First-in-human, phase 1/2 study of GSK4524101, an oral DNA polymerase theta inhibitor, alone or combined with the poly(ADP-ribose) polymerase inhibitor niraparib in adults with solid tumors

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Background

- Double-stranded DNA breaks (DSBs) in human cells are typically repaired via nonhomologous end joining (NHEJ) or homologous recombination (HR)[1,2]
- Deficiency of HR-mediated DNA repair plays a role in the initiation and progression of many tumor types[3]
- In tumors with HR deficiency (HRd), poly(ADP-ribose) polymerase (PARP) inhibition leads to generation of DSBs that cannot be effectively repaired because of the HR defect, resulting in synthetic lethality[4]
- This finding has led to the clinical development and approval of several PARP inhibitors (PARPi) for the treatment of various tumors including certain ovarian, breast, prostate, and pancreatic cancers that are prone to display HRd[5,6]
- DNA polymerase theta (encoded by *POLQ*) mediates an alternative DNA repair mechanism, microhomology-mediated end joining (MMEJ)[7]
- DNA polymerase theta is generally not detectable in normal tissues but is upregulated in many tumor types[8]
- In preclinical studies, POLQ inhibitor (POLQi) plus PARPi treatment demonstrated superior efficacy to PARPi alone in preventing the growth of HRd tumors[9]
- GSK4524101, an investigational POLQi, is a prodrug that is cleaved to generate the active moiety GSK4364973 before absorption
- To evaluate the clinical potential of combining POLQi and PARPi, this first-in-human study has been designed to investigate treatment with GSK4524101 with or without the PARPi niraparib in participants with solid tumors

Summary

- This study opened in October 2023 and is actively recruiting in the United States and Canada and may enroll as many as 135 participants
- As of February 28, 2024, 3 participants have been dosed
- Participants enrolled in part 1 will receive GSK4524101 alone or GSK4524101 plus niraparib; participants enrolled in part 2 will be randomized to either GSK4524101 plus niraparib or niraparib alone
- Part 1 of this study is expected to be completed in 2025

Key objectives

- To determine the maximum tolerated dose (MTD) of GSK4524101 monotherapy and of GSK4524101 in combination with niraparib (part 1)
- To determine the safety, tolerability, and pharmacokinetics (part 1) and preliminary anticancer activity (part 2) of GSK4524101 alone or with niraparib

Enrolling sites

Canada

United States

Participants

Key inclusion criteria

- Aged ≥18 years
- Histologically diagnosed advanced or metastatic solid tumor
- Eastern Cooperative Oncology Group performance status score of 0–2
- Life expectancy of ≥3 months
- All standard treatment options were exhausted

Key exclusion criteria

- Incomplete recovery[a] from prior chemotherapy-induced adverse events
- Current or prior participation in a treatment study of any investigational agent within 4 weeks of the first dose of treatment
- Symptomatic uncontrolled brain or leptomeningeal metastases
- Uncontrolled hypertension[b]
- Known history of myelodysplastic syndrome or acute myeloid leukemia
- Known additional malignancy that has progressed or required active treatment in the past 2 years

[a]Recovery to grade ≤1 or to baseline.
[b]Sustained systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg.

Study design

- This open-label, multicenter, phase 1/2 study (NCT06077877) comprises dose-finding and dose-expansion parts

Part 1: Dose escalation (N≤75 enrolled)

Monotherapy GSK4524101

Combination GSK4524101 + niraparib (initiated after monotherapy dose level 4 has cleared safety)

Food effect GSK4524101

→

Part 2: Dose expansion (N=60 enrolled)

Monotherapy niraparib
vs
Combination GSK4524101 + niraparib (1:1 randomization)

Outcomes

Part 1: Dose escalation (N≤75 enrolled)

Endpoints

Primary: Safety during first 28 days

- Incidence of DLTs per dose level in the DLT observation period
- Incidence, duration, and severity of TEAEs and SAEs
- Percentage of participants receiving all planned doses
- Percentage of participants requiring dosage interruptions, dose reductions, and drug discontinuations for adverse reactions per dose level in the DLT observation period

Secondary

- PK parameters (AUC, C_{max}, T_{max}, half-life) of GSK4364973 (active metabolite of GSK4524101)
- Plasma concentration of niraparib
- Incidence and duration of TEAEs and SAEs beyond the DLT observation period

Part 2: Dose expansion (N=60; randomized 1:1)

Endpoints

Primary: Clinical response

- ORR (investigator-assessed by RECIST v1.1)

Secondary

- PFS (investigator-assessed by RECIST v1.1)
- DOR (investigator-assessed)
- Safety (incidence and duration of TEAEs and SAEs) of GSK4524101 + niraparib
- PK parameters (C_{max}, C_{min}, etc) of GSK4364973 (active metabolite of GSK4524101)
- Plasma concentration of niraparib

Exploratory

- Biomarker analyses will be conducted to correlate treatment response with potential biomarkers identified from blood and tumor-based testing

AUC, area under curve; C_{max}, maximum concentration; C_{min}, minimum concentration; DLT, dose-limiting toxicity; DOR, duration of response; ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; TEAE, treatment-emergent adverse event; T_{max}, time to maximum concentration; v, version.

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