A Phase 1b/2 Study of the Oral CDK4/6 Inhibitor Ribociclib in Combination with Docetaxel plus Prednisone in Metastatic Castration Resistant Prostate Cancer

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Background: Up-regulation of cell cycle progression is a frequent driver of aggressive phenotypic metastatic castration resistant prostate cancer (mCRPC), in particular in tumors with neuroendocrine histology. Transcriptional analysis of mCRPC biopsies obtained predominantly in the post-abiraterone and/or enzalutamide setting has demonstrated significant up-regulation of expression and inferred activity of MYC transcriptional targets including the cyclin-dependent kinases (CDKs). Ribociclib is a potent and selective CDK 4/6 inhibitor with significant pre-clinical activity across a variety of enzalutamide-resistant prostate cancer cell lines. CDK inhibitors have demonstrated synergistic activity with taxane chemotherapy in triple negative breast cancer in early phase clinical studies. We designed the ongoing multi-institutional investigator-initiated phase 1b/2 study to evaluate the safety and efficacy of oral ribociclib in combination with docetaxel in patients with mCRPC.

Methods:
Patients with chemotherapy-naïve, progressive, metastatic castration resistant prostate cancer are eligible for study participation. Other key eligibility criteria include prior progression on abiraterone and/or enzalutamide, and for the phase 2 portion of the study, patients with accessible lesion are required to undergo mandatory tumor biopsy. Dose escalation is proceeding using a standard 3+3 design, with a starting dose level of ribociclib 200 mg daily on days 2-14 in combination with docetaxel IV on day 1 of an every 21-day cycle, along with prednisone 5 mg twice daily and G-CSF support. The primary objective of the phase 1b portion of the study is to determine the maximally tolerated and recommended phase 2 dose of the treatment regimen. In Phase 2, patients will be enrolled in a Simon two-stage single arm study with a primary objective to determine the 6-month radiographic progression-free survival rate. The null hypothesis based on historical control with docetaxel monotherapy is 35%, and the target radiographic PFS rate is 55%. A total sample size of 29 evaluable patients for the phase 2 portion of study has 80% power to detect this magnitude of difference with a unidirectional level of significance of 0.1.

Correlative study objectives include: (1) determining the association between genomic alterations in mCRPC tumor tissue, including Rb1, CCND1, and MYC, with clinical outcomes; (2) analysis of circulating tumor cells for presence or absence of Rb1 loss using immunofluorescence assay; (3) paired gallium citrate PET scans as a potential biomarker of MYC transcriptional activity, and (4) application of Differential Pathway Signature Correlation (DiPSC) integrating clinical and genomic data to define a signature associated with response to study treatment.

Results:
Study accrual in the dose escalation phase is ongoing. Observed adverse events have been predominantly hematologic nature, with neutropenia dose-limiting in two of the five patients enrolled. The other three patients have all achieved rPFS durations of > 6 months. Alternative dosing schedules are being investigated to potentially mitigate hematologic toxicity.

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Potential Conflicts of Interest: None