



Docetaxel at Beginning of Androgen Deprivation Therapy Boosts Overall Survival by Over 1 Year

Written by Brian Hoyle

Christopher Sweeney, MBBS, Dana-Farber Cancer Institute, Boston, Massachusetts, USA, described the results of the Androgen Ablation Therapy With or Without Chemotherapy in Treating Patients With Metastatic Prostate Cancer trial [CHAARTED; NCT00309985]. The trial demonstrated that the use of docetaxel at the beginning of androgen deprivation therapy (ADT) increases overall survival (OS) in patients with metastatic prostate cancer by >1 year compared with ADT alone.

The knowledge that ADT can limit prostate cancer dates back to the 1940s [Huggins C et al. *Cancer Res* 1941]. More recently, the benefit of docetaxel in improving OS in men with metastatic, castration-resistant prostate cancer was demonstrated [Tannock IF et al. *N Engl J Med* 2004]. Nonetheless, the combination of early chemotherapy and ADT is debatable. The randomized Phase 3 CHAARTED trial was undertaken to address this debate. The hypothesis of the trial was that docetaxel added at the start of ADT in men with hormone-naïve metastatic prostate cancer would prolong OS. The design of the trial is shown in Figure 1.

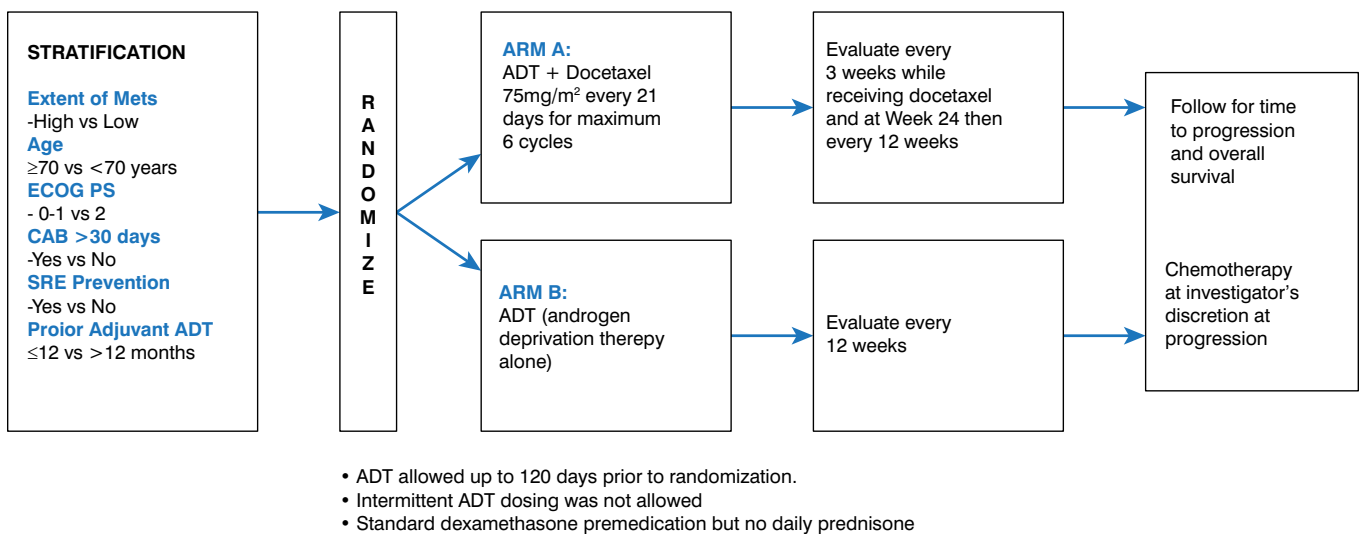
The key eligibility criteria were the presence of metastatic prostate cancer, ADT limited to 120 days before study randomization or to adjuvant treatment within the prior 24 months with no disease progression within 12 months after completion of the treatment, Eastern Cooperative Oncology Group performance status of 0 to 2 (the latter only if due to prostate cancer), functions of select organs judged suitable for docetaxel application, and no previous use of docetaxel.

A total of 790 men (89% Caucasian; median age, 63 years; range, 36 to 91 years) newly diagnosed with hormone-sensitive metastatic prostate cancer were recruited from June 2006 to November 2012 and randomly assigned to ADT plus docetaxel (n=397) or standard ADT alone (n=393). Docetaxel was given as a 75 mg/m² dose every 3 weeks for 6 cycles within 4 months of starting ADT.

Both arms were similar at baseline. Patients were stratified with respect to high-volume (visceral metastases and/or ≥4 bone metastases) or low-volume disease, androgen suppression >30 days, age, Eastern Cooperative Oncology Group performance status 0 or 1 versus 2, prior adjuvant ADT, and the use of an approved drug to delay skeletal-related events. Radiotherapy and prostatectomy had each been performed in 24% of the subjects.

The primary endpoint was OS. Secondary endpoints included the rate of prostate-specific antigen level <0.2 ng/mL at 6 and 12 months, time to progressive disease (biochemical, radiographic, or symptomatic),

Figure 1. Design of the CHAARTED Trial



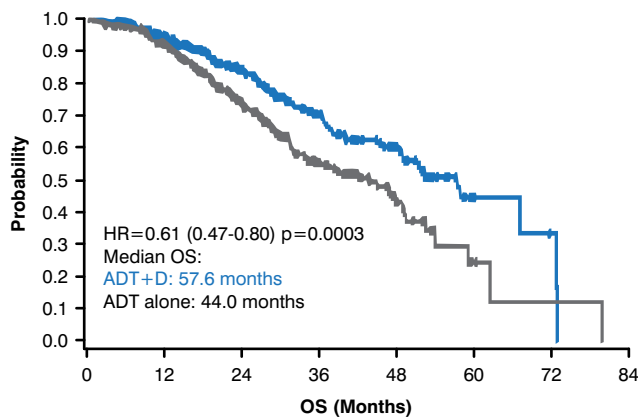
ADT=androgen deprivation therapy; ECOG PS=Eastern Cooperative Oncology Group performance status.

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adverse events and drug tolerability, and quality of life up to 12 months following randomization.

The primary endpoint of OS was met. The median OS of the ADT-plus-docetaxel arm was 57.6 months compared with 44.0 months for men who received ADT only (HR, 0.61; 95% CI, 0.47 to 0.80; $p=0.0003$; Figure 2).

Figure 2. Overall Survival



ADT=androgen deprivation therapy; D=docetaxel; OS=overall survival.
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The 13-month difference translated to a 39% reduction in the survival hazard (HR, 0.61; 95% CI, 0.47 to 0.80; $p=0.0003$). Those with a high disease burden at the time of enrollment displayed an even more pronounced survival difference, with median OS of 49.2 months for ADT plus docetaxel treatment compared with 32.2 months for ADT alone (HR, 0.60; 95% CI, 0.45 to 0.81; $p=0.0004$). The secondary outcomes significantly favored ADT plus docetaxel treatment: prostate-specific antigen response (<0.2 ng/dL at 6 months: 27.5% vs 14.0% [$p<0.0001$]; <0.2 ng/mL at 12 months: 22.7% vs 11.7% [$p<0.0001$]), time to castration resistance (20.7 vs 14.7 months, $p<0.0001$), and time to clinical progression (32.7 vs 19.8 months, $p<0.0001$).

The trial was ended prematurely when a planned interim analysis revealed the compelling statistically significant survival difference between the treatment arms.

As of mid-January 2013, at a median follow-up of 29 months, there had been 237 deaths: 101 in the ADT-plus-docetaxel arm, of which 84 (83.2%) were due to prostate cancer, and 136 in the ADT-alone arm, of which 112 (83.6%) were due to prostate cancer. The adverse events in the patients treated with docetaxel were generally mild and were manageable. There were no Grade 5 adverse events, although there were 9 cases of Grade 4 neutropenia.

The data demonstrated that ADT and 6 cycles of docetaxel significantly improved OS compared with ADT alone in men with hormone-sensitive prostate cancer. The results are likely practice changing.

Lenvatinib Improves Progression-Free Survival in Refractory Thyroid Cancer

Written by Rita Buckley

Martin Schlumberger, MD, University of Paris-Sud, Orsay, France, reported outcomes from a Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Lenvatinib (E7080) in ¹³¹I-Refractory Differentiated Thyroid Cancer (SELECT; NCT01321554) [Schlumberger M et al. *J Clin Oncol* 2014]. The trial compared the progression-free survival (PFS) of subjects with ¹³¹I-refractory differentiated thyroid cancer who were treated with lenvatinib versus placebo.

Lenvatinib (E7080) is an oral multi-tyrosine kinase inhibitor of VEG1-3, FGFR1-4, PDGFRa, RET, and KIT. It demonstrated clinical activity in a Phase 2 study of patients with radioiodine-refractory differentiated thyroid cancer [Sherman S et al. *J Clin Oncol* 2011].

In the SELECT trial, 392 patients aged ≥ 18 years from 136 study locations were randomly assigned to either 24 mg of the investigational tyrosine kinase inhibitor lenvatinib orally once daily (on a 28-day cycle) or a matching 24-mg placebo tablet. All had radiographic evidence of disease progression within the prior 13 months.

In total, 261 patients in the SELECT trial received the study drug compared with 131 who received the placebo. Patients were treated until confirmed disease progression. They could cross over to open-label lenvatinib treatment if their disease progressed.

Treatment with lenvatinib resulted in substantial gains in PFS. Patients who received lenvatinib had median PFS of 18.3 months, whereas those taking the placebo had median PFS of 3.6 months—a significant 14.7-month difference ($p<0.0001$). At Year 2, progression events occurred in 86% of subjects in the placebo arm and in only 41% of those in the treatment arm. Complete responses were seen in 2% of patients.

Gains were not seen in overall survival. The lack of improvement in overall survival compared with placebo might have been an artifact of the crossover design of the study, such that those who started on placebo but required lenvatinib after clinical progression may not have derived the same benefit. This would lower overall survival rates.