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# Burden of Metastatic Castrate Naive Prostate Cancer Patients, to Identify Men More Likely to Benefit from Early Docetaxel: Further Analyses of CHAARTED and GETUG-AFU15 Studies

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**Abstract**

***Background:*** Docetaxel (D) at the time of starting androgen deprivation therapy (ADT) for metastatic castrate naive prostate cancer shows a clear survival benefit for patients with high-volume (HV) disease. It is unclear whether patients with low-volume (LV) disease benefit from early D.
***Objective:*** To define the overall survival (OS) of aggregate data of patient subgroups from the CHAARTED and GETUG-AFU15 studies, defined by metastatic burden (HV and LV) and time of metastasis occurrence (at diagnosis or after prior local treatment [PRLT]).
***Design, setting, and participants:*** Data were accessed from two independent phase III trials of ADT alone or ADT + D—GETUG-AFU15 ($N$ = 385) and CHAARTED ($N$ = 790), with median follow-ups for survivors of 83.2 and 48.2 mo, respectively. The definition of HV and LV disease was harmonized.
***Outcome measurements and statistical analysis:*** The primary end point was OS.
***Results and limitations:*** Meta-analysis results of the aggregate data showed significant heterogeneity in ADT + D versus ADT effect sizes between HV and LV subgroups ($p$ = 0.017), and failed to detect heterogeneity in ADT + D versus ADT effect sizes between upfront and PRLT subgroups ($p$ = 0.4). Adding D in patients with HV disease has a consistent effect in improving median OS (HV-ADT: 34.4 and 35.1 mo, HV-ADT + D: 51.2 and 39.8 mo in CHAARTED and GETUG-AFU15, respectively; pooled average hazard ratio or HR (95% confidence interval [CI]) 0.68 ([95% CI 0.56; 0.82], $p < 0.001$). Patients with LV disease showed much longer OS, without evidence that D improved OS (LV-ADT: not reached [NR] and 83.4; LV-ADT + D: 63.5 and NR in CHAARTED and GETUG-AFU15, respectively; pooled HR (95% CI) 1.03 (95% CI 0.77; 1.38). Aggregate data showed no evidence of heterogeneity of early D in LV and HV subgroups irrespective of whether patients had PRLT or not. Post hoc subgroup analysis was based on aggregated data from two independent phase III randomized trials.
***Conclusions:*** There was no apparent survival benefit in the CHAARTED and GETUG-AFU15 studies with D for LV. Across both studies, early D showed consistent effect and improved OS in HV patients.
***Patient summary:*** Patients with a higher burden of metastatic prostate cancer starting androgen deprivation therapy (ADT) have a poorer prognosis and are more likely to benefit from early docetaxel. Low-volume patients have longer overall survival with ADT alone, and the toxicity of docetaxel may outweigh its benefits.


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## 1. Introduction

Despite an important increase in the number of therapeutic options, prostate cancer remains the fifth leading cause of cancer death in males worldwide [1] and the third cause in Western countries [2]. The management of metastatic castration-resistant prostate cancer is based on chemotherapy [3–5] and new hormone therapies [6–9]. In the metastatic castrate naive prostate cancer (mCNPC) setting, androgen deprivation therapy (ADT) has been the standard of care for decades, until clinical studies established the benefits of adding docetaxel (D) to ADT. Three clinical trials evaluated this strategy—two phase III randomized trials that compared D + ADT versus ADT alone (CHAARTED [10] and GETUG-AFU15 [11]) and the multiarm, multistage STAMPEDE trial [12]. The CHAARTED study demonstrated a significant improvement in overall survival (OS) in the ADT + D arm (57.6 vs 44 mo), which was more pronounced in patients with high-volume (HV) disease (49.2 vs 32.2 mo) [10]. The updated results, presented at the European Society for Medical Oncology congress in 2016, after a median follow-up of 54 mo confirmed significantly longer OS in the overall population. A post hoc subset analysis according to the extent of disease suggests that the survival benefit could primarily be limited to patients classified as having HV disease but not in those with low-volume (LV) disease [13]. The STAMPEDE study also demonstrated longer OS when D was added to standard of care in metastatic patients (hazard ratio [HR] 0.80, 95% confidence interval [CI] 0.65; 0.99, $p = 0.033$) but did not classify patients by volume of metastases. In contrast, the French GETUG-AFU15 study showed no significant difference in OS between ADT + D and ADT-alone arms (58.9 vs 54.2 mo, HR 1.01 [95% CI: 0.75; 1.36], $p > 0.9$) [11]. A further analysis, published in 2016 after a median follow-up of 84 mo, confirmed a non–statistically significant improvement in median OS for ADT + D (62.1 vs 48.6 mo, HR 0.88 [95% CI 0.68; 1.14], $p = 0.3$) [14].

A meta-analysis of these three trials (2992 patients) demonstrated an absolute improvement of 9% in 4-yr OS when D was added to ADT, corresponding to a 23% reduction in the risk of death (HR 0.77 [95% CI 0.68; 0.87], $p < 0.001$), along with a 16% absolute improvement in failure-free survival [15]. The authors concluded that the addition of D should be considered as the new standard of care for patients with mCNPC who are starting first-line therapy. However, they observed that the majority of patients included were newly diagnosed with metastatic disease, which is not the most frequent situation in clinical practice due to the development of screening programs [16,17]. In the GETUG-AFU15 study, it had been suggested that patients who developed metastases after failure of local treatment had significantly longer median OS than those with metastases at diagnosis (83.1 vs 46.5 mo, $p = 0.015$) [14]. In the present study, we analyzed OS in specific subgroups of patients from the CHAARTED and GETUG-AFU15 studies, defined by same definitions of metastatic burden (HV or LV) and time of metastasis occurrence (at diagnosis or after failure of local therapy), to see if the outcomes of the different subgroups are reproducible across the two studies.

## 2. Patients and methods

The CHAARTED and GETUG-AFU15 studies are phase III, open-label, randomized trials. Eligible patients were aged at least 18 yr and had histologically confirmed prostate cancer with radiological evidence of metastases, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate organ function, allowing the administration of D. ADT for metastatic disease was allowed if it had been initiated no more than 2 mo (GETUG-AFU15) or no more than 4 mo (CHAARTED) before randomization. Patients were randomized in a 1:1 ratio to ADT (orchiectomy or luteinizing hormone–releasing hormone agonists) or ADT + D (75 mg/m$^2$ every 21 d). Patients received premedication with a corticosteroid without subsequent administration of daily prednisone. The planned duration of chemotherapy was six cycles in CHAARTED and nine cycles in GETUG-AFU15. Patients randomized in the ADT + D arm underwent physical examination and blood tests every 3 wk during chemotherapy and every 3 mo thereafter, while these parameters were recorded every 3 mo from the onset of studies for patients in both ADT arms. Imaging (computed tomography [CT] scan and bone scintigraphy) was performed every 3 mo in the GETUG-AFU15 study, at baseline, at the time of documented castration resistance, or as clinically indicated in the CHAARTED study. Time to castration-resistant prostate cancer (CRPC) was defined as the time from randomization to prostate-specific antigen (PSA) progression, or radiological or clinical progression, whatever occurred first. Clinical progression was determined using RECIST criteria, version 1.0, for measurable lesions or the occurrence of (new) bone lesions. In the CHAARTED study, patients were stratified at randomization according to age (<70 vs ≥70 yr), ECOG performance-status score (0 or 1 vs 2), planned use of combined androgen blockade for more than 30 d (yes vs no), and agents approved for prevention of skeletal-related events (yes vs no) [10]. Patients were also stratified according to the duration of prior adjuvant ADT (<12 vs ≥12 mo) and the extent of metastatic disease group as HV disease, defined as the presence of visceral metastases and/or at least four bone metastases with at least one outside the vertebral bodies and pelvis, and LV disease for other patients. Of note, at study inception, only patients with HV disease were eligible; then an amendment allowed inclusion of patients with LV disease. In the GETUG-AFU15 study, patients were stratified at randomization according to the use of prior hormonal therapy, use of prior chemotherapy treatment, and Glass prognostic group (poor, intermediate, and good) [11]. For the GETUG-AFU15 study, a post hoc analysis was performed, through chart review, to distinguish between patients with HV and LV disease defined by the same criteria as CHAARTED.

### 2.1. Statistical analysis

The main objective of our study was to conduct a post hoc analysis to assess the OS benefit of ADT plus D and ADT alone in specific subgroups of patients from the CHAARTED and GETUG-AFU15 studies, defined by metastatic burden (HV or LV) and time of metastasis occurrence (at diagnosis or after failure of local therapy). The main baseline characteristics evaluated in both trials were summarized using standard descriptive statistics (median and interquartile range for continuous variables, and frequency and percentages for categorical variables). Prior to analysis, patients not known to have died were censored at the date of the last known follow-up evaluation. OS data from these two studies were first analyzed separately to estimate the HRs between the ADT + D

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