P042 A phase 2 study of the combination of PLK1 inhibitor, onvansertib, with abiraterone and prednisone in patients with metastatic castration-resistant prostate cancer

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Introduction & Objectives: Polo-like kinase 1 (PLK1) is a serine/threonine kinase, master regulator of mitotic progression and inhibition of PLK1 induces G2/M arrest and apoptosis in tumor cells. Preclinical studies demonstrate a significant synergy of onvansertib, a first-in-class, 3rd-generation, oral and highly-selective PLK1 inhibitor (also known as PCM-075 and NMS-1286937), in combination with abiraterone in an in-vivo castration-resistant prostate cancer (CRPC) model. A recommended phase 2 dose has been established for Onvansertib from a previous phase 1 trial in patients with solid tumors (Weiss et al., 2017, Invest New Drugs). The goal of this phase 2 study (NCT03414034) is to observe the effects of onvansertib in combination with abiraterone + prednisone in patients with mCRPC with early abiraterone resistance.

Materials & Methods: Patients are enrolled at time of PSA progression while on standard abiraterone. In this two-arm, open-label trial, the dosing regimen in Arm A is onvansertib, days 1-5 (21-day cycle) + abiraterone/prednisone daily for 4 cycles (12 weeks) and Arm B is onvansertib, days 1-5 (14-day cycle) + abiraterone/prednisone daily for 6 cycles (12 weeks), with a primary endpoint of disease control (PSA stabilization or decline). Treatment is then continued until time of radiographic or symptomatic progression. Correlative studies include assessment of AR-V7 in circulating tumor cells (CTCs) and genomic alterations within circulating tumor DNA (ctDNA).

Results: To date, 9 patients in Arm A have been evaluated for efficacy after 4 cycles of treatment (12 weeks): 1 patient had partial response, 3 patients had stable disease (2 patients are still on treatment) and 5 patients had progressive disease (RECIST v1.1 criteria). Patient with partial response was positive for AR-V7, had no increase in CTC and had PSA stabilization meeting the primary efficacy endpoint. The PSA trajectory of this patient changed from 100% increase (16.05ng/ml to 34.23 ng/ml) in the 60 days prior to study to 8.4% increase during 84 days on study, indicating alteration of the natural history of early abiraterone resistance. PSA data from patients enrolled in Arm A suggest that reducing cycle time from 3 weeks to 2 weeks may maximize response to treatment; therefore, Arm B was added with a shortened dosing schedule. The safety lead-in of 3 subjects for this Arm is ongoing.

Conclusions: Preliminary results indicate activity for the combination of onvansertib with abiraterone/prednisone. Further updates of this trial will be presented.