1 Protocol synopsis

Title of study

A randomized phase II study to explore the efficacy and feasibility of upfront rotations between sunitinib and everolimus versus sequential treatment of first line sunitinib and second line everolimus until progression in patients with metastatic clear cell renal cancer.

Rationale

In the last years a great progress has been achieved in the treatment of metastatic renal cell carcinoma (mRCC) with new agents been introduced targeting molecular pathways. The standard of care in 1st line treatment is at the moment vascular endothelial growth factor (VEGFR) tyrosine kinase inhibitors (TKIs) and in most cases the agent used is sunitinib (Pfizer). Upon progression, another targeted therapy is used and at the moment the recommended agent upon progression on TKIs is everolimus (Novartis).

Even though the progress that has been achieved, there are a few clinical aspects that need further attention such as compliance and even more the resistance that emerges from the use of the TKIs. Cancer cells tend to escape the anti VEGFR blockage. There is therefore a rationale to alternate treatment to prevent or delay the occurrence of resistance. Having two different mechanisms of action, alternating each other, will block two hallmarks of cancer without forcing escaping pathways.

Our hypothesis is that by using alternating mode of action of the agents in RCC may reduce the side effects, improve tolerability and compliance of treatment and further delay the progression of the cancer. As mentioned above, the current first line standard of care in mRCC is sunitinib. Based on the available information the Spanish Oncology Research group APRO has decided to run a study in rotational scheme with sunitinib and everolimus as investigational treatment of choice for this study. The design places sunitinib first in the alternating regimen with everolimus second because there are limited data on everolimus in first line treatment. There will be two arms, the rotational scheme and the standard treatment algorithm of sunitinib in 1st line and upon progression patients will receive everolimus.

Objectives

Primary objective: Progression-free survival (PFS) rate at 1 year.

Secondary objectives:

a. PFS of rotational arm versus PFS of the 2 lines in control arm.
b. Objective tumor response rate (ORR) per arm
c. Overall Survival (OS)
d. Safety Profile

Methodology and Study design

This is an open-label, randomized phase II study to investigate the feasibility of alternating cycles of treatment with sunitinib and everolimus compared to sequential treatment of sunitinib followed by everolimus. Up to 4 countries and 20 centers will participate in the study.

The study population consists of adult patients (over 18 years old) with clear cell mRCC who have not received prior therapy for their metastatic disease.

The purpose of the study is to determine the progression free survival, feasibility and safety profile of the experimental arm compared to standard of care.

In the experimental arm alternating treatment will consist of repeating cycles of 24 weeks of treatment consisting of 12 weeks of sunitinib 4weeks on 2 weeks off, 50 mg pd followed by 12 weeks of everolimus 10 mg per day 11 weeks on 1 week off in patients with metastatic clear cell renal cancer. The comparative arm will be the standard regimen of sunitinib (50 mg pd 4/2) until progression, followed thereafter by everolimus (10 mg per day continuously, 11/1) until progression.

Statistical considerations

The primary objective of this study is to assess whether the rotational arm has anti-tumor activity, higher than the standard arm, worthwhile to be further explored in larger scale study. The primary endpoint will be the progression-free survival rate at 1 year in each arm.

In clear-cell renal cell carcinoma, the current standard approach of first line sunitinib yields a PFS of approximately 10 months. For this study, it is determined that if the experimental arm (alternating sunitinib and everolimus) yields a PFS of around 15 months then this regimen deserves to be further explored. In order to control whether the initial assumption of a PFS of 10 months induced by the standard arm (sunitinib) applies to the population included in this study, this study will be conducted in a randomized setting allocating 68 patients to the investigational arm and 34 patients in

the control arm (allocation ratio= 2:1). This control arm will further help to compare safety and toxicity profiles.

Simon's MinMax two stage design will be used for the investigational arm with 80% power to demonstrate an increase in 1 year PFS rate to 58% compared to 43% in the control arm.

No formal design will be employed for the standard arm; it will act as control especially in case of poor response for the investigational drug, to ascertain the possible presence of selection bias in the patient population. This will be the case if the response rate for the sequence sunitinib-everolimus is notably lower that 43%.

In order to compensate for non-evaluable patients, a surplus of 15% will be included meaning that in total 115 patients will be included in this study.

Main inclusion criteria

- Histologically confirmed diagnosis of progressive metastatic predominant clear cell renal cell cancer.
- Evaluable disease.
- No prior systemic treatment. But adjuvant treatment is ok if stopped from ≥ 24 months

Main exclusion criteria

- Any malignancy within the previous 5 years.
- Recent cardiovascular event, bleeding disorder.
- Use of any targeted therapy for the metastatic disease
- Active/symptomatic brain metastasis.

Study duration

The enrollment period of all patients (estimate) is approximately 2 years

- Estimated time for study start (FPFV) : FEB 2013
- Recruitment end (LPFV) : FEB 2015
- Interim analysis at the time of 38 evaluable patints: JAN 2015
- Completion of study (LPLV) estimate : AUG 2016
- Completion of study report (CSR) : FEB 2017
- Publication date : JUN 2017