Safety and Efficacy of the Investigational Agent Orteronel (TAK-700) Without Prednisone in Nonmetastatic Castration-Resistant Prostate Cancer (nmCRPC) Patients with Rising Prostate-Specific Antigen (PSA): Updated Results from a Phase 2 Study

Introduction and Objectives: Orteronel is an investigational, oral, non-steroidal, selective 17,20-lyase inhibitor that suppresses androgen production. Orteronel has less effect on cortisol synthesis than similar agents due to limited inhibition of 17α-hydroxylase, thus potentially allowing for steroid-free dosing. Orteronel 300 mg BID was examined in patients with nmCRPC and rising PSA.
Materials and Methods: Eligible patients had nmCRPC with PSA ≥2ng/mL (PSA ≥8ng/mL if doubling time >8 months), and surgical/medical castration, with testosterone <50ng/dL. Prior chemotherapy, ketoconazole, or concomitant corticosteroids were excluded. Patients received orteronel 300 mg BID and continued treatment without steroids until PSA progression, metastases, or unacceptable toxicity. The primary endpoint was the percentage of patients achieving a PSA level ≤0.2ng/mL after 3 months. Secondary/exploratory endpoints included safety, PSA declines of 50%, 90%, time to metastases, changes in endocrine markers, and circulating tumor cells (CTCs).
Results: There were 39 patients enrolled: median age 71 years, ECOG PS ≤1, median PSA 12.1ng/mL (range 2.6–67.8), testosterone 7.9ng/dL (1.4–17.3), ACTH 19ng/L (n=33; 0–47). Median cycles=6 (1–17); 3 patients had a dose reduction and 8 discontinued due to adverse events (AEs). There were 16 patients (drug-related=14) who had Gr≥3 AEs; Gr≥3 AEs observed in ≥5% were hypertension (13%), dyspnea (8%), fatigue, hypokalemia, pneumonitis (5% each). No patient required corticosteroids for mineralocorticoid syndrome. At 3 months, 6 patients (16%) achieved PSA ≤0.2ng/mL; PSA50 and PSA90 rates were 76% and 32%, respectively; median PSA declined by 83% (n=34); median testosterone declined by 89% to 0.78ng/dL (n=31), and median ACTH increased by 171% to 43ng/L; median cortisol declined by 21%. At 6 months, PSA50 and PSA90 rates were 45% and 21%, respectively. Kaplan-Meier estimate of median time to PSA progression was 14.8 months; 97% of patients were free from metastases at 6 months (17/39 were treated >6 months). Seven patients had >1 baseline CTC/7.5mL; 1 patient with a CTC count ≥5 converted to <5/7.5mL; 6 had 1–4 baseline CTCs; none converted to ≥5 during treatment.
Conclusions: Orteronel without steroids produces marked and durable declines in PSA and testosterone, has manageable toxicities, and is feasible in patients with nmCRPC.