**Background**

- With the rapid evolution of treatment options for metastatic castration-resistant prostate cancer (mCRPC), it has become of critical importance to determine the optimal sequencing of therapies.
- We recently reported in vitro cross-resistance between the taxanes docetaxel and cabazitaxel, and the AR targeting agents abiraterone and enzalutamide (van Soest et al. Eur J Cancer 2013 49:3821-30), indicating that the efficacy of the taxanes might be impaired by prior AR-targeted therapies.
- Enzalutamide has demonstrated a significant OS benefit in patients with mCRPC pre-chemotherapy, however, the clinical efficacy of docetaxel and cabazitaxel after first-line treatment with enzalutamide is yet unknown.
- In the present study, we aimed to investigate the efficacy of docetaxel and cabazitaxel in an in vivo model of CRPC previously treated with enzalutamide.

**Results**

- **Cabazitaxel is more effective as compared to docetaxel in an in vivo model of CRPC with acquired resistance to enzalutamide**

  - To investigate the efficacy of docetaxel and cabazitaxel in a model of enzalutamide-resistant CRPC, we first confirmed that the PC346Enza xenograft was resistant to enzalutamide in vivo. Immuno-deficient mice were subcutaneously injected with the PC346Enza cell line in which acquired resistance to enzalutamide was developed in vitro. Mice were castrated when the tumors reached a volume of 120-150 mm³. Upon regression of tumors to a tumor volume of 150 mm³, mice were treated with oral enzalutamide 60 mg/kg once daily or placebo.

  - Enzalutamide did not inhibit growth as compared to placebo in castrated male mice harboring PC346Enza tumors. Our data, however, show that tumors still demonstrated responses to enzalutamide when compared to docetaxel. Cabazitaxel treatment led to tumor shrinkage in all mice, whereas most docetaxel-treated tumors rapidly progressed after a short period on initial response (Fig 2). Mean tumor volumes and a comparison between treatments is shown in Table 1.

- To investigate the efficacy of docetaxel and cabazitaxel in the enzalutamide-resistant PC346Enza xenograft, male mice bearing enzalutamide-resistant PC346Enza tumors were castrated at a tumor volume of 120-150 mm³. When tumors reached a volume of 300 mm³, mice were randomized to receive an intraperitoneal injection of docetaxel 33 mg/kg, cabazitaxel 33 mg/kg, or placebo.

- Cabazitaxel demonstrated greater anti-tumor activity as compared to docetaxel. Cabazitaxel treatment led to tumor shrinkage in all mice, whereas most docetaxel-treated tumors rapidly progressed after a short period on initial response (Fig 2). Mean tumor volumes and a comparison between treatments is shown in Table 1.

- These data are concordant with clinical studies demonstrating that cabazitaxel retains activity as second-line chemotherapy, even after prior AR-targeted treatment in mCRPC.

**Conclusions**

- **Our in vivo data demonstrated that cabazitaxel was more effective as compared to docetaxel in a model of enzalutamide-resistant CRPC.**

- The current findings provide the rationale for a clinical study investigating the efficacy of cabazitaxel versus docetaxel, given as first-line chemotherapy in patients previously treated with enzalutamide.

**Methods**

- The PC346Enza cell line was generated by continuous culturing of PC346C cells in PGM medium supplemented with 2% deoxyn-coated charcoal stripped serum (DCC), with the addition of 1μM enzalutamide. After initial cell death, resistant cells started to grow out under the selection conditions used.

- PC346Enza cells were subcutaneously inoculated in nude mice. Castrated mice were treated with a single intraperitoneal dose of docetaxel 33 mg/kg, cabazitaxel 33 mg/kg, or placebo when a tumor volume of 300 mm³ was reached.

- Castrated and non-castrated mice received oral enzalutamide 60 mg/kg daily or placebo.

- Tumor volumes were measured twice a week, and blood samples were taken every 2 weeks and analysed for serum PSA.

**References**

