# Is Docetaxel Chemotherapy a New Standard of Care for Metastatic Hormone-Sensitive Prostate Cancer?

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Abstract

Optimal management of metastatic hormone-sensitive prostate cancer (mHSPC) has been controversial in recent years, as 2 large phase III studies, GETUG-AFU 15 and CHAARTED, reported conflicting results on the benefits of early docetaxel therapy. Unprecedented survival advantages reported by CHAARTED, especially in men with high-volume metastatic disease, have convinced many clinicians to consider adding docetaxel to androgen-deprivation therapy in newly diagnosed mHSPC. However, others cited the negative long-term results from GETUG-AFU 15 as a reason to be cautious about early adoption of chemotherapy. Despite demonstrating a significant survival benefit in the overall study population, subgroup analysis of men in CHAARTED with low-volume metastatic disease did not reach significance for survival, and remains an ongoing point of contention. Recently, at the 2015 Annual Meeting of the American Society of Clinical Oncology, the STAMPEDE trial was shown to validate the clinical benefit of early docetaxel therapy in an unselected mHSPC population similar to CHAARTED. Further data from both CHAARTED and STAMPEDE will bring more clarity to these issues, but in the interim, clinicians must decide how best to interpret the current information. In our practice, we have adopted docetaxel chemotherapy in mHSPC for most patients with high-volume disease and for selected patients with low-volume disease.

**Key words:** hormone sensitive, prostate cancer, early docetaxel, androgen-deprivation therapy, GETUG-AFU 15, CHAARTED, STAMPEDE

## Introduction

Docetaxel forever changed the treatment landscape of advanced prostate cancer when it demonstrated the first-ever survival benefit in metastatic castration-resistant prostate cancer (mCRPC).[1,2] Its impact on the mCRPC frontier persists to this day, with all subsequently approved CRPC agents proving themselves in clinical arenas defined by their relation to the timing of docetaxel.

With androgen-deprivation therapy (ADT) firmly established as first-line therapy for metastatic hormone-sensitive prostate cancer (mHSPC), multiple variations of suppressing androgen production and signaling have been evaluated. Our playbook for HSPC has grown, and now includes continuous ADT, intermittent ADT, combined androgen blockade, and antiandrogen monotherapy. However, outside of disrupting the androgen pathway, the treatment paradigm for mHSPC has not been significantly challenged until more recently. Docetaxel again returns to the vanguard, now for the upfront treatment of mHSPC—but not without some controversy in tow.

## Phase III Studies

Following TAX 327 and SWOG 99-21, given the relative scarcity of effective agents, there was a great need to further develop docetaxel therapy. In bringing docetaxel into the hormone-sensitive setting, the rationale was to preemptively eradicate cancer cells inherently insensitive to ADT by acting on cellular targets outside of the androgen-signaling pathway, thus improving clinical outcomes. At least 3 large, randomized, phase III trials were launched to evaluate the value of upfront docetaxel therapy in mHSPC.

The GETUG-AFU 15 study[3] randomized 385 men with mHSPC to receive ADT plus docetaxel (75 mg/m$^2$ every 3 weeks, up to 9 cycles) or ADT alone. While the addition of docetaxel was associated with an improvement in biochemical progression-free survival (PFS; 22.9 vs 12.9 months; hazard ratio [HR], 0.7; 95% CI, 0.6-0.9; $P$ = .0021),[3] there was no improvement in overall survival (OS) with the addition of docetaxel, even with long-term follow-up (60.9 vs 46.5 months; HR, 0.9; 95% CI, 0.7-1.2; $P$ = .44).[4]

Running in parallel, CHAARTED (E3805)[5] similarly randomized 790 men with mHSPC to ADT plus docetaxel (75mg/m$^2$ every 3 weeks × 6 cycles) or ADT alone. In stark contrast, CHAARTED found at the time of planned interim analysis that the addition of docetaxel resulted in a dramatic improvement in the primary endpoint of OS (57.6 vs 44.0 months; HR, 0.61;

**TABLE.** Clinical Outcomes and Effect of Disease Volume From Phase III Trials of Early Docetaxel Therapy in mHSPC

| | GETUG-AFU 15[4] | | | | CHAARTED (E3805)[5] | | | | STAMPEDE (M1 subgroup)[6] | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | ADT + D (n=192) | ADT (n=193) | HR | *P* value | ADT + D (n=397) | ADT (n=393) | HR | *P* value | ADT + D (n=362) | ADT (n=725) | HR | *P* value |
| **Primary Endpoint** | **Overall Survival (months)** | | | | **Overall Survival (months)** | | | | **Overall Survival (months)** | | | |
| All Patients | 60.9 | 46.5 | 0.9 | .44 | 57.6 | 44.0 | 0.61 | <.001 | 65 | 43 | 0.73 | .002 |
| High-Volume | 39 | 35.1 | 0.8 | .35 | 49.2 | 32.2 | 0.60 | <.001 | – | – | – | – |
| Low-Volume | 83.1 | NR | 1 | .87 | NR | NR | 0.60 | .11 | – | – | – | – |
| **Secondary Endpoint** | **Biochemical PFS (months)** | | | | **Time to Clinical Progression (months)** | | | | – | | | |
| All Patients | 22.9 | 12.9 | 0.7 | .0021 | 33.0 | 19.8 | 0.61 | <.001 | – | – | – | – |
| High-Volume | 15.2 | 9.2 | 0.6 | .0039 | – | – | – | – | – | – | – | – |
| Low-Volume | 40.9 | 22.4 | 0.7 | .0533 | – | – | – | – | – | – | – | – |

ADT indicates androgen-deprivation therapy; D, docetaxel; HR, hazard ratio; mHSPC, metastatic hormone-sensitive prostate cancer; NR, not reached; PFS, progression free survival.

95% CI, 0.47-0.80; *P* = .001).[5] Secondary endpoints of time to castration resistance, time to clinical progression, and achieving a serum prostate-specific antigen (PSA) less than 0.2 ng/mL at 6 and 12 months all uniformly favored docetaxel, as well.

The largest of the 3 trials, STAMPEDE,[6] accrued 2962 men with either high-risk localized (24%), node-positive (15%), or mHSPC (61%) to 4 separate treatment arms: ADT alone, ADT plus zoledronic acid, ADT plus docetaxel, or ADT plus zoledronic acid and docetaxel. The addition of docetaxel demonstrated significance in both its primary endpoint of OS (77 vs 67 months; HR, 0.76; 95% CI, 0.63-0.91; *P* = .003) and secondary endpoint of failure-free survival (37 vs 21 months; HR, 0.62; 95% CI, 0.54-0.70; $P < 1 \times 10^{-10}$) in the overall study population.[6,7]

## Trial Design Differences

The composition of patients recruited to the 3 trials is distinct. CHAARTED was initially conceived as a trial for high-volume metastatic disease, defined as the presence of visceral metastasis and/or 4 or more osseous metastases, with at least 1 being extra-axial. The protocol was later amended to allow enrollment of low-volume disease, as well, the end result being that the CHAARTED study cohort was enriched with high-volume patients (65.8%).[5] The number and location of metastases have proven to be of prognostic value,[8,9] drawing the parallel between high-volume and high-risk disease.

In comparison, GETUG-AFU 15 stratified patients according to the Glass risk criteria, which similarly incorporates location of metastases (appendicular vs axial), but also includes ECOG performance status (PS), Gleason score, and PSA,[10] all validated prognostic markers in their own right. Only 22% of men in GETUG-AFU 15 were high-risk by the Glass criteria,[3] but how this compares or correlates with the CHAARTED volume/risk criteria is unclear. To facilitate cross-comparison, GETUG-AFU 15 later retrospectively recategorized its patients to CHAARTED criteria, finding 47.5% to have high-volume disease.[4]

Ultimately, even with the alignment of standards, comparison remains difficult (Table). The large difference in median OS of the 2 control cohorts provides insight into the risk disparities that exist between the 2 study populations (54.2 vs 44.0 months in GETUG-AFU 15 and CHAARTED, respectively). Enrichment of patients with high-volume disease in CHAARTED likely plays a large role in this discrepancy. Additionally, CHAARTED included a slightly higher proportion of patients with Gleason score 8-10 (60.8% vs 56.1%).

Consideration also should be paid to the availability of other therapeutic agents with proven survival benefits (ie, cabazitaxel, abiraterone, and enzalutamide), as differences in post-trial treatment patterns are often a confounding variable. GETUG 15 had a much higher percentage of men who received salvage docetaxel therapy as compared with CHAARTED (45.2% vs 22.5%), likely because no other drugs were approved for mCRPC until years after accrual closed for GETUG-AFU 15, whereas the availability of newer second-line agents overlapped considerably with the enrollment period for CHAARTED.

Although the absolute differences in OS between the study arms were comparable in both GETUG-AFU 15 and CHAARTED (14.4 and 13.6 months, respectively), significance was only met in CHAARTED, likely owing to greater statistical power because of its larger sample size. STAMPEDE, a far larger and much more inclusive study, reported a 22-month improvement in OS with the addition of docetaxel in the subgroup of patients with metastatic (M1) disease (65 vs 43 months; HR, 0.73; 95%

CI, 0.59-0.89; $P$ = .002).[7] The similarity in OS gains across the 2 largest trials strongly suggests that the effect of early docetaxel therapy is consistent.

### High-Volume Disease

An important potential selection criterion for benefit in CHAARTED was a planned subgroup analysis showing an unprecedented 17-month OS improvement with the addition of docetaxel in men with high-volume mHSPC (49.2 vs 32.2 months; HR, 0.60; 95% CI, 0.45-0.81; $P$ <.001).[5] In comparison, docetaxel conferred a relatively modest 2.9-month OS benefit in CRPC.[11] The strongly positive subgroup analysis favoring high-volume disease was sufficiently convincing that docetaxel for mHSPC has been embraced by the National Comprehensive Cancer Network (NCCN), and has since become a standard-of-care for high-volume disease in the United States.[12]

The adoption of early docetaxel therapy for high-volume disease has been delayed in many European countries until the discrepancy between GETUG-AFU 15 and CHAARTED is reconciled. Subgroup analysis of the recategorized high-volume GETUG-AFU 15 cohort still did not show improvement in OS (39.0 vs 35.1 months; HR, 0.8; 95% CI, 0.6-1.2; $P$ = .35),[4] though this trial was not designed or powered to evaluate this endpoint using CHAARTED criteria.

Ongoing analyses of STAMPEDE data should provide further data on specific subgroups,[13] although high- and low-volume metastatic diseases were not prespecified subgroups in this trial design. That being said, the power and consistency of the primary OS analysis from STAMPEDE strongly validate the findings from CHAARTED. We believe that docetaxel for mHSPC will soon become the new standard of care for management of high-volume mHSPC worldwide.

### Low-Volume Disease

There is ongoing debate about how best to interpret the data generated by GETUG-AFU 15 and CHAARTED for men with low-volume disease. Although both trials failed to show an OS advantage with docetaxel in this subgroup, the CHAARTED study reported a tantalizing HR of 0.60 (95% CI, 0.32-1.13; $P$ = .11).[5] Longer follow-up is needed to see whether this promising signal will translate into a true OS benefit. Forthcoming data from STAMPEDE may also shed more light on this specific clinical question. Until then, there is insufficient evidence to *strongly* recommend the routine use of early docetaxel therapy for low-volume mHSPC, although it may still represent an appropriate choice for some men.

Controversy surrounds whether a negative subgroup analysis should strongly influence our interpretation of an otherwise significantly positive overall study. Knowing that the addition of docetaxel conferred such a substantial OS benefit in patients with high-volume disease, who comprised the majority of the CHAARTED study population, it raises the question of whether a negative outcome in patients with low-volume disease could have been overshadowed.

An argument can be made that the underlying principle of proactively eradicating androgen-independent clones with upfront cytotoxic therapy still applies regardless of volume, as low-volume disease may not necessarily equal low-risk disease. As previously mentioned, CHAARTED criteria did not incorporate other commonly used prognostic factors, such as Gleason score or PSA levels. Should patients with bulky disease that does not strictly qualify as high-volume disease by CHAARTED standards still be considered for docetaxel therapy? Would high-performing younger patients benefit from a more aggressive upfront approach regardless of disease volume or presence of risky prognostic factors? In the STAMPEDE trial, patients with nonmetastatic disease did not experience a survival benefit, but they had a significant improvement in failure-free survival.[6] Perhaps, even patients with locally advanced disease should receive docetaxel chemotherapy? These questions currently remain unanswered.

Toxicity, of course, is a key consideration. GETUG-AFU 15, CHAARTED, and STAMPEDE all report higher rates of febrile neutropenia (7%, 6%, 12%, respectively)[3,5,7] than what historically has been seen with docetaxel therapy in CRPC (3%), as reported in TAX327.[1] In fact, treatment-related deaths attributed to neutropenia led the GETUG-AFU 15 investigators to add prophylactic granulocyte colony-stimulating factor to the study protocol.[3] While grade 3 or higher fatigue, sensory neuropathy, and peripheral edema were reported to be low in both GETUG -AFU15 and CHAARTED, anecdotal experience with early docetaxel therapy has seen a disproportionately greater need for dose reduction or addition of growth factor to mitigate these adverse effects.

With current data in this space still in a state of immaturity, we propose an individualized approach, favoring the use of chemotherapy in low-volume disease with features associated with poor prognosis or consistent with rapidly progressing disease. In this way, patients farther on the spectrum of developing high-volume disease are captured and can derive benefit from early docetaxel therapy. Serious consideration should be given to patients with Gleason 8 or higher disease, poor PSA response to primary ADT, rapid PSA doubling time, disproportionately high or low PSA levels, bulky lymph node disease, and symptomatic disease. Additionally, men with good PS, who are young or have little to no medical comorbidities, should also be considered for docetaxel therapy in order to maximally prolong time to disease progression and OS. The potential treatment-related toxicities must be clearly discussed with patients in order to facilitate a fully informed decision.

### Future Directions

The full impact of early docetaxel therapy for mHSPC, especially

in low-volume disease, is still to be determined, awaiting more mature data from both CHAARTED and STAMPEDE. The value of aggressive early chemotherapy in the modern context, where multiple other agents with proven OS benefits in mCRPC are now widely available, will also need to be assessed during long-term follow-up. In fact, the strongly positive results from CHAARTED and STAMPEDE set the stage for evaluating other CRPC therapies in earlier stages of disease. As these other agents move into the hormone-sensitive space, optimal sequence and duration of treatment will become even more of a challenge than it is now for CRPC.

As demonstrated by CHAARTED, incorporating enrichment strategies can greatly benefit future trial design. It is unlikely that there will exist only one, unified, optimal approach to managing this heterogeneous disease. Further development of predictive biomarkers, such as molecular signatures derived from whole blood or circulating tumors cells, could help guide treatment selection and management strategies for prostate cancer, as well as facilitate recruitment to future clinical studies.

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