TPS3174 **Poster Session**

A phase 1/2 dose escalation study of the oral DNA polymerase theta inhibitor (POLQi) GSK4524101 ± niraparib in adults with advanced or metastatic solid tumors.

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Background: In homologous recombination-deficient (HRd) tumors, use of a PARP inhibitor (PARPi) leads to generation of DNA breaks that cannot be effectively repaired, thus selectively killing cancer cells via synthetic lethality. An alternative DNA repair mechanism, microhomology-mediated end joining, is mediated by DNA polymerase theta (encoded by *POLQ*). In preclinical studies, POLQi + PARPi demonstrated superior efficacy vs PARPi alone in preventing HRd tumor growth. To evaluate the clinical potential of this combination, this first-in-human study investigates treatment with GSK4524101, an investigational POLQi, and niraparib, a PARPi, in patients with solid tumors. **Methods:** This open-label, phase 1/2, multicenter study opened in October 2023 and includes a phase 1a/b, dose-escalation portion (part 1; potential enrollment to n≈75). Sites in the US and Canada are enrolling patients for part 1, which aims to assess the maximum tolerated dose, pharmacokinetics (PK), and safety of oral GSK4524101 ± oral niraparib. Eligibility criteria include age ≥18 years, Eastern Cooperative Oncology Group performance status of 0–2, life expectancy ≥3 months, and diagnosis of advanced or metastatic solid tumor with all standard-of-care treatment options exhausted. Exclusion criteria include unresolved chemotherapy-induced adverse events (AEs) or symptomatic uncontrolled brain or leptomeningeal metastases, uncontrolled hypertension, history of myelodysplastic syndrome or acute myeloid leukemia, or another malignancy that has progressed or required active treatment in the past 2 years. Outcome measures include dose-limiting toxicity (DLT) incidence during the DLT observation periods (up to 28 days; primary); treatment-emergent AEs (TEAEs) and serious AEs (SAEs); percentage of patients receiving all planned doses; and percentage of patients requiring AE-related dose interruptions, reductions, and discontinuations in the DLT observation period. Secondary endpoints include the PK of niraparib and the metabolite of GSK4524101 and incidence and duration of TEAEs and SAEs beyond the DLT observation period. The study is currently recruiting, with 17 patients having received doses across 9 sites in 2 countries as of January 10, 2025. Clinical trial information: NCT06077877. Research Sponsor: GSK.