BSCI-18. IDENTIFYING NOVEL DRIVERS OF LUNG-TO-BRAIN METASTASIS THROUGH *IN VIVO* FUNCTIONAL GENOMICS

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INTRODUCTION: Brain metastases, the most common tumors of the central nervous system, occur in approximately 20% of primary adult cancers. In particular, 40% of patients with non-small cell lung cancer develop brain metastasis. As systemic therapies for the treatment of non-small cell lung cancer become increasingly effective at controlling primary disease, patients are ironically succumbing to their brain metastases. This highlights a large unmet need to develop novel targeted therapies for the treatment of lung-to-brain metastases (LBM). We hypothesize that an *in vivo* functional genomic screen can identify novel genes that drive LBM. METHODS: To do this, we developed a patient-derived xenograft (PDX) mouse model of LBM using patient lung cancer cell lines. This PDX model of LBM enables the use of fluorescent and bioluminescent *in vivo* imaging to track the progression of lung tumor and brain metastases. RESULTS: We have performed an *in vivo* genome-wide CRISPR activation screening to identify novel drivers of LBM. We will derive candidate genes through mouse brain and lung tissue sequencing after mice reach endpoint. EXPECTED AREA OF FINDINGS: This platform will lead to potential therapeutic targets to prevent the formation of LBM and prolong the survival of patients with non-small cell lung cancer. LIMITATIONS: There may be limitations in getting candidate hits that overlap in all mice in our first replicate. This can be remedied by conducting the *in vivo* screen in at least three biological replicates. CONCLUSION: To the best of our knowledge, this is the first genome-wide *in vivo* CRISPR activation screen searching for drivers of LBM using a PDX animal model. This study can provide a framework to gain a deeper understanding of the regulators of BM formation which will hopefully lead to targeted drug discovery.

BSCI-19. THERAPEUTIC INTERVENTION OF LUNG-, BREAST-, AND MELANOMA-BRAIN METASTASIS

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BACKGROUND: The incidence of brain metastases (BM) is tenfold higher than that of primary brain tumours. BM predominantly originate from primary lung, breast, and melanoma tumours with a 90% mortality rate within one year of diagnosis, posing a large unmet clinical need to identify novel therapies against BM. METHODS: Using a large in-house biobank of patient-derived BM cell lines, the Singh Lab has generated murine orthotopic patient-derived xenograft models of BM and captured a "premetastatic" population of BM cells that have just seeded the brains of mice before forming clinically detectable tumours: a cell population that is impossible to detect in human patients but represents a therapeutic window wherein metastasizing cells can be targeted and eradicated before establishing clinically detectable tumours. RESULTS: RNA sequencing of pre-metastatic BM cells from all three primary tumour models with subsequent Connectivity Map analysis identified a lead compound that exhibits selective anti-BM activity *in vitro*. Preliminary *in vivo* work has shown that this lead compound reduces the tumor burden of treated mice compared to vehicle control while providing a significant survival advantage. Ongoing mechanistic investigations aim to delineate the protein target of this compound in the context of the observed selective anti-BM phenotype. CONCLUSION: Therapeutic targeting of premetastatic BM cells could prevent the formation of BM and dramatically improve the prognosis of at-risk cancer patients.

CLINICAL TRIALS

TRLS-01. 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 are the most common intracranial tumor in adults, occurring in 10–40% of patients with cancer. Despite multimodal treatment approaches, the prognosis remains poor and post-treatment follow-up with conventional MRI (CE-T1-weighted and FLAIR/T2-weighted) of the brain is recommended 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 has 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 could help physicians identify patients for whom non-effective or unneeded treatments can be ceased in order to minimize treatment-associated morbidity, and to avoid erroneous premature cessation of potentially effective therapy. ^{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 18F-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 brain metastasis and are planned for craniotomy. Subjects will undergo 18F-fluciclovine PET <28 days after the equivocal MRI and 2–21 days before planned craniotomy. Outcome measures comprise diagnostic performance of 18F-fluciclovine PET at different thresholds of 18F-fluciclovine uptake compared with histopathology, subject- and lesion-level diagnostic performance based on application of the established image interpretation criteria, and safety evaluations. Enrolment began in August 2020 and the trial is open at the time of submission.

TRLS-02. TRIAL IN PROGRESS: A MULTICENTER PHASE 3 STUDY TO ESTABLISH THE DIAGNOSTIC PERFORMANCE OF ^{18}F-FLUCICLOVINE PET IN DETECTING RECURRENT BRAIN METASTASES AFTER RADIATION THERAPY (REVELATE)

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BACKGROUND: Brain metastases occur in up to 40% of patients with cancer and are associated with poor prognosis and considerable levels of recurrence. Consequently, close follow-up with serial brain MRI is performed post-treatment to monitor for recurrent disease. Although conventional MRI (CE-T1-weighted and FLAIR/T2-weighted) is the recommended follow-up modality, it has poor specificity with limited ability to differentiate between true disease recurrence and treatment-related changes such as radiation necrosis. Therefore, alternative imaging options are sought in order to help physicians confidently diagnose treatment-related changes and thus reliably stratify the risk of continuation of a therapeutic regimen, especially given the morbidity associated with current treatments. Amino acid PET imaging agent, 18F-fluciclovine, has increased uptake in brain tumors relative to normal tissue and may be useful for detecting recurrent brain metastases. METHODS: NCT04410133 is a prospective, open-label, single-arm, single-dose (185 MBq ±20%) study with a primary objective to confirm the diagnostic performance of ^{18}F-fluciclovine PET (read with conventional MRI for anatomical reference) for detection of recurrent brain metastases where MRI is equivocal. Approximately 150 subjects with solid tumor brain metastases who have undergone radiation therapy will be enrolled in this multicenter trial (~18 US sites) if they have a lesion considered equivocal on MRI that requires further confirmatory diagnostic procedures such as biopsy/neurosurgical intervention or clinical follow-up. Subjects will undergo 18F-fluciclovine PET <28 days after the equivocal MRI and 2–21 days pre-biopsy/neurosurgical intervention. Clinical follow-up will occur for 6m post-18F-fluciclovine PET. Secondary objectives include evaluation of subject- and lesion-level 18F-fluciclovine negative and positive percent agreement (equivalent to specificity and sensitivity respectively) for recurrent brain metastases, inter-reader and intra-reader agreement, and safety evaluations. Enrolment began in October 2020 and the trial is open at the time of submission.

TRLS-03. INTRACRANIAL ACTIVITY OF TEPOTINIB IN PATIENTS WITH *MET* EXON 14 (*MET*EX14) SKIPPING NSCLC ENROLLED IN VISION

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BACKGROUND: Brain metastases (BMs) are reported in 20–40% patients with *MET*ex14 skipping NSCLC. Tepotinib, a highly selective MET inhibitor, has demonstrated an objective response rate (ORR) of 45% and median duration of response (mDOR) of 11.1 months, in *MET*ex14 skipping NSCLC patients in Cohort A of the Phase II VISION study. Here, we report the intracranial activity of tepotinib in Cohort A. METHODS: Patients received oral tepotinib 500 mg QD. Study eligibility allowed for patients with BM (asymptomatic and symptomatic/stable). Primary endpoint: systemic objective response (RECIST v1.1); subgroup analysis in patients with BM (RECIST v1.1) was predefined. An *ad hoc* retrospective analysis of brain lesions (by CT/MRI) was conducted by an IRC using Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. Responses were determined in patients with ≥1 evaluable post-baseline tumor assessment. For non-measurable lesions (enhancing and non-enhancing non-target lesions [NTL]), disease control in the brain was defined as non-complete response/non-progressive disease. Data cut-off: July 1, 2020. RESULTS: Twenty-three patients had baseline BM. Systemic efficacy in patients with BM (ORR 47.8% [95% CI: 26.8, 69.4]; mDOR 9.5 months [95% CI: 5.5, not estimable]) was consistent with the overall population. Fifteen patients were evaluable by RANO-BM; 12 received prior radiotherapy for BM (median 6.4 weeks before treatment). Systemic best objective responses (BORs) were partial response (PR, n=9), stable disease (SD, n=3), and progressive disease (PD; n=3). Of seven patients with measurable CNS disease (all of whom received prior radiotherapy), intracranial BORs were PR (n=5), SD (n=1), and PD (n=1). For patients with NTL only (n=8), one had PD, and seven achieved intracranial disease control with three patients achieving CR of the enhancing NTL. CONCLUSIONS: Tepotinib demonstrated intracranial activity in patients with *MET*ex14 skipping NSCLC with BM. Prospective evaluation of intracranial activity in VISION Cohort C is ongoing.

TRLS-04. A NOMOGRAM FOR PREDICTING SURVIVAL IN PATIENTS WITH BRAIN METASTASES

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BACKGROUND: Brain metastases are the most common intracranial tumors in adults, with a very poor prognosis, and poses distinct clinical challenges. This study aimed to develop a more accurate prognostic nomogram for predicting overall survival (OS) of patients with Brain Metastases. METHODS: We conducted a retrospective analysis of 1062 patients with brain metastases at the Sun Yat-sen University Cancer Center (SYSUCC, Guangzhou, China) between January 2010 and January 2018, Among them, 331 patients underwent surgery to remove brain metastases. Kaplan–Meier analysis was performed to screen for potential clinical variables that could be used to establish the nomogram for predicting overall survival. RESULTS: We found that age,gender, whether to remove intracranial lesions, radiotherapy, ECOG were independent prognostic factors for predicting the overall survival with brain metastases,and surgical resection for brain metastatic lesions could significantly improve OS,but only in certain groups of patients with brain metastases can benefit from intracranial lesion resection, such as no extracranial metastasis. And patients with brain metastases whose primary tumor is lung adenocarcinoma or breast cancer are more likely to benefit from surgery in terms of overall survival time.A nomogram for predicting 1- and 2-year overall survival rates was constructed, which exhibited good accuracy in predicting overall survival. CONCLUSION: Through statistical analysis, we have found the factors related to the surgical benefit of patients with brain metastases, and established a prognostic nonogram,This nomogram may be used to guide individual treatments and in selecting an appropriate patient population for clinical trials.

Keywords: brain metastases | overall survival | nonogram | surgery

TRLS-05. A MULTICENTER OBSERVATIONAL STUDY OF CS-131 SEEDS EMBEDDED IN A COLLAGEN CARRIER TILE FOR NEWLY DIAGNOSED AND RECURRENT OPERABLE INTRACRANIAL NEOPLASMS –TRIAL IN PROGRESS

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BACKGROUND: For patients with operable intracranial neoplasms, there are opportunities to augment local control beyond traditional methods, such as external beam radiation therapy (EBRT),. Brachytherapy, the implantation of radioactive sources into the resection cavity, can be useful in this setting by providing immediate initiation of radiation and limiting the exposure of surrounding normal tissue to radiation. Traditional intracranial brachytherapy methods have been limited by uneven dose distributions, complicated workflows, extended procedural times, the cost of dedicated equipment, and frequent adverse events. To address these issues, a permanently implanted device with Cs-131 radiation seeds embedded in a bioresorbable collagen carrier tile (GammaTile, GT Medical Technologies, Tempe, AZ USA) was developed. Described as surgically targeted radiation therapy (STaRT), it is FDA-cleared for use in newly-diagnosed malignant intracranial neoplasms and recurrent intracranial tumors, including brain metastases, and has demonstrated excellent safety and local control in early commercial use. The primary objectives of this multicenter, prospective, observational (phase IV) registry study [NCT04427384] are to evaluate "real-world" clinical outcomes and patient-reported outcomes that measure the safety and efficacy of STaRT using the device. METHODS: Subjects (N=600) at up to 50 enrolling sites undergoing resection of brain tumors of any pathology with intra-operative GammaTile placement are eligible for enrollment. We project 40% of enrollees to have brain metastasis. Tumor pathology, overall survival, radiation- and surgery-related adverse events, quality of life, serial MRIs, and timing of surgical bed recurrence and/or distant recurrence will be collected. The powered primary endpoint for recurrent brain metastases, surgical bed-progression free survival, will compare STaRT to standard-of-care benchmarks. This study will be the first observational study of resection plus GammaTile. Results will be used to benchmark clinical outcomes in the real-world setting, allow for comparisons to existing treatments, and facilitate the design of future clinical trials.

TRLS-06. A PHASE 1–2 CLINICAL TRIAL OF EO1001 (APL-122), A NOVEL IRREVERSIBLE PAN-ERBB INHIBITOR WITH PROMISING BRAIN PENETRATION

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CNS metastases are a prominent driver of cancer morbidity and mortality, especially as targeted therapies have improved systemic outcomes. Mutations in the ErbB/HER kinase family are known oncodrivers in many cancers. Extensive cross-talk among ErbB/HER receptors suggests that inhibition of multiple family members may benefit treatment and limit drug resistance. There is a desperate need for new agents that are more tolerable and effective in treating CNS metastases. EO1001 (APL-122) is a first-in-class, oral, irreversible pan-ErbB inhibitor targeting ErbB1, ErbB2 and ErbB4 with promising CNS penetration in preclinical models. Preclinical data suggests a favorable pharmacokinetic and safety profile and activity against ErbB-driven cancers in patient-derived xenograft models. We report on a first-in-human Phase 1–2 clinical trial in progress. Adult participants with confirmed ErbB-positive cancer, including patients with CNS involvement, who have progressed after standard-of-care, with adequate bone marrow, renal and liver function are eligible. MATERIALS AND METHODS: **Escalation:** One subject per dose cohort is enrolled in an accelerated dose-escalation design until drug-related toxicity (≥G2) is observed in the first cycle, after which dose escalation will revert to a 3 + 3 design to determine the maximum tolerated dose (MTD). *Cycle 1:* Patients receive a single oral dose of EO1001 on day 1; single-dose pharmacokinetics are measured. Beginning on day 8, EO1001 is administered once daily for 21 days; multi-dose pharmacokinetics are measured. *Cycles 2–6:* EO1001 is administered once daily in continuous 28-day cycles for up to 20 weeks. **Expansion:** EO1001 is administered once daily to 20 patients at the MTD in continuous 28-day cycles for up to 6 cycles to determine a recommended Phase 2 dose