OPEN LABEL, NON-RANDOMIZED, MULTICENTER PHASE I/IIA STUDY INVESTIGATING SAFETY AND EFFICACY OF PQR309 AND ERIBULIN COMBINATION IN PATIENTS (PTS) WITH LOCALLY ADVANCED (LA) OR METASTATIC HER2 (-) AND TRIPLE-NEGATIVE BREAST CANCER (TNBC) (PIQHASSO STUDY)

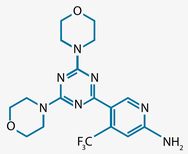
Authors: Elena López[1], Joaquin Gávila[2], Sonia Pernas[3], Cristina Saura[4], Mafalda Oliveira[4], Violeta Serra[4], Peter Schmid[5], Simon Lord[6], David Paez[7,10], José Pérez[8,10], Antoni Llombart[9,10], Katarina Petrovic[11], Sasa Dimitrijevic[11], Javier Cortes[1,4]

[1]Hospital Ramón y Cajal, Madrid, Spain [2]IVO, Valencia, Spain [3]ICO L'Hospitalet, Barcelona, Spain [4]Hospital Vall Hebrón, Barcelona, Spain [5]Barts Cancer Institute, London, United Kingdom [6]Churchill Hospital, Oxford, United Kingdom [7]Hospital de la Santa Creu i Sant Pau, Spain [8]Baselga Institute of Oncology – Quiron Barcelona, Spain [9]Hospital Arnau de Vilanova, Valencia, Spain [10]Medica Scientia Innovation Research (MedSIR ARO), Barcelona, Spain [11]PIQUR Therapeutics AG, Basel, Switzerland

BACKGROUND

- PQR309 is an oral pan-PI3K and mTOR inhibitor that penetrates the blood-brain barrier with potent in vitro as well as in vivo antitumor activity (Figure 1).
- The combination of eribulin and PI3K inhibitors has shown promising tumor inhibition in luminal breast cancer and TNBC preclinical models, supporting the clinical development of this therapeutic strategy[1].
- The aim of this trial is to identify the maximum tolerated dose (MTD) in the phase I part as well as to evaluate the efficacy and safety in the phase II part of the combination of PQR309 and eribulin in LA or metastatic HER2[-] and TNBC patients, respectively.

Figure 1. PQR309



[1]Luyimbazi D et al. Effect of eribulin on cell growth and PI3K pathway (…) HER2-expressing breast cancer. Journal of Clinical Oncology. 2013; BCS, 31(26_suppl): 173.

TRIAL DESIGN

- This is an open label, non-randomized, multicenter phase I/IIa clinical trial (Figure 3).

Phase I principal selection criteria are (Table 1):

(1) Non-resectable LA or metastatic HER2[-]breast cancer;

(2) 2 to 5 prior chemotherapy regimens in advanced disease;

(3) Adequate organ function and performance status.

Phase II specific selection criteria are (Table 1):

(1) Non-resectable LA or metastatic TNBC;

(2) RECIST v.1.1 evaluable disease.

- Pts will receive oral PQR309 in combination with intravenous (i.v.) eribulin mesylate 1.4 mg/m2 on days 1 and 8 of a 21-day cycle until disease progression, unacceptable toxicity or consent withdrawal.

TRIAL REGISTRATION: NCT02723877. Date of registration: 21/12/2015.

Table 1. Key eligibility criteria for the PIQHASSO study

A) Inclusion Criteria:	B) Exclusion Criteria:
Phase I (Escalation part)	**Phase I (Escalation part)**
1. Women ≥ 18 years with histologically or cytologically confirmed locally advanced or metastatic HER2-negative breast cancer.	1. Symptomatic CNS metastases.
2. Known estrogen and progesterone receptor status.	2. Clinically manifested diabetes mellitus.
3. Radiological evidence of inoperable locally advanced or metastatic breast cancer.	3. Concurrent malignancy other than HER2 negative BC or malignancy within 3 years of study enrollment.
4. Required treatments: • 2 to 5 prior chemotherapeutic regimens in locally advanced and/or metastatic setting. • anthracycline and/or a taxane. • >4 weeks from any investigational agent. • prior anti-hormonal therapy is allowed.	4. Prohibited treatments: • Other antineoplastic agents. Radiotherapy ≤ 3 weeks. • Major surgery ≤ 14 days. • High doses of corticosteroids ≤ 2 weeks. • Warfarin or other coumarin derived anti-coagulant. • Medicinal products that increase the pH / alter the absorption of PQR309. • Medication with known risk to prolong the QT interval or inducing Torsades de Pointes.
5. Eastern Cooperative Oncology Group (ECOG) performance status≤2.	5. Adverse event ≥ 1 (except alopecia).
6. Adequate bone marrow and organ function.	6. Clinical significant cardiac, hepatic or kidney function.
7. Written informed consent obtained according to local guidelines.	7. GI disease that alter the absorption of PQR309.
Phase II (Extension part)	**Phase II (Extension part)**
8. Triple-negative breast cancer.	8. Previous systemic treatment with PI3K, mTOR or AKT inhibitors.
9. Measurable disease according to RECIST v.1.1 or non-measurable bone lesions with a soft tissue component that meets the RECIST v.1.1 criteria.	9. Previous treatment with eribulin.

PHASE I (ESCALATION PART):

- The primary objective is to determine the maximum tolerated dose (MTD) of 3 different dosing schedules of PQR309 in combination with eribulin.
- MTD is defined as the highest dose level at which 0 of 3 pts or ≤1 of 6 pts experience dose-limiting toxicity (DLT) during the 1st cycle (Table 2).
- The phase I part of the trial uses the "3 + 3" design for each of three PQR309 dosing schedules in combination with eribulin.
- The continuous daily dosing schedule will investigate continuous once-daily administration of PQR309.
- After MTD of continuous daily PQR309 dosing has been established, two PQR309 intermittent dosing schedules in 7 days cycles will be investigated: 2 days of once daily PQR309 followed by 5 days without PQR309 dosing (intermittent consecutive days), and dosing on Day 1 and Day 4 (intermittent non-consecutive days) (Figure 2).
- Based on efficacy, safety, and pharmacokinetic results, MTD in one of the three dosing schedules (continuous, intermittent consecutive, or intermittent non-consecutive) will be selected for the phase II part of the study (Figure 3).

Figure 2. Schematic administration of study treatment Phase I

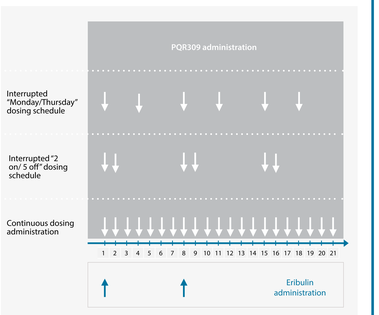
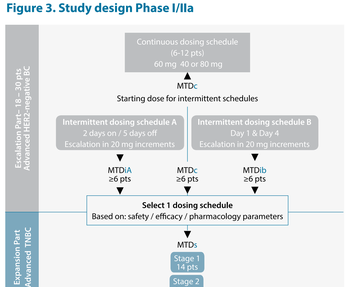


Table 2. Dose-limiting toxicity (DLT) definitions

DLT: is defined as any drug-related toxicity (CTCAE v.4) described as:

Haematological:	Non-haematological:
• G≥3 neutropenia requiring 2nd eribulin dose postponement > 7 days	• Any G≥3 AE, except hyperglycemia
• Febrile neutropenia	• G2 pneumonitis or stomatitis recurring in the same cycle
• G4 thrombocytopenia	• Any AE requiring treatment reduction or discontinuation (Table 3)
• G3 thrombocytopenia requiring transfusion	
• G2-3 thrombocytopenia requiring 2nd eribulin dose postponement > 7 days.	

Figure 3. Study design Phase I/IIa



MTDc: Maximum tolerated dose on continuous dosing schedule
MTCIA: Maximum tolerated dose on intermittent dosing schedule A (2 days on/ 5 days off)
MTCIB: Maximum tolerated dose on intermittent dosing schedule B (Day 1 & Day 4)
MTDS: Maximum Tolerated dose of SELECTED dosing schedule

PHASE II (EXTENSION PART):

- The primary objective is to evaluate the efficacy of the combination in terms of clinical benefit rate (CBR).
- CBR is defined as the percentage of pts with objective response (CR or PR) or stable disease ≥24 weeks according to RECIST v1.1.
- The trial applies a Simon's minimax two-stage design (Figure 3).
- ≥4 pts with clinical benefit (CB) among 14 pts enrolled in the first stage will be necessary to continue on to the second stage.
- At the study end, ≥10 pts with CB out of 28 pts will be required to justify this strategy in further clinical trials. Assuming 10% dropout rate, 31 pts will be recruit in the phase II part.
- With this design, there is an 80% probability of a positive finding if the true CBR is ≥43% and a 5% probability of a positive finding if the true CBR is ≤21%.
- Secondary endpoints include safety-related outcomes, efficacy measures, pharmacokinetics and pharmacodynamics parameters and predictive biomarkers (PI3K/AKT/mTORpathway alterations and mutational status).
- Management of treatment-related toxicities and dose modifications are described in Table 3.

Table 3. Summary of dose modifications and discontinuations related with AEs.

Non Hematologic		PQR309	Eribulin	
Type of event	**Adverse reaction**	**Dose reductions*, interruptions and discontinuations**	**Dose reductions**, interruptions and discontinuations**	
Non Hematologic	G4	• Stop treatment permanently	• 1st week of cycle***. Postpone until AE ≤ G2.	• 2nd week of cycle, Postpone until AE ≤ G2. -AE resolves: ≤7 days; reduce 1 dose level. >7 days; must be suspended.
	G3	• Interrupt until AE ≤ G2. -AE resolves: ≤7 days; reduce 1 dose level. >7 days; must be discontinued.		
Pneumonitis	G2	• 1st occurrence: Interrupt until AE ≤ G1. -AE resolves: ≤14 days; reduce 1 dose level. >14 days; must be discontinued. • 2nd occurrence: treatment discontinued.	• no dose adjustments should be made	
Stomatitis	G2	• 1st occurrence: Interrupt until AE ≤ G1. -AE resolves: ≤7 days; same dose level. 8-14 days; reduce 1 dose level. >14 days; must be discontinued. • 2nd occurrence: discontinued. : Interrupt administration until AE ≤ G1 -AE resolves: ≤ 14 days, reduce 1 dose level. > 14 days; must be discontinued.	• no dose adjustments should be made	
Other AE	G1/2	• no dose adjustments should be made	• no dose adjustments should be made	
Hematologic		**PQR309**	**Eribulin**	
Type of event	**Adverse reaction**	**Dose reductions*, interruptions and discontinuations**	**Dose reductions**, interruptions and discontinuations**	
Neutropenia	G4	• Interrupt until AE ≤ G3. -AE resolves: ≤7 days; same dose level. 8-14 days; reduce 1 dose level. >14 days; must be discontinued.	• 1st week of cycle***, postpone until Neutropenia ≤ G2.	• 2nd week of cycle, postpone until Neutropenia ≤ G2. -AE resolves: in cycle 1; same dose level. ≤7 days; reduce 1 dose level. >7 days; must be suspended.
	G3	• Continue treatment		
Thrombocytopenia **Febrile neutropenia**	-G4 -G3 (blood transfusion) G3/4	• Interrupt until Neutropenia ≤ G2 & Thrombocytopenia ≤ G1. -AE resolves: ≤7 days; reduce 1 dose level. 8-14 days; reduce 1 dose level or discontinue. >14 days: must be discontinued.	• 1st week of cycle***, postpone until Neutropenia ≤ G2 & Thrombocytopenia ≤ G1.	• 2nd week of cycle, postpone until Neutropenia ≤ G2 & Thrombocytopenia ≤ G1. -AE resolves: ≤7 days; reduce 1 dose level. >7 days; must be suspended.
Thromobocytopenia	G3	• Interrupt until AE ≤ G1. -AE resolves: ≤7 days: same dose level. 8-14 days; reduce 1 dose level or discontinue. >14 days: must be discontinued.	• 1st week of cycle***, postpone until Thrombocytopenia ≤ G1.	• 2nd week of cycle, postpone until Neutropenia ≤ G1. -AE resolves: in cycle 1; same dose level. ≤7 days; reduce 1 dose level. >7 days; must be suspended.
	G2	• no dose adjustments should be made		

* Dose reductions of PQR309 will be in 20 mg steps. Only 1 dose reduction per patient is allowed. Dose reduction below 40 mg/day is not allowed. However, patient not tolerating 40 mg continuous daily but showing clinical benefit may be treated with the 40 mg administered in one of the intermittent schedules. The agreement between study investigator and study sponsor is mandatory.

** 1st eribulin mesylate dose reduction: reduce to 1.1 mg/m2; 2nd dose reduction: reduce to 0.7 mg/m2. If further dose reduction below 0.7 mg/m2 is required, discontinue the treatment.

*** The eribulin dose will be reduced in 1st week of the cycle if any of the following AE has developed in the last treatment cycle: G3/4 non-hematological AE, G4 neutropenia, G3 neutropenia with fever or infection, G4 Thrombocytopenia, G3 Thrombocytopenia requiring blood transfusion or suspension of treatment in 2nd week due to AE.

ACCRUAL:

The study is **open for enrollment** and first patient was enrolled on April 2016.

CONTACT:

E-mail: elemiranda@hotmail.com

ACKNOWLEDGMENTS: