**Epreuve de l’UE O3 M2 Pharmacologie Filière Pro 2018-2019**

**22 janvier 2019 de 10h à 12h**

**Question A :** Citer les principales méthodes d’explorations fonctionnelles de la peau et préciser leurs principales applications dans le cadre des essais cliniques de médicaments topiques.

**Question B :** Sont extraits d’un article publié dans European Journal of Cancer publié en 2018 (Vol. 96, Pages 6-16) :

# **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)**

## 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, pharmacokinetics (PK) and pharmacodynamics in patients with advanced solid tumours.

## Results

Twenty-eight patients were included in six dosing cohorts ***(voir Question 4)*** 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 (***voir Question 7)***. 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.

## Highlights *(= Principaux résultats de cette étude)*

The maximum tolerated dose and recommended phase 2 dose of PQR309 is 80 mg orally OD.

Pharmacodynamics shows phosphatidylinositol-3-kinase (PI3K)–mammalian target of rapamycin (mTOR)–S6 pathway inhibition in paired tumour biopsies *(= biopsie tumorale avant et après traitement)*.

Pathway inhibition is more pronounced in patients with tumour shrinkage *(=diminution du volume de la tumeur”)*.

Activity was observed in patients with and without PI3K pathway dysregulation.

## 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 …

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 p110α H1047R/E542K/E545K somatic mutations often observed in human cancers. PQR309 demonstrates anti-proliferative activity in a variety … (***voir Question 1***).

The primary objectives of this first-in-human, phase 1, dose-escalation study were to assess the … (***voir Question 2***). Secondary objectives included characterisation of … (***voir Question 2)***.

## 2 Patients and methods

## 2.1 Study design

This was a multicenter, open-label first-in-human trial (***voir Question 3***). Based on the no-observed-adverse-effect-level in dogs of 4 mg/kg, the starting dose in humans was 10 mg. An accelerated modified ‘3 + 3’ dose-escalation design was used (***voir Question 5***) . Dose level 1 and 2 enrolled a single patient. If a drug-related toxicity ≥ grade (G) 2 occurred, two additional patients were to be enrolled at the same dose level and then the trial would continue as a classical 3 + 3. From dose level 3 and thereafter, the classical 3 + 3 design was used. Doses were increased by 100% between dose levels until dose level 4. After dose level 4 or the first toxicity ≥ G2, subsequent dose levels could increase between 30 and 100%, according to the type and grade of toxicity after discussion with the independent Data Safety Monitoring Board (IDSMB). In dose levels 2 to 4, the administered dose was adjusted according to weight (75% dose if < 60 kg, 125% dose if > 80 kg). Eligible patients received once daily oral PQR309 capsules continuously on a 21-d cycle until progression, unacceptable toxicity, investigator judgement or withdrawal of consent. …

## 2.2 Patients' eligibility

The study enrolled adult patients (age ≥ 18 years) with a histological or cytologically confirmed diagnosis of advanced solid tumour and evidence of tumour progression with measurable or evaluable disease. The inclusion criteria were updated after recruitment of the four initial cohorts to require tumours accessible to biopsy (***voir Question 8***).

## 2.3 Dose-limiting toxicity, MTD and management of toxicity

Dose-limiting toxicities (DLTs) were defined as any of the following: G4 neutropenia for >7 d, febrile neutropenia, G4 thrombocytopenia, G4 non-haematological toxicity (e.g. hyperglycaemia >27.8 mmol/L) or G3 lasting >7 d (unless controlled with supportive care), treatment delay > 14 d because of unresolved toxicity or non-haematological toxicity ≥ G2 deemed dose limiting by the IDSMB. DLTs were based on adverse events (AEs) observed during the first cycle (21 d). The MTD was defined as the highest dose level at which ≤1 of six patients experience a DLT.

## 2.4 Safety and efficacy assessments

AEs were graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.03. Efficacy parameters were defined using the Response Evaluation Criteria in Solid Tumours (RECIST, version 1.1) (***voir Question 6)***.

## 2.5 Pharmacokinetics

Blood samples for PK analysis were taken …

## 2.6 Pharmacodynamics

Tumour biopsies were taken before the start of the treatment and after 3 weeks of therapy.

## 3 Results

## 3.1 Patient characteristics

Twenty-eight patients (20 female, 8 male) were treated between January 2014 and February 2015 at six centres (Switzerland, the United Kingdom and Spain; [Table 1](https://www.clinicalkey.fr/tbl1) ). Patients were enrolled into six dosing cohorts (10 mg n = 1; 20 mg n = 1; 40 mg n = 4; 80 mg n = 9; 100 mg n = 7; 120 mg n = 6), with dose adjusted for body weight in the first four cohorts ( [Table 2](https://www.clinicalkey.fr/tbl2) ). The median age of patients was 58 years (range 21–75). The most frequent primary tumour types were colorectal cancer (n = 7) and ovarian cancer (n = 6). The median number of lines of prior treatment was 4 (range 0–9; [Table 1](https://www.clinicalkey.fr/tbl1) ). Fourteen patients (50%) discontinued trial treatment because of progressive disease. Five patients discontinued because of AEs (18%)…

**Questions :**

1. Compléter la phrase tronquée (page 2) correspondant aux études précliniques qui ont constitué le prérequis de cet essai clinique.
2. Compléter la phase tronquée (page 2) en indiquant quels étaient les objectifs principaux et secondaires de cet essai clinique ?
3. Justifier le choix d’une étude multicentrique ainsi que d’une étude en ouvert (page 2).
4. A quoi correspondent, de façon générale, les cohortes d’une étude phase 1 (page 1) ?
5. Pour quelle(s) raison(s) le schéma de l’étude est-il qualifié de « accelerated modified » (page 2) ? Justifier ce choix par rapport à un schéma « 3 + 3 » classique.
6. Principe des critères RECIST (page 3).
7. Que signifie le terme « dose proportionality » (page 1) ? Est-ce un résultat attendu ? Doit-il être considéré comme positif ou péjoratif ? Pour quelle raison(s) ?
8. Justifier l’amendement effectué relatif aux critères d’inclusion ; pour quel est raison cette biopsie tumorale a-t-elle mise en place alors que cela n’est jamais pratiqué pour les essais de phase des médicaments cytotoxiques (page 3) ?
9. Les résultats de cet essai vont-ils permettre de choisir les critères d’inclusions des patients du ou des future(s) étude(s) de phase 2 ? Quelles sont les autres informations guidant ces choix ?
10. De façon générale, quand le développement d’un futur « companion diagnostic CDX» est décidé, quels sont les principaux conseils qui sont donnés au chef de projet pour réussir ce développement conjoint molécule et CDX ?