CLRM-13. INTRAOPERATIVE MICRODIALYSIS: GLIOMA INTELLIGENCE FROM BEHIND ENEMY LINES

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INTRODUCTION: Gliomas present a formidable challenge for translational progress. Heterogeneity within and between tumors may demand empirically individualized and adaptive paradigms requiring rapid mechanistic feedback. We asked if tumor-associated metabolic biomarkers from glioma extracellular fluid could impart mechanistic "intelligence" reflecting intra- and inter-tumoral heterogeneity. METHODS: Five live human gliomas (2 oligos; 2 IDH-WT GBMs; 1 IDH-mutant GBM), were evaluated in situ with high molecular weight (100kDA) intraoperative microdialysis using 3 disparately placed catheters. Isotonic 3% dextran perfusate was collected in 20 min (40mL) aliquots. CSF samples (n=21) were additionally evaluated from these and other patients with diverse brain tumors. The IDH-mutant glioma-associated oncometabolite D2-hydroxyglutarate (D2-HG) was quantified with targeted Liquid Chromotography-Mass Spectrometry (LC-MS). Over 200 metabolites were further evaluated via untargeted LC-MS using the Metabolon platform. Correlation, clustering, ROC and enrichment analyses were employed to identify correlations within and between patient samples. RESULTS: CSF samples from patients with IDH-mutant gliomas contained over twenty-fold higher levels of D2-HG (median 4.1 mM, range 1.6-13.2, n=7) compared to those from IDH-wild type tumors (median 0.19 mM; range 0.89-0.35, n=14). Microdialysate from IDH-mutant gliomas contained 10-953mM D2-HG, 9-63x higher than paired CSF samples. Interestingly, IDH status failed to predict the global metabolic signature of microdialysate. Microdialysate samples clustered into 2 major metabolic phenotype clusters with IDH-WT and IDH-mutant gliomas in each cluster. A superimposed metabolic signature distinguishing enhancing from non-enhancing tumor, was conserved in both patient clusters. Amino acid and carnitine metabolism predominated in microdialysate signatures. TCA cycle and Warburg-associated metabolites were differentially enriched in CSF samples after prior therapy independent of tumor burden. CONCLUSIONS: Intra-operative microdialysis may complement currently available "intelligence" regarding the phenotype, burden, and metabolism of live human gliomas and is feasible within standard-of-care surgical procedures. Future work will evaluate utility for pharmacodynamic feedback following novel early phase candidate therapies.

CLRM-14. OPEN-LABEL, MULTINATIONAL, MULTICENTER, PHASE 3B/4 STUDY OF TRASTUZUMAB DERUXTECAN (T-DXD) IN PATIENTS WITH OR WITHOUT BASELINE BRAIN METASTASIS (BM) WITH PREVIOUSLY TREATED ADVANCED/METASTATIC HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2–POSITIVE BREAST CANCER (HER2+ BC): DESTINY-BREAST12

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BACKGROUND: Despite treatment advances, up to 50% of patients with advanced HER2+ BC develop BM (Zimmer. Cancer Rep. 2020). Patients with HER2+ BC with BM have a worse prognosis than patients without BM. In DESTINY-Breast01, T-DXd demonstrated efficacy in the overall population and preliminary efficacy in a subgroup with stable BM, with a confirmed objective response rate (ORR) of 61.4% and an extracranial confirmed ORR by independent central review (ICR) of 58.3%, median progression-free survival (PFS) of 19.4 and 18.1 mo, and median duration of response (DOR) of 20.8 and 16.9 mo (Modi. Cancer Res. 2021; Jerusalem. Ann Oncol. 2020). Here we describe a trial evaluating T-DXd in patients with previously treated advanced/metastatic HER2+ BC ±BM. DESIGN: DESTINY-Breast12 (NCT04739761) is an open-label, multicenter, international (86 sites in the US, Europe, Australia, and Japan), phase 3b/4 study assessing T-DXd 5.4 mg/kg q3w efficacy and safety in patients with previously treated advanced/metastatic HER2+ BC ±BM that progressed with ≥1 prior anti-HER2–based regimen and received ≤2 lines of therapy in the metastatic setting (excluding patients with prior tucatinib). Patients (n=250/cohort) will be enrolled in cohort 1 (–BM at baseline) or 2 (+BM at baseline). BM must be untreated and not needing immediate local therapy or previously treated and stable or progressing. Primary endpoints are ORR (cohort 1) and PFS (cohort 2) (both by RECIST version 1.1 per ICR). Secondary endpoints are OS, DOR, time to progression, duration of subsequent therapy, PFS2, safety, and changes in symptoms, functioning, and QOL in both cohorts; incidence of new symptomatic CNS metastasis (CNSM) in cohort 1; and ORR and CNS ORR by RECIST 1.1 per ICR, CNS PFS and DOR, and time to new CNSM in cohort 2. This is an encore; the original presentation will be at The European Society for Medical Oncology 2021.

FINAL CATEGORY: IMMUNOTHERAPY

IMMU-01. TEM-GBM: AN OPEN-LABEL, PHASE I/IIA DOSE-ESCALATION STUDY EVALUATING THE SAFETY AND EFFICACY OF GENETICALLY MODIFIED TIE-2 EXPRESSING MONOCYTES TO DELIVER IFN-A WITHIN GLIOBLASTOMA TUMOR MICROENVIRONMENT

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Temferon is a macrophage-based treatment relying on ex-vivo transduction of autologous HSPCs to express immune-payloads within the TME. Temferon targets the immune-modulatory molecule IFN-a, to a subset of tumor infiltrating macrophages known as Tie-2 expressing macrophages (TEMs) due to the Tie2 promoter and a post-transcriptional regulation layer represented by miRNA-126 target sequences. As of 31st May 2021, 15-patients received Temferon (D+0) with follow-up of 3 – 693 days. After conditioning neutrophil and platelet engraftment occurred at D+13 and D+13.5, respectively. Temferon-derived differentiated cells, as determined be the number of vector copy per genome, were found within 14 days post treatment and persisted albeit at lower levels up to 18-months. Very low concentrations of IFN-a in the plasma (8.7 pg/ml-D+30) and in the CSF (1.6 pg/ml-D+30) were detected, suggesting tight regulation of transgene expression. Five-deaths occurred at D+322, +340, +402, +478 and +646 due to PD, and one at D+60 due to complications following the conditioning regimen. Eight-patients had progressive disease (range: D-11 to +239) as expected for this tumor type. SAEs include GGT elevation (possibly related to Temferon) and infections, venous thromboembolism, brain abscess, hemiparesis, seizures, anemia and general physical condition deterioration, compatible with ASCT, concomitant medications and PD. Four-patients underwent 2ndsurgery. Recurrent tumors had gene-marked cells and increased expression of ISGs compared to first surgery, indicative of local IFNa release by TEMs. In one patient, a stable lesion had a higher proportion of T cells and TEMs within the myeloid infiltrate and an increased ISGs than in the progressing lesion, detected in the same patient. Tumor-associated clones expanded in the periphery. TME characterization by scRNA and TCR-sequencing is ongoing. To date, Temferon is well tolerated, with no DLTs identified. The results provide initial evidence of Temferon potential to activate the immune system of GBM patients, as predicted by preclinical studies.

IMMU-02. PHASE I/II STUDY OF LASER INTERSTITIAL THERMOTHERAPY (LITT) COMBINED WITH CHECKPOINT INHIBITOR FOR RECURRENT GLIOBLASTOMA (RGBM): PRELIMINARY RESULTS

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BACKGROUND: Recurrent glioblastoma (rGBM) has poor response rate and survival. Laser Interstitial Thermotherapy (LITT), a minimally invasive approach, improves survival but is not curative alone. Previous studies