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Clinical Trial

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)

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KEYWORDS
PQR309;
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Abstract ***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,

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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_{max} 1–2 h) and dose proportionality for C_{max} 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.

1. Introduction

The phosphatidylinositol-3-kinase (PI3K) and mammalian target of rapamycin (mTOR) signalling cascade serves physiological and pathophysiological cell functions and is of major importance in cancer and inflammatory disease. As a key downstream effector of receptor tyrosine kinases (RTKs) and G protein–coupled receptors, PI3K activation initiates a signal transduction pathway that stimulates glucose metabolism, cell proliferation and survival [1–9]. One of the principal downstream effectors of PI3K is mTOR. mTOR also integrates growth signals that are independent of PI3K activation [6]. Dysregulation of the PI3K/mTOR pathway is associated with many cancers and may occur through several mechanisms including (i) activation of the p110α subunit (PI3KCA); (ii) activation of upstream RTKs; (iii) constitutive recruitment and activation by Ras oncogene mutants; (iv) loss or inactivating mutations of phosphatase and tensin homologue (PTEN) or (v) overexpression and activating mutations of downstream kinases (e.g. Akt) [2,6]. In addition, dysregulation of the PI3K/mTOR pathway has been implicated in chemotherapy resistance [2,6,9–12].

To date, PI3K and PI3K/mTOR inhibitors have demonstrated clinical efficacy in cancer patients with or without PIK3CA [13] or PTEN aberrations. Idelalisib, a selective inhibitor of PI3Kδ is licenced for use in chronic lymphocytic leukaemia and follicular lymphoma [14–16]. Everolimus, a selective inhibitor of mTORC1, is licenced for use in advanced breast cancer, neuroendocrine tumours and renal cell carcinoma. Although these clinical data are encouraging, clinical resistance to kinase inhibitors occurs because of either novel mutations within the targeted kinase or other compensatory mechanisms [17–19]. In particular, it has been shown that idelalisib resistance is due to increased expression of PI3Kα [20]. Alternatively, inhibiting all PI3K isoforms results in upregulation of the mTOR pathway or inactivation of PTEN, accompanied by resistance to these agents [21]. Persistent mTOR activation has been detected in patients with PIK3CA inhibitor–resistant tumours. Thus, targeting two nodal points within a pathway may reduce the probability of resistance [21]. Dual inhibition of PI3K and mTOR is, therefore, a promising strategy for anticancer therapy.

PQR309 (PIQUR Therapeutics AG, Basel, Switzerland) is an oral pan-class I PI3K inhibitor that selectively targets all four isoforms of class I PI3K (α, β, γ, δ), with a balanced activity against mTOR. It is equipotent against $p110\alpha^{H1047R/E542K/E545K}$ somatic mutations often observed in human cancers [22]. PQR309 demonstrates anti-proliferative activity in a variety of cell lines with and without inappropriate PI3K pathway activation [23–27].

The primary objectives of this first-in-human, phase 1, dose-escalation study were to assess the safety and tolerability and to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) of oral PQR309 with once-daily continuous dosing in patients with advanced solid tumours. Secondary