(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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