

A Phase 1b Study of the Oral CDK4/6 Inhibitor Ribociclib in Combination with Docetaxel plus Prednisone in Metastatic Castration Resistant Prostate Cancer (mCRPC): a Prostate Cancer Clinical Trials Consortium Study

Catriona Lewis¹, Russell Szmulewicz², Benedito Carneiro³, David Smith⁴, Charles Ryan⁵, and **Rahul Aggarwal¹**

1. University of California San Francisco; 2. University of Chicago; 2. Brown University; 4. University of Michigan; 5. University of Minnesota

Background: Ribociclib is a potent and selective cyclin-dependent kinase (CDK) 4/6 inhibitor with significant pre-clinical activity in enzalutamide-resistant prostate cancer cell lines. Prior pre-clinical studies have demonstrated synergy with taxane chemotherapy. We conducted a multi-institutional phase 1b study to evaluate the safety and preliminary efficacy of ribociclib in combination with docetaxel in patients (pts) with mCRPC.

Methods: Pts with mCRPC with prior progression on abiraterone and/or enzalutamide, and no prior chemotherapy for mCRPC were eligible. Dose escalation utilized a 3+3 design with escalating doses of ribociclib starting at 200 mg daily in combination with docetaxel 75 mg/m², with mandatory G-CSF prophylaxis. The primary objective was to determine the maximally tolerated and recommended phase 2 dose (RP2D). Secondary objectives included pharmacokinetics (PK), PSA50 response rate ($\geq 50\%$ decline from baseline in PSA), and objective response rate (ORR).

Results: 14 pts were enrolled, with a median age of 68 (55-80) and baseline PSA of 206 (40-1714). 2 dose limiting toxicities (DLTs) (febrile neutropenia and grade 4 neutropenia) were observed at the starting dose/schedule. Using an alternative dosing schema with docetaxel 60 mg/m² and ribociclib days 1-4 and 8-15, with G-CSF support on days 5-7, no further DLTs were observed. Most common grade ≥ 3 AEs included neutropenia (64%) and febrile neutropenia (14%). Reasons for treatment discontinuation included disease progression (N = 7), adverse event (N = 5), and study withdrawal (N = 1); one pt remains on treatment. PK analyses demonstrated a modest and predictable impact of ribociclib on docetaxel clearance. The RP2D is ribociclib 400 mg daily in combination with docetaxel 60 mg/m².

Conclusions: With intermittent dosing and G-CSF support, combining ribociclib with docetaxel chemotherapy is feasible with neutropenia as the most commonly observed AE. A phase 2 study of the combination is ongoing to further assess efficacy and safety.

Conflicts of Interest:

Rahul Aggarwal has received research funding from Novartis for the conduct of this clinical trial.

Funding Acknowledgments:

We acknowledge the Prostate Cancer Foundation and Novartis for providing funding support for the conduct of this clinical trial.