TPS2089 **Poster Session**

A multicenter, randomized, controlled, pivotal trial of microbubble-enhanced transcranial focused ultrasound for patients with NSCLC brain metastases (LIMITLESS).

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Background: The efficacy of systemic therapies for brain metastases (BM) is hindered by the blood-brain barrier (BBB) and brain-tumor barrier. Transcranial low-intensity focused ultrasound combined with IV microbubble oscillators (MB-FUS), allows for localized, controlled, non-invasive and temporary BBB opening, which has been shown to enhance tumor drug delivery of systemic therapies, as well as impro efficacy of immunotherapies. Non-small cell lung cancer (NSCLC) is the most common cause of BM, and this randomized controlled trial (RCT) aims to evaluate the safety and efficacy of MB-FUS-mediated BBB opening combined with standard of care (SOC) systemic therapy versus systemic therapy alone for patients with NSCLC BM. **Methods:** LIMITLESS is prospective, multicenter, parallel-arm, RCT, ongoing at up to 30 centers, that randomizes patients with NSCLC BM, in a 2:1 ratio to either: (i) Arm 1: MR-guided MB-FUS plus all FDA approved on-label use of immune checkpoint inhibitors (ICIs) with or without chemotherapy regimen (SOC systemic therapy), or (ii) Arm 2: SOC systemic therapy alone. Included patients are ≥18 years aged, with normal organ function, KPS ≥70, and have ≥0.5 cm size BM meeting measurable disease criteria as per RANO-BM. Patients on both arms receive standard-of-care therapy, while those on arm 1 also undergo MB-FUS. Patients undergo pre-treatment brain MRI, followed by IV administration of microbubbles for enhanced sonication effects. BBB opening is performed using a transcranial 220 kHz device with 1024-element phased array transducer with real-time acoustic feedback-based power control for maintaining effective microbubble activation. The primary study outcome is the overall objective response rate (ORR) at 6 months as assessed using RANO-BM criteria. Using a Bayesian design for power analysis, a superior ORR of 60% is assumed for MB-FUS arm versus 30% in the control arm for a total sample size of N = 96, 64 participants in MB-FUS and 32 in control arm, for 80% power using a two-sided chi-square test with an alpha of 0.05. For the upper-bound estimate, ORR of 45% in MB-FUS arm and 30% in the control arm, the study needs N = 369 participants: 246 in LIFU arm and 123 in control arm. The secondary outcomes are best objective response rate and median time-to-response per treatment arm. Exploratory outcomes are median progression-free survival (PFS), overall survival (OS), median intracranial PFS, median extracranial PFS, and quality of life. Patient enrollment commenced in 2022 and is ongoing (ClinicalTrials.Gov Registration: NCT05317858). Clinical trial information: NCT05317858. Research Sponsor: Insightec Inc.