Editorial

# Treatment of metastatic prostate cancer after STAMPEDE

**Philipp Wolf**

Department of Urology, Medical Center, University of Freiburg, Freiburg im Breisgau, Germany

*Correspondence to:* Philipp Wolf. Department of Urology, Medical Center, University of Freiburg, Freiburg im Breisgau, Germany. Email: philipp.wolf@uniklinik-freiburg.de.

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Over decades, long-term hormone therapy has been considered as the standard of care (SOC) for men with advanced prostate cancer. The problem is that several months after the commencement of treatment, tumors become castration-resistant and virtually all patients show disease progression. In 2004, two randomized Phase 3 trials demonstrated a modest overall survival benefit of about 3 months with docetaxel chemotherapy in patients with metastatic castration-resistant prostate cancer (mCRPC) (1,2). This led to the use of docetaxel as first-line SOC in this stage of the disease.

In the STAMPEDE (Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy; NCT00268476) study, a multi-arm, multi-stage platform was used to determine whether docetaxel in combination with long-term hormone therapy (SOC) was effective in patients with prostate cancer in the hormone-naïve stage (3). The study involved 2,962 men with high-risk, locally advanced, metastatic or recurrent disease, who were starting first-line hormone therapy. The treatment with docetaxel plus SOC led to a survival advantage of 10 months, compared to the SOC-only group (81 *vs.* 71 months; HR 0.78, 95% CI 0.66–0.93; P=0.006). In a subset analysis of 1,817 patients with metastatic disease (M+), an overall survival benefit of 15 months was observed for the docetaxel plus SOC versus the SOC-only group (60 *vs.* 45 months; HR 0.76, 95% CI 0.62–0.92; P=0.005). This was accompanied by improvements in prostate cancer-specific survival, failure-free survival, and skeletal-related events. These results are in line with the CHAARTED study, in which a survival advantage of 13.6 months for men with hormone-naïve metastatic disease was demonstrated with docetaxel plus SOC, compared to SOC alone (57.6 *vs.* 44 months; HR 0.61, 95% CI 0.47–0.80; P<0.001) (4). In a comparable study (GETUG-AFU 15), a prolonged, albeit not statistically significant enhanced overall survival was also demonstrated (5). A recent meta-analysis of the three studies [2,992 (93%) of 3,206 men randomized] confirmed a 4-year survival benefit of combinatorial treatment (HR 0.77, 95% CI 0.68–0.87; P<0.0001) (6). The role of docetaxel in newly diagnosed metastatic prostate cancer is being increasingly discussed (7,8), and the remarkable findings of the studies have been reflected in medical guidelines recommending docetaxel plus hormone therapy as SOC in metastatic hormone-naïve prostate cancer (mHSPC) (9).

What are the next steps in the treatment of advanced prostate cancer? Firstly, it has to be noted that this still remains an incurable disease. However, the STAMPEDE study has now paved the ways for the testing of different drugs in the hormone-naïve setting, especially such that have failed to improve the situation in CRPC. An overall survival benefit of 15 months in mHSPC, compared to only 3 months in mCRPC, shows evidence that there are molecular alterations during hormone therapy that negatively affect the efficacy of docetaxel, and presumably of other active drugs. Indeed, numerous events altering signaling, gene expression and cellular outcome were identified during hormone therapy. These lead to the formation of aggressive cancer cells with an enhanced propensity to proliferate, grow, and metastasize. Pathways that are impaired encompass androgen receptor, growth factor, Wnt/ß-catenin and apoptotic pathways. There are

direct causal relationships between such molecular changes and therapeutic impairment or failure of drugs targeting these pathways (10). Several studies are therefore ongoing to test whether such substances could be more active in a hormone-naïve setting (11).

A further step in the future treatment of metastatic prostate cancer should be the reduction of adverse events. In the STAMPEDE study, Grade 3–5 adverse events were enhanced by 20% in the docetaxel plus SOC group, compared to the SOC-only group (52% *vs.* 32%). Toxicity was the reason for 13% of patients to discontinue the study before all docetaxel cycles were complete (3). Notably, a rate of 15% of febrile neutropenia in the docetaxel group was measured, which is 5-fold higher than that reported with docetaxel in the castration-resistant setting (1). Therefore it is recommended that only adequately fit men should be chosen for combinatorial treatment, or that Granulocyte-Colony Stimulating Factor (G-CSF) should be added to reduce neutropenia (12).

Personalized medicine can be used in future to identify drugs that are most effective in subpopulations of patients with mHSPC (13). This will allow smaller and faster trials with lower overall costs and patients will benefit from the increased safety and reduced adverse events. Moreover, time will tell whether hormone therapy in general will remain the basic treatment for metastatic prostate cancer.

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## Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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