IRST189.04_ PREV

Phase II study of oral PRednisone 5 mg bid plus EVerolimus in patients with metastatic renal cell cancer after failure of vascular endothelial growth factor receptor-tyrosine kinase inhibitors (PREV study)

IRST189.04_Final report

EudraCT number**: 2015-002419-14**

Title**: Phase II study of oral PRednisone 5 mg bid plus EVerolimus in patients with metastatic renal cell cancer after failure of vascular endothelial growth factor receptor-tyrosine kinase inhibitors (PREV study)**

Protocol: **ID IRST189.04**

Promoter: **IRCCS Istituto Romagnolo per la Cura dei Tumori "Dino Amadori" IRST S.r.l., Meldola (FC)**

Coordinating Center: IRCCS IRST

Study Chair: Dr. Ugo De Giorgi

Study Activated: 10/09/2015

First Patient Enrolled: 22/09/2015

Target**: 42 patients**

Actual accrual: **8 patients**

Rationale	Patients with non resectable or metastatic renal cell carcinoma (mRCC) are currently treated with a sequence of vascular endothelial growth factor receptor tyrosine kinase receptor inhibitors (VEGFR TKIs) and mTOR agents. Everolimus is a standard of care in the treatment of metastatic RCC. Results from the Phase III study, published in Lancet in 2008, showed that treatment with everolimus prolongs progression-free survival compared with placebo in patients with metastatic renal cell carcinoma who had progressed on other targeted therapies. However, in the pivotal study, at least 1 treatment interruption occurred in 38% of everolimus-treated patients and 11% of placebo-treated patients. Mouth ulcers, stomatitis, and oral mucositis occurred in everolimus-treated patients with an incidence ranging from 44% to 78%. Grade 3 and 4 stomatitis have been reported in 4% to 9% of patients. In these cases, topical treatments are recommended to treat stomatitis. In addition, non infectious pneumonia (NIP) has been reported in 19 to 30% of everolimus-treated patients. The incidence of grade 3 and 4 non infectious pneumonia according to CTC was 4.0% and 0.2%, respectively. Non infectious pneumonia has been managed

	through dose reduction or discontinuation of treatment until symptoms disappear and through the use of corticosteroids. The development of pneumonia has also been reported at a reduced dose. In a recent literature review, nearly 23 percent of patients treated with everolimus developed non infectious pneumonia. Symptoms included cough, dyspnea, and fever. Finally, analysis of data reported in literatures suggests that stomatitis and noninfectious pneumonia may be predictive markers of favorable outcome in patients with mRCC treated with everolimus. The administration of prednisone could reduce the incidence of stomatitis. In addition, prednisone is commonly used for the treatment of noninfectious pneumonia, so it is hypothesized that low doses of prednisone could reduce the incidence and/or severity of everolimus-induced noninfectious pneumonia). These side effects could therefore be avoided and better managed through a supportive therapy program based on the use of prednisone 5 mg bid. Therefore, we designed a phase 2, multicenter study based on the use of prednisone 5 mg bid associated with everolimus 10 mg/day in patients with non resectable or metastatic renal cell carcinoma (mRCC).
Treatment	Everolimus was administered to the patient at a dosage of 10 mg (one 10 mg tablet or two 5 mg tablets) once daily (QD); prednisone was administered to the patient at a dosage of 5 mg twice a day (BID). Both drugs were self-administered orally continuously from day 1 (visit 2) until progression of disease, unacceptable toxicity, death, or discontinuation for any other reason. A cycle of treatment consisted of 28 days.

This study was authorized by AIFA on 12/06/2015 and authorized by the coordinating Italian Ethical Committee on 02/09/2015.

Objectives

- *The primary objective* of the study was to evaluate the safety and tolerability of prednisone 5 mg bid and everolimus 10 mg/day in RCC.
- *The secondary objectives* of the study was to evaluate the activity and the clinical outcome of these patients.
- *The explotratory objectives* was to evaluate the influence of prednisone on trough concentration of everolimus and correlation with the incidence of side effects, in particular stomatitis and non-

infectious pneumonitis. Infiammation markers such as pentraxin 3 (PTX3), IL-6, TGF-β and neutrophil-lymphocyte ratio will be correlated with clinical outcome (ORR, PFS, OS).

Endpoints:

- *Primary endpoint*: to evaluate the incidence of grade ≥ 2 stomatitis and non-infectious pneumonitis in RCC patients treated with prednisone 5 mg bid and everolimus 10 mg/day.
- *Secondary endpoint*: to evaluate overall response rate, PFS and OS in this patient population. *Exploratory endpoints*: To evaluate the influence of prednisone on trough concentration of everolimus and correlation with the incidence of side effects, in particular stomatitis and non-infectious pneumonitis. Infiammation markers such as pentraxin 3 (PTX3), IL-6, TGF-β and neutrophil-lymphocyte ratio will be correlated with clinical outcome (ORR, PFS, OS).

Sample Size

This was a proof-of principle open-label, single-arm, phase II trial of prednisone 5 mg bid added to everolimus 10 mg/day in patients with RCC who failed at least one prior VEGFR TKI.
The study should have recruited 42 patients.

Conclusions:

The study included a target of 42 patients over a period of 2 years of recruitment, but only 8 subjects were recruited.
The combination of everolimus and low-dose prednisone administered daily was hypothesized to prevent noninfectious pneumonitis (NIP) and mucositis, two common adverse events related to everolimus. Although mucositis was detected in only one case, all-grade NIP occurred in four of eight cases (50%), and this was considered enough to stop accrual of the study. This study suggests a need to better investigate the real pathogenesis of NIP and to carefully monitor for toxicities in patients treated with everolimus and concomitant chronic corticosteroids taken for any clinical reason.
The observations of this study were published here http://dx.doi.org/10.1634/theoncologist.2017-0154, as attached at the present report.