TPS2096 **Poster Session**

A global phase 3, open-label, randomized 2-arm study comparing the clinical efficacy and safety of niraparib with temozolomide in adult participants with newly-diagnosed, MGMT unmethylated glioblastoma.

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Background: Glioblastoma (GBM) is associated with dismal prognosis and poor quality of life. In approximately 60% of tumors, the O6-methylguanine methyltransferase (MGMT) promoter is unmethylated and the prognosis is even more dire, with a median overall survival (OS) of 12.7 months following surgical resection, temozolomide (TMZ), and fractionated radiotherapy (RT). Poly (ADP-ribose) polymerase (PARP) mediates DNA damage response in GBM and niraparib is an investigational PARP1/2-selective inhibitor. At ASCO 2024, we reported on a Phase 0/2 study of niraparib plus radiotherapy in newly-diagnosed, MGMT-unmethylated glioblastoma (GBM), demonstrating superior tumor pharmacokinetic and pharmacodynamic performance compared to other studied PARP inhibitors and a median overall survival (OS) of 21.7 months. Based on the proof-of-concept data, a global registrational Phase 3 study (Gliofocus) was initiated. **Methods:** This Phase 3, open-label, randomized 2-arm study (NCT06388733) will compare niraparib versus TMZ in 450 adult participants with newly-diagnosed, MGMT-unmethylated GBM. Participants must have a biopsied or resected GBM, per 2021 World Health Organization classification. MGMT promoter methylation status is determined locally by validated pyrosequencing or quantitative methylation-specific polymerase chain reaction assays. Other key inclusion/exclusion criteria include: (1) Karnofsky performance status of ≥70, (2) no prior treatment for GBM (including brachytherapy or BCNU wafers), (3) no tumor-treating field therapy, and (4) suitability for RT of 60 Gy in 30 fractions using ESTRO-EANO ‘single phase’ targeting approach. Following 1:1 randomization, niraparib (Arm A) or TMZ (Arm B) is administered concomitantly with RT and then adjuvantly until disease progression by Blinded Independent Central Review (BICR) or until completion of 6 cycles of TMZ. . The primary endpoints of the study are progression-free survival (PFS) (per RANO 2.0; HR = 0.612, 90% power, 1-sided alpha = 0.001) and overall survival (OS) (HR = 0.698, 90% power, 1-sided alpha = 0.0239). Secondary endpoints include overall response rate, health-related quality of life, neurocognitive function, and the safety and tolerability of niraparib compared to TMZ. The first patient was accrued in June 2024 and an interim futility analysis is planned in 2025. This study, sponsored by the Ivy Brain Tumor Center and with drug and funding provided by GSK, is expected to enroll in a minimum of 115 clinical sites across 11 countries. Clinical trial information: NCT06388733. Research Sponsor: GSK.