolerable safety profile in patients with glioblastoma. The objective of the pivotal METIS trial [NCT02831959] is to evaluate the efficacy and safety of TTFields therapy in NSCLC patients with brain metastases. METHODS: NSCLC patients (N=270) with 1–10 brain metastases will be randomized 1:1 to stereotactic radiosurgery (SRS) followed by continuous TTFields therapy using NovoTTF-200M (150 kHz, recommended >18 h/day) with best standard of care (BSC) or SRS followed by BSC alone. Follow-ups will be conducted every 2 months until second intracranial progression. Key inclusion criteria are: Karnofsky Performance Status ≥70, new diagnosis of 1 inoperable or 2–10 supra- and/or infratentorial brain metastases from NSCLC amenable to SRS, and optimal therapy for extracranial disease. Key exclusion criteria are: prior whole brain radiotherapy, single operable, or recurrent brain metastases. Primary endpoint is time to first intracranial progression. Secondary endpoints include time to neurocognitive failure, overall survival, radiological response rate (RANO-BM and RECIST V1.1), quality of life, adverse events, time to first/second intracranial progression for patients with 1–4 and 5–10 brain metastases, bi-monthly intracranial progression rate from 2–12 months, and time to second intracranial and distant progression. The study is powered at 80% (2-sided alpha of 0.05) to detect a hazard ratio of 0.57. In July 2021, an independent Data Monitoring Committee (DMC) reviewed the study data and recommended continuation as planned. The trial is currently recruiting at 92 sites in North America, Europe, Israel, mainland China and Hong Kong.

## CLRM-11

### CURRENT STATE OF CLINICAL TRIALS FOR PATIENTS WITH MELANOMA BRAIN METASTASES

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INTRODUCTION: Clinical trials have traditionally excluded patients with melanoma brain metastasis (MBM), despite evidence of CNS activity of systemic therapy. The true extent of variation in MBM-related enrollment criteria in ongoing melanoma clinical trials has not been evaluated. METHODS: A systematic search of clinicaltrials.gov website was performed to characterize trends in clinical trial enrollment of MBM patients in interventional drug trials. Trial data search was limited to "open", "interventional studies" and advanced stage melanoma in adult patients. Logistic regression was used to model inclusion of active MBMs. Covariates considered were phase of study, location, therapy type, melanoma specific, and sponsor category RESULTS: Of a total of 475 trials identified, 365 met inclusion criteria. 230 (63.0%) were phase I, 119 (32.6%) were phase II, 14 (3.8%) were phase III and 2 (0.5%) were phase IV trials. 184 (50.4%) were pharmaceutical industry sponsored, 183 (50.1%) were specific for melanoma. Forty-seven (12.8%) trials strictly excluded brain metastasis and 173 (47.3%) strictly excluded leptomeningeal disease (LMD). 261 (71.5%) trials allowed patients with previously treated MBM, and 73 (20.0%) allowed patients with active MBMs. No explicit mention of CNS metastasis was made in 13.6% of trials and no mention of LMD was made in 43.8% trials. In univariate models, trials not employing immunotherapy (odds ratio 2.23; 95% CI: 1.2, 4.3; p = 0.0174) and non-pharma trials (odds ratio 1.98; 95% CI 1.0, 3.9; p= 0.0461) were twice as likely to include MBM patients. In a combined model, only therapy type remained significant at the $\alpha$=0.05 level. CONCLUSION: Despite the evidence of CNS activity of immunotherapy in randomized trials, only 20% ongoing trials are enrolling patients with active MBMs. Efforts should be made to tailor future clinical trial designs to include MBM patients to assess CNS activity of systemic therapeutics early on in drug development.

## CLRM-12

### TITLE: STEREOTACTIC RADIOSURGERY (ADJUVANT OR NEOADJUVANT) COMPARED TO HIPPOCAMPAL AVOIDANCE WHOLE BRAIN RADIATION THERAPY WITH SIMULTANEOUS INTEGRATED BOOST FOR LIMITED BRAIN METASTASES (SRS-CHART): PHASE III OPEN-LABEL PARALLEL-GROUP RANDOMIZED CONTROLLED TRIAL

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BACKGROUND: Surgery is indicated for large or symptomatic lesions in patients with limited brain metastasis (BM), followed by adjuvant stereotactic radiosurgery (A-SRS) to the cavity. Emerging evidence suggests promising role of neoadjuvant SRS (NA-SRS) before surgery with potentially lesser risk of leptomeningeal disease (LMD) and radionecrosis (RN). Hippocampal avoidance whole brain radiotherapy (HA-WBRT) results in better neurocognitive outcomes than standard WBRT, and use of simultaneous integrated boost (SIB) to surgical cavity can improve the local control. Absence of high-quality evidence forms the basis of current study comparing these three treatment strategies. OBJECTIVES: Primary endpoint is 1-year event-free survival (EFS) a composite endpoint comprising any local failure, LMD, DBF, symptomatic RN, or death as events. Other endpoints include individual endpoints and longitudinal neuro-cognitive function and quality-of-life assessment. METHODS: Target population includes adults with newly diagnosed BM (≤3 lesions) with life expectancy >1 year and one target lesion needing surgery. Patients will be randomized (1:1:1) to A-SRS (control arm) or one of two test arms (NA-SRS or HA-WBRT-SIB). In A-SRS arm, patients will receive single fraction (16-20Gy) or hypofractionated-SRS (24-27Gy/3 fractions or 30-32.5Gy/5 fractions) based on volume and location of cavity and other intact BM. In the test arms, patients will be allocated to either NA-SRS group (single/multi-fraction) followed by surgery within 2 weeks or HA-WBRT (30Gy/10 fractions) with SIB to cavity plus other intact BM (40-50Gy/10 fractions) combined with memantine within 6 weeks of surgery. A sample size of 168 patients is required to prove the superiority of test arms individually compared to the control arm with assumption of 1-year EFS of 43% versus 25% with a hazard ratio of 0.6 (two-sided alpha=0.05, power=80%, and 15% attrition rate). DISCUSSION: The study will generate level 1 evidence investigating the role of NA-SRS or HA-WBRT-SIB compared to A-SRS in limited brain metastases.

## CLRM-13

### RELEVANCE OF RECURSIVE PARTITIONING ANALYSIS (RPA) CLASSIFICATION IN THE CURRENT CARE OF PATIENTS WITH BRAIN METASTASES (BMETS).

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