TPS2094 **Poster Session**

A multicenter, pivotal trial of microbubble-enhanced transcranial focused ultrasound (MB-FUS) for plasma-based liquid biopsy in patients with glioblastoma (LIBERATE).

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Background: Liquid biopsy in glioblastoma (GBM) is hindered by a lack of requisite circulating tumor (ct) and cell-free (cf) DNA levels in blood due to the blood-brain barrier (BBB). This limits the identification of blood-based tumor biomarkers along with the development and use of biomarker-driven systemic therapies. Low intensity focused ultrasound combined with intravenously administered microbubble oscillators (MB-FUS), leads to non-invasive BBB opening. This trial aims to evaluate the utility of LIFU for bolstering blood ctDNA and cfDNA for enhance liquid biopsy in patients with GBM. **Methods:** LIBERATE is an ongoing, prospective, multi-center, self-controlled, pivotal trial evaluating safety and technical efficacy of transcranial MR-guided MB-FUS for increasing blood ctDNA and cfDNA levels in adults, aged 18-80 years with GBM. Patients with suspected GBM planned for tumor biopsy or resection at 17 centers in US and Canada are being enrolled. Patients with multifocal tumors or tumors arising from deep midline, thalamus, cerebellum, or brainstem are excluded. Patients are administered IV microbubbles for enhanced sonication, after which MR-guided BBB opening using a 220 kHz device, with 1024-element phased array transducer, is performed with real-time acoustic feedback control for effective cavitation. Pre- and post-procedure, phlebotomy and MRI brain are done. Patients are offered optional 2nd procedure during adjuvant chemotherapy phase if willing. Primary efficacy endpoint is correlation between biomarker patterns in tumor tissue collected during surgery/biopsy and blood collected following MB-FUS procedure. Confirmatory secondary efficacy endpoint is ratio between greatest yield of cfDNA in blood post-MB-FUS compared to cfDNA level in blood pre-MB-FUS. The primary study hypothesis is that agreement rate on biomarker pattern between resected/biopsied tumor tissue and blood is $> 70\%$. The secondary hypothesis is that MB-FUS BBBO leads to a $\geq$2-fold rise in blood cfDNA. Assuming the true agreement rate expected is 89%, a sample of N = 50 patients will provide 90% power to meet the primary endpoint (Exact test, Binomial Proportion, one-sided Alpha = 0.025). Exploratory endpoints include (1) sensitivity of detection of known specific somatic mutations in ctDNA from blood samples collected before and after MB-FUS, (2) estimation of ctDNA levels in samples collected at 30-minutes, 1-hour, 2-hour, and 3-hour post-MB-FUS to determine time of greatest yield, (3) correlation of MRI parameters related to grading of BBB opening and ctDNA-based biomarkers from post-MB-FUS blood samples, (4) biomarker correlation between plasma cfDNA sampled during adjuvant chemotherapy phase and tumor tissue harvested at surgery. Patient enrollment commenced in 2022 and is ongoing (NCT05383872). Clinical trial information: NCT05383872. Research Sponsor: Insightec Inc.