MDV3100, an Androgen Receptor Signaling Inhibitor, Improves Overall Survival in Patients with Prostate Cancer Post Docetaxel: Results from the Phase 3 AFFIRM Study

Introduction and Objective: MDV3100, a novel androgen receptor signaling inhibitor (ARSI), competitively inhibits binding of androgens to the androgen receptor (AR), inhibits AR nuclear translocation, and inhibits AR association with DNA (Tran et al, Science. 2009;324:787). MDV3100 was selected for development based on activity in prostate cancer cell model systems with overexpressed AR, and was found to be active in a Phase 1-2 trial enrolling pre- and post-chemotherapy treated patients with progressive castration resistant disease (CRPC) (Scher et al, Lancet. 2010;375:1437). The AFFIRM trial evaluated whether MDV3100 could prolong overall survival in patients with metastatic CRPC post docetaxel-based chemotherapy.
Materials and Methods: In this randomized, double-blind, placebo-controlled, multinational Phase 3 study (NCT00974311), metastatic CRPC patients who had received ≤2 regimens of chemotherapy, 1 with docetaxel, were randomized 2:1 to MDV3100 160 mg/day or matching placebo. Treatment with corticosteroids was not required, but allowed. Patients were stratified by baseline Eastern Cooperative Oncology Group performance status and mean brief pain inventory score. The primary endpoint was overall survival. Secondary efficacy endpoints included radiographic progression-free survival, time to first skeletal-related event, time to prostate-specific antigen (PSA) progression.
Results: There were 1,199 patients randomized between Sept 2009 and Nov 2010**.** Based on a planned interim analysis at 520 death events, the Independent Data Monitoring Committee (IDMC) recommended the study be halted and eligible placebo patients offered MDV3100 due to a significant survival benefit. Patients on MDV3100 had a median overall survival of 18.4 months, an increase of 4.8 months compared to placebo (13.6 months), $P<0.0001$, hazard ratio 0.631. All secondary endpoints were met, additional analyses are ongoing and results will be presented at the meeting including time to progression (radiographic and PSA) and safety.
Conclusions: MDV3100, a novel ARSI, significantly improved overall survival in men with post-docetaxel CRPC reducing the risk of death by 37% compared to placebo.

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