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BACKGROUND: Brain metastases (BMs) are reported in 20–40% patients with METex14 skipping NSCLC. Tepotinib, a highly selective MET inhibitor, demonstrated an objective response rate (ORR) of 45% and median duration of response (mDOR) of 11.1 months, in METex14 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 symptomatic and asymptomatic (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 [NLTs]), 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, 13 of whom received tepotinib 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=5). Of seven patients with measurable CNS disease (all under 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 METex14 skipping NSCLC. A 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 to predict overall survival (OS) for 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, 311 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 nomogram. This nomogram may be used to guide individual treatments and in selecting an appropriate patient population for clinical trials.

Keywords: brain metastases | overall survival | nomogram | surgery

TRLS-05: A MULTICENTER OBSERVATIONAL STUDY OF CS-131 SEEDS EMBODIED 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 irradiation 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 embodied in a biodegradable 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 intracranial tumors, which are unresectable or resectable with limited exposure of surrounding normal tissue, and has demonstrated excellent safety and local control in early clinical use. The primary objectives of this multicenter, prospective, observational (phase IV) registry study [NCT04427384] are to evaluate (1) 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 metastases. 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 registries.

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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CN5 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 suggest 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 performed beginning on day 8, EO1001 is administered once daily for 21 days; multiple-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 for 28 cycles for up to 6 cycles to determine a recommended Phase 2 dose
CONCLUSIONS: pVP shunts successfully deliver drugs to the ventriculothecal space with 80% of studies having minimal (<12%) peritoneal drug activity. Though efficacy varies by shunt model, low numbers preclude conclusions regarding model superiority. CSF flow scintigraphy studies reliably assess drug distribution.

LMD-02. CEREBROSPINAL FLUID DIVERSION FOR METASTATIC LEPTOMENINGEAL CARCINOMATOSIS: PALLIATIVE, PROCEDURAL AND ONCOLOGIC OUTCOMES

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BACKGROUND: Leptomeningeal disease (LMD) occurs in 3–5% of patients with solid metastatic tumors and often portends a severe prognosis including symptomatic hydrocephalus and intracranial hypertension. Cerebrospinal fluid (CSF) shunting can provide symptomatic relief in this patient subset; however, few studies have examined the role of shunting in the palliation, prognosis and overall oncologic care of these patients. OBJECTIVE: To identify and evaluate risk factors associated with prognosis after CSF diversion and assess surgical, symptomatic and oncologic outcomes in this population. METHODS: A retrospective study was conducted. Eligibility criteria included LMD treatment at an NCI-designated Comprehensive Cancer Center between 2010–2019. RESULTS: One hundred and ninety patients with metastatic LMD underwent CSF diversion. Overall survival was 4.14 months from LMD diagnosis (95% CI:3.29–4.70) and 2.43 months (95% CI:2.01–3.09) from shunting. KPS at time of shunting and BrM number at LMD diagnosis demonstrated significant associations with survival (HR=0.66; 95% CI:0.51–0.86, p=0.002; HR=1.40; 95% CI:1.01–1.93) per 10 BrM, p=0.04, respectively. Eighty-three percent of patients experienced symptomatic relief, and 79% were discharged home or to rehabilitation facilities post-shunting. Post-shunt, 56% of patients received additional systemic therapy or started or completed WBRT. Complications included infection (5%), symptomatic subdural hygroma/hematoma (6.3%), and shunt externalization/repair (5%). CONCLUSIONS: CSF diversion for LMD with hydrocephalus and intracranial hypertension secondary to metastasis can achieve symptomatic relief, hospital discharge, and return to further oncologic therapy, with a complication profile unique to this patient population. However, a significant proportion must incorporate end-of-life goals of care given limited prognosis.

LEPTOMENINGEAL DISEASE

LMD-01. QUANTIFYING INTRATHecal DRUG DELIVERY UTILIZING PROGRAMMABLE VENTRICULOPERITONEAL SHUNTS

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BACKGROUND: Programmable ventriculoperitoneal shunts (pVP shunts) are increasingly utilized for intraventricular chemotherapy, radioimmunotherapy, and cellular therapy. Shunt adjustments allow optimization of thecal space drug concentrations with minimization in the peritoneum. Drug delivery quantification using several types of pVP shunts has not been reported. METHODS: We performed a retrospective analysis on patients with CNS tumors and pVP shunts at Memorial Sloan Kettering Cancer Center from 2003–2020, noting shunt model. CSF flow through the pVP shunt was evaluated using In-111-DTPA scintigraphy at approximately 4 and 24 hours after injection. pVP shunts were calibrated pre-injection to minimize peritoneal flow and re-calibrated to baseline setting 4–5 hours following injection. Scintigraphy studies quantified ventricular-thecal and peritoneal drug activity at these 2 time points. RESULTS: Twenty-one CSF flow studies were administered to 15 patients, ages 1–27 years. Diagnoses included medulloblastoma (N=10), metastatic neuroblastoma (N=3), pineoblastoma (N=1), and choroid plexus carcinoma (N=1). Models of pVP shunts included Aesculap Miethke proGAV (N=3), Aesculap Miethke proGAV (N=3), Codman HAKIM (N=2), Codman Certas Plus (N=1), Medtronic STRATA (N=3), and Sophysa Polaris (N=1). Minimal to no peritoneal uptake included: Aesculap Miethke proGAV (N=2), Aesculap Miethke proGAV2.0 (N=3), Codman HAKIM (N=2), Codman Certas Plus (N=1), Medtronic STRATA (N=3), and Sophysa Polaris (N=1). Aesculap Miethke proGAV2.0 (N=3), Codman HAKIM (N=2), Codman Certas Plus (N=1), Medtronic STRATA (N=3), and Sophysa Polaris (N=1). All 21 studies (100%) demonstrated ventriculo-thecal drug activity. 29% (6 of 21) of the studies had minimal peritoneal uptake (<12%), and 24% (5 of 21) demonstrated moderate peritoneal uptake (12–37%). Models of pVP shunts measuring minimal peritoneal uptake included: Aesculap Miethke proGAV (N=3), Aesculap Miethke proGAV2.0 (N=3), Codman HAKIM (N=2), Codman Certas Plus (N=1), Medtronic STRATA (N=3), and Sophysa Polaris (N=1).