Response to the reviewer

1. Is there any mechanism that might attenuate the benefit of prostate CA therapy with PPI? Is there any PK/PD or Cytochrome P450 interaction beyond just gastric pH and absorption issues?

Our response: That’s really a good question. In our assumption (which was not written in YODA proposal), we intend to further explore the PK/PD through clinical trials after completing data analysis if PPI has a significant impact on the survival of patients receiving androgen-annihilation therapy (abiraterone, apalutamide, bicalutamide and SHR3680).

To elaborate our plan. First, we will analyze patients’ data from clinical trials including androgen-annihilation therapy, to compare the radiographic progression-free survival (rPFS) and overall survival (OS) in patients with or without long-term PPI use. If the outcome is positive, for example, patients simultaneously used abiraterone and PPI had better outcome than those used abiraterone alone, we will then design a clinical trial to explore the PK/PD. The clinical trial will be a randomized two-armed, three-phase, crossover study, with reference to the previous literatures [1,2].

In brief, patients enrolled will be randomized into two sequence groups: sequence phase A-B-C or phase C-B-A. In phase A, patients will receive abiraterone and PPI. In phase B and phase C, patients will receive abiraterone alone. Patients’ testosterone concentration and blood drug concentration (abiraterone) will be measured in each phase. At present, the design of clinical trial is relatively simple and somewhat incomplete. We will consider whether to register clinical trial based on the results of data analysis. If the outcome is positive, we will register the clinical trial design to further explore the PK/PD.

However, the deeper pharmacological mechanism (perhaps relative to Cytochrome P450) is still unknown. It will be a tough job. We will challenge it if all the previous trials are completed. At that time, we may consider reporting this work on a prestigious journal.

Thank you again for your advice!

Reference:
