**LANDMARKS**

**Reports of recent research**

Report from the American Society of Clinical Oncology Annual Meeting

**Prostate cancer**

**IMPROVING SURVIVAL IN METASTATIC PROSTATE CANCER**

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**TRIAL SUMMARY: Adding docetaxel to ADT brings survival benefit**


Docetaxel (D) improves overall survival (OS) of men with metastatic prostate cancer (mPrCa) who have progressed on androgen deprivation therapy (ADT). This trial aimed to assess the benefit of upfront chemohormonal therapy for mPrCa. The trial enrolled 790 men between 2006 and 2012; 393 were randomized to ADT alone and 397 received ADT plus docetaxel (ADT+D) dosed 75 mg/m² every 3 weeks for 6 cycles within 4 months of starting ADT. The two arms were balanced for demographic factors, with a mean age of 63 years and a majority (89%) of Caucasian participants. Balance was also achieved for stratification, with 64% on ADT and 67% on ADT+D presenting with high-volume (HV) disease, defined as visceral metastases and/or 4 or more bone metastases. In each group, 98% presented with Eastern Cooperative Oncology Group (ECOG) performance status (ECOG PS) 0 or 1, 24% had undergone prior radiotherapy, and 24% had prior prostatectomy. All had suitable organ and neurologic function for D, had been receiving adjuvant ADT for 24 mos or less, and had no progression within 12 mos of adjuvant ADT. OS was the primary endpoint: projected median OS for ADT alone is 33 months in HV disease and 67 mos in low-volume (LV) disease.

**Results:** Initial data were released after the 4th interim analysis in Sept 2013. The presentation at ASCO reflects data up to January 2014, with median followup of 29 mos. There were 137 deaths on ADT alone vs 104 deaths on ADT+D. OS was 42.3% for those on ADT alone vs 52.7% for those on ADT+D (HR=0.63, p=0.0006). For men with HV disease, OS was 32.2% in those on ADT alone vs 49.2% for those on ADT+D (HR=0.62, p=0.0012). The OS endpoint was not reached for the 270 men with LV disease. Side effects in men in the ADT+D arm included grade 3/4 neutropenic fever (4%/2%), grade 3 neuropathy (1% sensory, 1% motor), and 1 death due to treatment (vs no deaths due to treatment on ADT). After disease progression, 123 pts on ADT alone and 45 pts on ADT+D received docetaxel. The authors conclude that ADT+D improves OS over ADT alone in men with HV mPrCa. Longer followup is needed for men with LV mPrCa.

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**COMMENTARY: The National Institutes of Health (NIH)-sponsored, ECOG-led CHAARTED study (Chemohormonal Therapy versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) represents a significant breakthrough in the management of metastatic hormone-sensitive prostate cancer.**

From July 2006 to November 2012, 790 men with mPrCa were randomized to receive ADT alone, or ADT+D for a maximum of 6 cycles. Importantly, ADT was only allowed up to 120 days prior to randomization and intermittent ADT was not allowed. Patients in the ADT+D arm received dexamethasone premedication, but not daily prednisone. Patients in the ADT arm were allowed to receive chemotherapy at the investigator’s discretion upon evidence of disease progression. Patients were stratified at enrolment by: extent of metastasis (HV vs LV), age (older or younger than 70), Eastern Cooperative Oncology Group (ECOG) performance status (0–1 vs 2), prior adjuvant ADT (more or less than 12 months), skeletal-related event (SRE) prevention (yes vs no) and complete androgen blockade for more than 30 days (yes vs no). The CHAARTED study was originally designed for HV disease, defined as visceral metastases and/or 4 or more bone metastases with at least one bony metastasis beyond the pelvis and vertebral column, but due to lower than predicted enrolment, LV disease patients were also enrolled. Interestingly, patients with a “clinical scenario” compatible with mPrCa could be enrolled without a tissue biopsy diagnosis of the prostate or of metastases; however, only 40 patients in the ADT+D arm and 50 patients in the ADT arm did not have a tissue diagnosis. Almost all patients in the ADT+D arm completed 6 cycles (87.5%) and treatment was well tolerated with expected hematologic and non-hematologic toxicities. Both arms were well balanced in terms of HV disease (approximately ¾) and lack of local therapy to the prostate (approximately ¼).

Median OS was improved by 13.6 months in the ADT+D arm. In patients with HV metastatic disease, there was a 17-month improvement in median OS. Patients with LV disease did not have a statistically significant benefit, since median OS and data cutoff were not yet reached in both ADT and ADT+D arms.

The results show a clear survival benefit in men with HV hormone-sensitive mPrCa, so the study represents a groundbreaking paradigm shift in the management of PrCa.

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in this population. However, with a median follow-up of only 29 months, the benefit of docetaxel in patients with LV disease is unproven and thus the early addition of docetaxel is not yet indicated in these patients.

More time and maturation of the data will better determine which patients will benefit from early initiation of docetaxel chemotherapy. The study also raises some important questions: Do all patients with mPrCa diagnosed by urologists need to be seen by medical oncology? Is tissue biopsy essential before treatment with chemotherapy if the clinical picture is compatible with PrCa, as was the case in the study? Is there a benefit in starting docetaxel in men on ADT > 120 days with stable metastatic disease (ineligibility criterion for the study)? Regardless of how these questions are eventually answered, there is no doubt that this study will change the landscape of mPrCa management.

**IN BRIEF**

**Already known**
- Docetaxel (D) improves overall survival (OS) of men with metastatic prostate cancer (mPrCa) who have progressed on androgen deprivation therapy (ADT).

**What this study showed**
- Adding D to ADT in men with high-volume mPrCa before progression occurs extends OS by 13.6 months over that seen in men with high-volume disease who receive ADT alone until progression occurs.

**Next steps**
- Wait for more mature data to see whether the addition of D to ADT before progression offers men with low-volume disease a similar survival advantage.
- Investigate the benefit of starting docetaxel in men with stable metastatic disease who have been on ADT for more than 120 days.