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Clinical activity of fianlimab (REGN3767), a human anti-LAG-3 monoclonal antibody, combined with cemiplimab (anti-PD-1) in patients (pts) with advanced melanoma

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NEURO-ONCOLOGY ADVANCES

NEURO-ONCOLOGY ADVANCES SUPPLEMENT

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Submission Categories and Abbreviations:
CLRM – Clinical Research Methods
IMMU – Immunotherapy
NEIM – Neuroimaging
SCSS – Supportive Care and Survivorship
SYST – Systemic Therapeutics

FINAL CATEGORY: CLINICAL RESEARCH METHODS

CLRM-01. MACHINE LEARNING TO UNCOVER SIGNATURES OF VULNERABILITY IN GLIOBLASTOMA UMBRELLA SIGNATURE TRIAL (GUST)

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Glioblastoma is characterized by intra- and inter-tumoral heterogeneity. A glioblastoma umbrella signature trial (GUST) posits multiple investigational treatment arms based on corresponding biomarker signatures. A contingency of an efficient umbrella trial is a suite of orthogonal signatures to classify patients into the likely-most-beneficial arm. Assigning optimal thresholds of vulnerability signatures to classify patients as "most-likely responders" for each specific treatment arm is a crucial task. We utilized semi-supervised machine learning, Entropy-Regularized Logistic Regression, to predict vulnerability classification. By applying semi-supervised algorithms to the TCGA GBM cohort, we were able to transform the samples with the highest certainty of predicted response into a self-labeled dataset and thus augment the training data. In this case, we developed a predictive model with a larger sample size and potential better performance. Our GUST design currently includes four treatment arms for GBM patients: Arsenic Trioxide, Methoxyamine, Selinexor and Pevonedistat. Each treatment arm manifests its own signature developed by the customized machine learning pipelines based on selected gene mutation status and whole transcriptome data. In order to increase the robustness and scalability, we also developed a multi-class/label classification ensemble model that's capable of predicting a probability of "fitness" of each novel therapeutic agent for each patient. Such a multi-class model would also enable us to rank each arm and provide sequential treatment planning. By expansion to four independent treatment arms within a single umbrella trial, a "mock" stratification of TCGA GBM patients labeled 56% of all cases into at least one "high likelihood of response" arm. Predicted vulnerability using genomic data from preclinical PDX models correctly placed 4 out of 6 models into the "responder" group. Our utilization of multiple vulnerability signatures in a GUST trial demonstrates how a precision medicine model can support an efficient clinical trial for heterogeneous diseases such as GBM.

CLRM-02. TRIAL IN PROGRESS: A PROSPECTIVE, MULTICENTER PHASE 2B STUDY TO ESTABLISH IMAGE INTERPRETATION CRITERIA FOR ^{18}F-FLUCICLOVINE PET IN DETECTING RECURRENT BRAIN METASTASES AFTER RADIATION THERAPY (PURSUE)

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BACKGROUND: Brain metastases represent the most common intracranial tumor in adults, occurring in 10-40% of cancer patients. Most patients undergo multimodal treatment approaches and post-treatment follow-up with conventional MRI (CE-T1-weighted and FLAIR/T2-weighted) of the brain is performed to monitor for disease recurrence. However, owing to the similar appearance of treatment-related changes like radiation necrosis with that of true recurrence, conventional MRI alone suffers from low specificity. Given the high mortality of patients with brain metastases and the considerable treatment-associated morbidity, a need remains for an imaging modality that accurately differentiates recurrence from treatment-related changes. Accurate imaging is key to preventing unnecessary surgery or changes in effective therapy in patients mistaken for disease progression as well as prevent continuation of ineffective therapy if radiation necrosis is incorrectly diagnosed. To this end, ^{18}F-fluciclovine is a synthetic amino acid-based PET imaging agent that has potential to evaluate primary and metastatic brain cancers owing to its low normal background uptake in the brain and increased uptake in brain tumors. METHODS: NCT04410367 is a prospective, open-label, single-arm, single-dose (185 MBq ± 20%) study with a primary objective to establish visual image interpretation criteria for ^{18}F-fluciclovine PET studies of recurrent brain metastases. Forty subjects with solid tumor brain metastases who have undergone radiation therapy will be enrolled across ~8 US sites if they have a reference lesion considered equivocal on MRI for recurrent disease and are planned for craniotomy. Subjects will undergo ^{18}F-fluciclovine PET <42 days after the MRI and 1–21 days before planned craniotomy. Outcome measures comprise the diagnostic performance of ^{18}F-fluciclovine PET at different thresholds of ^{18}F-fluciclovine uptake compared with histopathology, subject- and lesion-level diagnostic performance based on established image interpretation criteria, and safety evaluations. Enrolment began in August 2020 and the trial is open at the time of submission.

CLRM-03. BGB-290 AND TEMOZOLOMIDE IN TREATING ISOCITRATE DEHYDROGENASE (IDH)1/2-MUTANT GRADE I-IV GLIOMAS – A NOVEL MODEL OF AYA TRIAL DEVELOPMENT AND DEPLOYMENT

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DESCRIPTION: The lack of enrollment of AYA patients on clinical trials is well documented and multivariant. Here we present the basic science, examination of its relevance to the AYA population specifically, and the parallel deployment of two international clinical trials via a pediatric neuro-oncology and adult brain tumor consortium. DISCUSSION: In February of 2017, the laboratory of Ranjit Bindra, MD, PhD, published a manuscript describing the finding that tumors with IDH1/2 mutations induce a BRCAness state leading to PARP inhibitor (PARPi) sensitivity and synergistic interactions with temozolomide chemotherapy [2]. Despite IDH1/2 mutations being rare in the pediatric high-grade glioma population, three independent groups confirmed that the incidence is significantly increased to ~30% in the adolescent and young adult (AYA) population. Upon discovery of a high blood-brain-barrier penetrant, high potency PARPi by BeiGene Pharmaceuticals, an international trial was launched through the Pacific Pediatric Neuro-Oncology Consortium (PNOC) [3] to test this drug in an AYA specific trial recruiting patients ages 13 to 25, with a concurrent trial being run for patients older than 25 years of age through the Adult Brain Tumor Consortium (ABTC) [4].

While most trials that enroll AYA patients are forced to assess them as a unique cohort in post-analysis, if at all, the PNOC trial mentioned above was designed from the ground up with the AYA population in mind. It has allowed us to base initial dosing, recruitment strategies, psychosocial assessments, and outcomes, specifically on the AYA population. Ultimately, we expect their distinctive biology to yield unique results when compared to the ABTC trial.

We propose that this is a model that could potentially be replicated in other disease processes and early phase drugs with the buy-in of the pharmaceutical industry and early phase consortiums.

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CLRM-04. PHASE I/II SAFETY AND EFFICACY STUDY OF BET BROMODOMAIN INHIBITOR OTX-015 WITH OLAPARIB AND LOMUSTINE IN PATIENTS WITH RECURRENT GLIOBLASTOMA

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Standard of care for patients with glioblastoma (GBM) includes resection with concurrent temozolomide (TMZ) and radiotherapy, with inevitable disease recurrence. Upon recurrence, tumors are often resistant to first-line therapies and/or have infiltrated eloquent or deep brain regions, precluding repeat resection. There is currently no standard of care for recurrent GBM and patients succumb to their disease burden within 12- 15 months of their