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

of LITT suggested the possibility of an abscopal effect. Indeed, GBM are known to harbor elevated levels of immunosuppressive cells such as T_{reg}, M2 macrophages and MDSC both in the tumor microenvironment as well as in the systemic circulation. Checkpoint inhibition (CPI) immunotherapy has proven highly effective for some solid tumors. CPI in newly diagnosed GBM demonstrated safety in phase I trials (NRG BN-002). Further, preclinical studies targeting PD-1 with concurrent RT appears to be synergistic and improve survival. We hypothesized that LITT would block tumor-induced immunosuppression and introduce tumor neoantigens. However, there was no data regarding safety of pembrolizumab combined with LITT. We thus conducted a phase I/II study of LITT + pembrolizumab starting at three times relative to LITT. METHODS: This is a three armed Phase I/II study based on timing of pembrolizumab (200 mg q 21 days) relative to LITT at 35d or 14d post-op, or 7d pre-op, with an expansion cohort phase II arm conducted at the earliest tolerated time of CPI administration. Adults with proven supratentorial rGBM with KPS >=70 and <= 2mg/d of dexamethasone were eligible. RESULTS: Arm 1-2 of the phase I trial demonstrated no SAEs grade II or greater, but limited evidence of response. Arm 3 (neoadjuvant) pembrolizumab appears to be equally safe and has been expanded to phase II, demonstrating at least two CR among the first 3 patients (66.6%) with >= 9 month follow-up and patients remain clinically stable at 10 and 15 months post-op. CONCLUSIONS: Neoadjuvant pembrolizumab combined with LITT for rGBM appears to be safe in this phase I trial, and demonstrates early evidence of response. The phase II trial is ongoing.

IMMU-03. MULTICENTER RANDOMIZED PLACEBO CONTROLLED PHASE III TRIAL OF AN AUTOLOGOUS FORMALINFIXED TUMOR VACCINE (CELLM-001) FOR NEWLY DIAGNOSED GLIOBLASTOMAS

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INTRODUCTION: The development of novel treatments for glioblastoma is desired and immunotherapy is theoretically expected for highly invasive glioblastoma. An autologous formalin-fixed vaccine (AFTV) derived from resected tumor tissue is stable, contains multiple tumor peptides, and could induce specific immunity. We have conducted three clinical trials in patients with glioblastoma, and the most recent trial was a double-blind, multicenter, phase IIb trial with 63 case enrollments. Although this Phase IIb study revealed no vaccine effects in the whole cohort (mOS: 25.6 months of AFTV group, 31.5 months of the placebo group), the 3-year PFS for patients with total tumor removal was 81% in the AFTV group versus 46% in the placebo group (P=0.067). AFTV vaccine (Cellm-001) may have an effect on certain patient subgroups, and a Phase III study has started in November 2021 (jRCT2031200153). Based on Phase IIb, the enrolled patients were those who could be completely resected on MRI. Cellm-001 administration to a patient in the placebo group at recurrence (crossover) was prohibited. In addition, photodynamic therapy (PDT) was added as a stratification factor because our retrospective study showed a good prognosis of 19 patients who underwent both PDT and AFTV (mOS 47.7 months). PATIENTS AND METHODS: Trial design: double-blind (1: 1), phase III multicenter, registration 4 years, observation 2 years. ESTIMATED ENROLLMENT: 112 patients with primary glioblastoma (18-75 years old) whose contrast-enhanced lesion could be completely removed on the image and who received standard local radiotherapy and temozolomide chemotherapy. STRATIFICATION FACTORS: presence or absence of PDT, age, KPS. ADMINISTRATION METHOD: Intradermal administration 3 times before radiochemotherapy and 6 times in parallel with maintenance chemotherapy after completion. PRIMARY ENDPOINT: OS, secondary endpoints: PFS and adverse events. https://jrct.niph.go.jp/en-latest-detail/jRCT2031200153. CONCLUSION: An investigator-initiated phase III trial will investigate the efficacy and safety of unique AFTV immunotherapy.

IMMU-04. VACCINATING AGAINST NOVEL CYTOMEGALOVIRUS ANTIGENS IN GLIOBLASTOMA USING A PEPTIDE VACCINE IN COMBINATION WITH TEMOZOLOMIDE

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INTRODUCTION: Cytomegalovirus (CMV) antigens are excellent antitumor immunotherapeutic targets in glioblastoma (GBM). The PERFORMANCE trial (IRB-pro34208, IND-15846) assessed the feasibility, safety and optimal adjuvant temozolomide (TMZ) regimen to be used with PEP-CMV vaccination in adults with newly-diagnosed GBM. METHODS: Seropositive CMV patients (n=16) were randomized into two arms and treated with standard of care RT-TMZ (SOC) (150-200 mg/m^2/day on days 1-5 per 28-day cycle) or dose-intensive TMZ (DI) (75-100 mg/m^2/day on days 1-21 per 28-day cycle). Patients received intradermal PEP-CMV vaccines (500μg of CMVpp65 synthetic long peptide (SLP) mixed with Montanide ISA-51) on days 23, 37 and 51 following TMZ. All patients received tetanus/diphtheria toxoid (Td) preconditioning at the vaccination site on day 22. Serum cytokine levels were measured pre-vaccination, 1-hour and 2-hours post vaccination. PEP-CMV specific circulating PBMCs were quantified at baseline and after each vaccine. RESULTS: Of the 16 trial patients, 7 experienced site-reactions, 4 had grade-II Immune Related Adverse Events (IRAEs), and 4 experienced flu-like grade-III IRAEs. Inflammatory cytokines (IL-2, IFNγ, MIP-1a, IL-8, TNFα, and IL-10) were elevated in patients with grade-III responses 2-hours post vaccine 1. Td p2/p30 specific PBMC levels were similar between IRAEs. However, pp65 responsive PBMCs were elevated at baseline in patients with grade-III reactions compared to site-reaction suggesting pre-existing peptide specific responses may lead to increased vaccine immunogenicity. PBMCs specific for pp65 increased with number of consecutive vaccines. No difference in progression free survival (PFS) or overall survival (OS) was observed between TMZ regimens. CONCLUSION: PEP-CMV vaccination with Td preconditioning is feasible and generates immune responses specific to pp65 in patients with newly diagnosed GBM. Importantly, IRAEs were associated with antitumor efficacy. The mild IRAEs in PERFORMANCE are likely indicative of vaccine potency and can be managed through standard premedication as has been used in other trials with similar IRAEs.

IMMU-05. A PHASE I STUDY IN PROGRESS OF HEGFRVIII-CD3 BI-SCFV (BRITE) IN PATIENTS WITH WHO GRADE IV MALIGNANT GLIOMA

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INTRODUCTION: Approximately 30% of glioblastomas harbor the tumor specific EGFRvIII mutation. hEGFRvIII-CD3 bi-scFv (Brain Bi-Specific T Cell Engager - BRiTE) is a novel bispecific antibody construct which can redirect a patient's entire repertoire of T cells (TCR-agnostic) to specifically lyse EGFRvIII-positive tumor cells. Compared to CAR-T therapy, it offers a highly potent yet off-the-shelf approach for glioblastoma. BRiTE is now entering Phase I clinical trials (NCT04903795) and will be trialed as a monotherapy or with autologous T cell infusion. Migration of T cell binding macromolecules across the blood-brain barrier may be facilitated by activated T cells which adhere to the microvascular endothelium and enter the brain parenchyma. Concurrent administration of activated T cells could therefore enhance trafficking of BRiTE and other antibody-based macromolecules into the intracerebral compartment. HYPOTHESIS: We hypothesize that treatment of EGFRvIII-positive WHO grade IV malignant glioma with BRiTE alone or with peripheral T-cell infusion is safe and can induce objective tumor shrinkage at tolerable doses. TRIAL DESIGN/OBJECTIVES: A maximum of 18 patients with newly diagnosed or recurrent WHO grade IV malignant EGFRvIII+ glioma will be enrolled after undergoing standard of care treatment. The primary objective will be evaluating the safety of BRiTE alone and with autologous T cell infusion. Patients will receive a single BRiTE infusion, followed 14 days later by an infusion of activated autologous T cells and a second bolus BRiTE infusion. Dose escalation and de-escalation will be managed using a Bayesian optimal interval design. Secondary objectives will be to describe clinical benefit as determined by objective response rate per mRANO criteria, and to evaluate BRiTE pharmacokinetics in serum. CONCLUSION: We describe a first-in-human trial of bispecific T cell engager therapy for glioblastoma. We also describe our novel approach for enhancing intracranial penetration of BRiTE using autologous T cell infusion.

IMMU-06. TARGETING IDH1 MUTANT GRADE II RECURRENT GLIOMAS USING A PEPTIDE VACCINATION STRATEGY

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INTRODUCTION: While primary GBM is largely heterogeneous and devoid of homogeneously expressed neoantigens, mutant IDH1 (R132H) is a uniformly expressed hallmark in >70% of low grade gliomas. As such, IDH1 mutations represent a potentially valuable vaccination target. METHODS: Here, we report an update on the immunogenicity results of the