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BACKGROUND: Patients diagnosed with BMETS want to know their prognosis and the benefit of treatment to make informed decisions. Clinician and patient biases frequently provide survival estimates that are too optimistic or pessimistic. We postulated that that RPA remains a useful tool to communicate prognosis and potential benefit from brain-directed treatment (BDT). We evaluated real-world data on RPA class and survival of patients with newly diagnosed BMETS from three academic institutions. **METHODS:** We retrospectively reviewed the records of patients with BMETS between 2017 and 2019 who had at least 6 months of follow up. Excluded were patients with leptomeningeal or only dural/calvarial metastases. We calculated the RPA and according to class compared Kaplan-Meier survival curves. **RESULTS:** We have data on 642 cases with median age of 65 years; 80% had lung, breast, melanoma, and renal as the primary cancer. Sixty (9.3%) patients received palliative care only, while 582 (90.7%) had BDT. The median survival of all patients according to RPA in months was 18.0 (I), 9.4 (II), and 2.4 (III) and for those receiving BDT (n=582), it was 19.2 (I), 11.2 (II), and 2.9 (III). There were statistically significant differences for BDT survival curves adjusted for multiple comparisons (I-II p=0.0124; II-III p<0.0001; I-III p<0.0001). For patients in RPA class III who received WBRT (n=62), the median survival was 2.9 months, and, for SRS (n=37), it was 3.5 months. We will present updated data including additional 238 cases and propose predictive/prognostic models based on our cohort that optimizes the RPA application in clinical practice. **CONCLUSION:** In contemporary practice, the RPA classification remains significantly relevant in making care decisions for patients diagnosed with BMETS. Treatment recommendations for patients in RPA class III should be the result of multidisciplinary discussions with consideration for early palliative care involvement to de-escalate and avoid inefficacious BDT.

CLRM-14

INTRATUMORAL EXTRACELLULAR METABOLIC IMPACT OF DFMO AND AMXT 1501 IN LIVE HUMAN GLIOMAS

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Gliomas may leverage alternate metabolic pathways in response to metabolism-targeted therapeutic intervention, all of which remain unexplored in the live human glioma, in situ. Defining emergent mechanisms of metabolic resistance in response to therapeutic challenge can help guide rational combinatorial therapies. To date, the metabolic response of gliomas in response to therapeutic intervention has remained poorly understood due to the relative inaccessibility of the live human tumor, in situ. Microdialysis is an underutilized tool that could be leveraged to overcome this longstanding challenge. Data from our ongoing intraoperative microdialysis trial have revealed an upregulation of polyamine metabolism and a novel glioma-associated metabolite, guanidinoacetate (GAA) -- a metabolite co-produced with ornithine, which is required for polyamine synthesis. In a Phase 0 trial, we will evaluate in situ glioma responses to polyamine depletion (difluoromethylornithine, DFMO) with or without blockade of polyamine uptake (AMXT 1501) to identify candidate extracellular biomarkers of target engagement and cytotoxicity in fifteen post-operative patients who have undergone a standard-of-care planned subtotal resection for high-grade glioma. Intraoperatively, high-molecular-weight catheters will be implanted into the residual tumor and brain adjacent to the resection cavity for post-operative longitudinal monitoring of extracellular metabolites via microdialysis. Polyamines and guanidinoacetate, a candidate biomarker of glioma-upregulated polyamine synthesis, will be monitored throughout therapeutic intervention from post-operative day (POD) 1 to POD5 via longitudinal microdialysis to determine live in situ glioma pharmacodynamic responses to polyamine depletion. Catheters will be removed on post-operative day five prior to discharge. We hypothesize that GAA will reflect local tumor production of polyamine metabolism. Additionally, in situ microdialysis in Phase 0 trials will allow for pharmacodynamic and pharmacokinetic, in addition to metabolic, monitoring, an opportunity which is rarely afforded in most clinical trials due to lack of access to the CNS.

CLRM-15

TRIAL IN PROGRESS: A PHASE 1B/2 STUDY OF GB5121, A NOVEL, HIGHLY SELECTIVE, POTENT, AND CNS-PENETRANT INHIBITOR OF BRUTON'S TYROSINE KINASE (BTKI) FOR RELAPSED/REFRACTORY PRIMARY/SECONDARY CNS LYMPHOMA (R/R PCNSL/SCNSL) AND PRIMARY VITREORETINAL LYMPHOMA (PVRL)

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BTK plays an important role in B cell receptor and Toll-like receptor signaling pathways, which are constitutively active in primary CNS lymphomas, and hence represents an excellent therapeutic target. Ibrutinib, a first-generation BTKi, was evaluated in phase 1/2 trials for R/R PCNSL, SCNSL, and PVRL, showing limited survival benefit. GB5121 is a novel, orally available, covalent BTKi with superior specificity, CNS penetration, and CNS target occupancy in preclinical testing versus other BTKis including ibrutinib. GB5121 is well-suited for evaluation in CNS lymphoma. This is a phase 1b/2 open-label study of GB5121 in adults with R/R PCNSL, isolated SCNSL or PVRL and will be conducted in three parts: phase 1b dose-escalation, expansion, and phase 2. Eligibility criteria for phase 1b dose-escalation and expansion (N≈30 for each) include age ≥18 years, ECOG≤2, R/R PCNSL, R/R SCNSL with CNS-only relapse, or R/R PVRL. Patients with newly diagnosed PCNSL who cannot tolerate standard high-dose methotrexate-based therapies are also eligible. Patients with prior allogeneic stem cell transplant are excluded. A Bayesian optimal interval design will be employed to perform dose escalation to determine the recommended phase 2 dose (RP2D). In the absence of dose-limiting toxicity (DLT), dose levels will increase sequentially according to a modified Fibonacci approach. Safety, tolerability, PK/PD, DLT, maximum tolerated dose, and preliminary therapeutic activity will be assessed to determine the optimal biological dose informing the RP2D. Phase 1b expansion will further explore therapeutic activity and characterize safety and tolerability of GB5121 at the RP2D. Phase 2 will initiate following RP2D determination. This is a single-arm, open-label study to investigate GB5121 safety and efficacy in patients with R/R PCNSL. Adverse events will be graded per CTCAE v5.0. Clinical response will be determined using International Primary CNS Lymphoma Collaborative Group criteria. Progression-free and overall survival will be evaluated. Enrollment begins May 2022 (NCT05242146).

CLRM-16

PATIENT-FOCUSED DRUG DEVELOPMENT IN NEURO-ONCOLOGY: A PILOT STUDY OF QUALITATIVE PATIENT INTERVIEWS EMBEDDED WITHIN A NEUROFIBROMATOSIS 2 CLINICAL TRIAL

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BACKGROUND: The Food and Drug Administration recently issued guidance on conducting qualitative research to support patient-focused drug development. In prior FDA submissions, qualitative data has been critical to demonstrate the content validity of and meaningfulness of change in quantitative trial endpoints. Qualitative patient interviews embedded within neuro-oncology trials can supplement traditional quantitative measures by providing nuanced information on patients' treatment priorities, benefit/risk assessments, and quality of life. **METHODS:** We interviewed people with neurofibromatosis 2 (NF2) in stage one of the brigatinib arm of a multicenter, phase II, adaptive platform-basket trial for progressive NF2-related tumors (NCT04374305). Transcripts were coded by two analysts using a hybrid inductive/deductive framework; cross-cutting themes were generated using the Framework Method. **RESULTS:** 16/20 trial enrollees participated in interviews May 2021-March 2022. The radiographic response rate (volume shrinkage ≥20% from baseline) at 6 months for target and non-target tumors was 5% and 22%, respectively. However, most participants rated their change in overall status as minimally (10/16) or much (3/16) improved. Several participants acknowledged their tumor size had not changed significantly but felt tumor stability was an improvement over previously accelerated growth rates; this importantly allowed them to avoid or postpone future surgery. Participants also valued prevention of symptomatic decline, minimal impact of side effects on social roles and activities, the convenience of oral medication, and the sense of hope and agency gained from participating in a trial. **CONCLUSIONS:** Virtual, in-depth qualitative interviews were feasible across multiple sites and provided unique information on NF2 patients' conceptualization of clinical benefit. Qualitative interviews embedded within neuro-oncology trials can reveal 1) whether trial design and choice of outcome measures align with patient priorities; 2) whether and how new treatments improve patients' quality of life; and 3) what degree of change in quantitative measures such as radiographic progression are clinically meaningful.