First-in human, phase 1, dose-escalation pharmacokinetic and pharmacodynamic study of the oral dual PI3K and mTORC1/2 inhibitor PQR309 in patients with advanced solid tumors (SAKK 67/13)


BACKGROUND

PQR309 is an orally bioavailable, balanced pan-phosphatidylinositol-3-kinase (PI3K), mammalian target of rapamycin (mTOR) C1 and mTORC2 inhibitor.

PATIENTS AND METHODS

This is an accelerated titration, 3 + 3 dose-escalation, open-label phase I trial of continuous once-daily (OD) PQR309 administration to evaluate the safety, pharmacokinetics (PK) and pharmacodynamics in patients with advanced solid tumours. Primary objectives were to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D).

RESULTS

Twenty-eight patients were included in six dosing cohorts and treated at a daily PQR309 dose ranging from 10 to 150 mg. Common adverse events (AEs; ≥30% patients) included fatigue, hyperglycaemia, nausea, diarrhoea, constipation, rash, anorexia and vomiting. Grade (G) 3 or 4 drug-related AEs were seen in 13 (46%) and three (11%) patients, respectively. Dose-limiting toxicity (DLT) was observed in two patients at 100 mg OD (>14-d interruption in PQR309 due to G3 rash, G2 hyperbilirubinaemia, G4 suicide attempt; dose reduction due to G3 fatigue, G2 diarrhoea, G4 transaminitis) and one patient at 80 mg (G3 hyperglycaemia >7 d). PK shows fast absorption (T 1-2 h) and dose proportionality for C and area under the curve. A partial response in a patient with metastatic thymus cancer, 24% disease volume reduction in a patient with sinonasal cancer and stable disease for more than 16 weeks in a patient with clear cell Bartholin’s gland cancer were observed.

CONCLUSION
The MTD and RP2D of PQR309 is 80 mg of orally OD. PK is dose-proportional. PD shows PI3K pathway phosphoprotein downregulation in paired tumour biopsies. Clinical activity was observed in patients with and without PI3K pathway dysregulation.

CLINICAL TRIAL REGISTRATION
ClinicalTrials.gov # NCT01940133.