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Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial

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Abstract

Background: The role of chemotherapy in metastatic non castrate prostate cancer (mNCPC) is debated. Survival benefits of docetaxel (D) added to androgen-deprivation therapy (ADT) were shown in the CHAARTED trial in patients with metastatic high-volume disease (HVD).
Objective: To assess the impact of metastatic burden and to update overall survival (OS) data of the GETUG-AFU15 study.
Design, setting, and participants: Randomized phase 3 trial of ADT plus D versus ADT alone in 385 mNCPC patients; median follow-up of 7 yr.
Outcome measurements and statistical analysis: Primary end point was OS. Secondary end points were biochemical progression-free survival (bPFS) and radiographic progression-free survival (rPFS). Retrospective analysis was by tumor volume.
Results and limitations: After a median follow-up of 83.9 mo, median OS in the overall population was 62.1 mo (95% confidence interval [CI], 49.5–73.7) and 48.6 mo (95% CI, 40.9–60.6) for ADT plus D and ADT arms, respectively (hazard ratio [HR]: 0.88 [95% CI, 0.68–1.14]; $p = 0.3$). Median OS in ADT plus D and ADT arms, respectively, was for HVD

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patients: 39.8 mo (95% CI, 28.0–53.4) versus 35.1 mo (95% CI, 29.9–43.6) (HR: 0.78 [95% CI, 0.56–1.09]; $p = 0.14$), for low-volume disease (LVD) patients; median was not reached (NR; 95% CI, 69.5–NR) and 83.4 mo (95% CI, 61.8–NR) (HR: 1.02 [95% CI, 0.67–1.55]; $p = 0.9$). For upfront metastatic patients, OS was 52.6 mo (95% CI, 43.3–66.8) and 41.5 mo (95% CI, 36.3–54.5), respectively (HR: 0.93 [95% CI, 0.69–1.25]; $p = 0.6$). The bPFS (HR: 0.73 [95% CI, 0.56–0.94]; $p = 0.014$) and rPFS (HR: 0.75 [95% CI, 0.58–0.97]; $p = 0.030$) were significantly longer in the ADT plus D arm. Limitations included the retrospective analysis of metastatic extent and the lack of statistical power to detect a significant difference in subgroups.

Conclusions: The post hoc analyses of the GETUG-AFU15 study demonstrated a nonsignificant 20% reduction in the risk of death in the HVD subgroup. Patients with LVD had no survival improvement with early D.

Patient summary: In this study, docetaxel added to castration did not improve survival in patients with metastatic hormone-sensitive prostate cancer, partly due to methodological issues. However, early chemotherapy should be discussed with all patients, given the data of three randomized trials including GETUG-AFU15.

1. Introduction

Androgen-deprivation therapy (ADT) has been the standard of care for decades in metastatic prostate cancer (PCa) [1]. In the setting of metastatic castration-resistant prostate cancer (mCRPC), docetaxel (D) demonstrated an improvement in overall survival (OS) and became the mainstay of treatment [2,3]. In recent years, several other compounds have shown survival benefits in mCRPC, such as abiraterone, enzalutamide, cabazitaxel, radium-223, and sipuleucel-T, either before or after D [4–8]. Therefore the treatment landscape of mCRPC has evolved dramatically. In contrast, no new strategy has been validated in metastatic noncastrate prostate cancer (mNCPC). However, it has been shown that patients with a high metastatic burden, whatever its definition, have a poor prognosis [9–12].

In the phase 3 GETUG-AFU15 study, we assessed the benefits of the addition of D to ADT in patients with mNCPC and previously showed that OS was not different in both arms after a median follow-up of 49.9 mo (54.2 and 58.9 mo in the ADT and ADT plus D arms, respectively (hazard ratio [HR]: 1.01; $p = 0.9$) [13]. Only biochemical progression-free survival (bPFS) and radiographic progression-free survival (rPFS) were improved in the D plus ADT arm.

The results of the CHAARTED trial that had the same design as ours were presented in 2014 [14] and published in 2015 [15]. Median OS was significantly improved in the ADT plus D arm (57.6 vs 44.0 mo; HR: 0.61; $p < 0.001$). There was a 17.0-mo difference between arms in patients with high-volume disease (HVD; 49.2 vs 32.2 mo; HR: 0.60; $p < 0.001$).

We retrospectively retrieved data on metastatic volume from medical files of all patients included in the GETUG-AFU15 study, applying the CHAARTED definition of HVD and low-volume disease (LVD) and updated survival analyses. We present long-term outcomes in the overall population and in the HVD and LVD subgroups.

2. Patients and methods

The GETUG-AFU15 trial is a French multicenter open-label randomized study [13]. From October 2004 to December 2008, 385 patients were enrolled including 193 in the ADT arm and 192 in the ADT plus D arm. Eligible patients were randomized in a 1:1 ratio to ADT plus D (75 mg/m^2 for 21 d, up to nine cycles) or ADT alone. ADT consisted of orchiectomy or luteinizing hormone-releasing hormone agonists, alone or combined with nonsteroidal androgen receptor inhibitors. Randomization was stratified according to systematic treatment for primary PCa, systemic therapy for biochemical relapse, and risk groups as defined by Glass et al (Supplementary Table 1) [16].

The investigators took the site of bone disease into account to classify patients among Glass risk groups at study entry; however, they did not specifically mention the number of bone metastases in case report forms or whether they were appendicular or axial. These data were retrieved retrospectively through chart review for all patients in 2014 to better define the metastatic burden, and investigators reviews all baseline bone scans to confirm the data. As in the CHAARTED study, HVD was defined as the presence of visceral metastases and/or at least four bone lesions, including at least one lesion in any bone structure beyond the spine or pelvis. Other patients were considered to have LVD.

Following the Prostate Specific Antigen (PSA) Working Group definition, biochemical progression was defined as a previous confirmed PSA decrease of at least 50% and an increase of at least 50% above the nadir, with a minimum increase of 5 ng/ml. For patients without a previous PSA decrease of 50%, progression was defined as a PSA increase at least 25% above the nadir and at least 5 ng/ml [17]. In patients with measurable lesions, radiographic progression was defined using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.0 criteria [18]. In patients with bone lesions only, radiographic progression was defined as one or more new bone lesions on bone scan. Radiographic progression was the occurrence of new bone lesions or RECIST progression, whichever happened first. Death was considered as an event.

2.1. Statistics

The primary end point was OS. Secondary end points included bPFS and rPFS. Survival end points were defined as the time between randomization and death from any cause (OS), radiographic progression or death (rPFS), PSA progression or radiographic progression or death (bPFS). The study was initially planned to detect a true HR for death of 0.62 (two-sided test with 0.05 significance level). According to standard design criteria [19], 146 deaths were needed to detect this HR in the ADT plus D arm versus ADT arm with 80% power. The planned number of patients ($n = 385$) was determined assuming a 3-yr accrual period, a 3-yr follow-up period for each patient, and a 36-mo median OS in the ADT arm.

The main objective of the present study was to conduct a post hoc subgroup analysis to assess separately the survival benefits of ADT plus D

and ADT alone in HVD and LVD patients enrolled in the GETUG-AFU15 trial. Our secondary objective was to update survival outcomes and to assess the homogeneity of the treatment effect in the different subgroups. The HRs for ADT plus D versus ADT alone were estimated with 95% confidence intervals (CIs) through a Cox proportional hazards regression model with terms for the randomized treatment arm and all factors taken into account in the random allocation process. A test of homogeneity of the treatment effects among the different subgroups was conducted by adding a treatment by stratum interaction term in our stratified Cox regression modeling approach.

Survival rates were estimated using the Kaplan-Meier method and compared with the log-rank test. Because the overall 0.05 type I error rate was used at the first analysis planned per protocol, no adjustment for multiple testing was performed to control the family error rate. All statistical analyses were done with R software v.2.15.1 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Kaplan-Meier survival curves were plotted using SAS software v.9.3 (SAS Institute, Inc., Cary, NC, USA). The trial is registered with ClinicalTrials.gov (NCT00104715).

3. Results

The GETUG-AFU15 trial randomized 385 patients including 193 in the ADT arm and 192 in the ADT plus D arm. We identified 183 patients (48%) with HVD and 202 patients (52%) with LVD. Table 1 presents their characteristics. Patients were equally distributed in the two arms with regard to their metastatic burden (percentages of patients with visceral metastases and HVD/LVD distribution).

3.1. Overall survival

After a median follow-up of 83.9 mo (95% CI, 82.9–84.7), 242 patients had died (127 in the ADT arm and 115 in the ADT plus D arm; 147 and 95 in the HVD and LVD subgroups, respectively). Causes of deaths were disease progression for 82%, other causes for 9.5%, and unknown for 8.2% of patients.

In the overall population, the median OS was not significantly different between the two arms: 62.1 mo (95% CI, 49.5–73.7) in the ADT plus D arm and 48.6 mo (95% CI, 40.9–60.6) in the ADT arm (HR: 0.88 [95% CI, 0.68–1.14]; $p = 0.3$) (Fig. 1, Table 2).

In patients with HVD, median OS was 4.7 mo longer in the ADT plus D arm, but the difference was not statistically significant: 39.8 mo (95% CI, 28.0–53.4) versus 35.1 mo (95% CI, 29.9–43.6) (HR: 0.78 [95% CI, 0.56–1.09]; $p = 0.14$) (Fig. 2).

In patients with LVD, median OS was not reached (NR; 95% CI, 69.5–NR) in the ADT plus D arm and 83.4 mo (95% CI, 61.8–NR) in the ADT arm (HR: 1.02 [95% CI, 0.67–1.55]; $p = 0.9$) (Fig. 3). The test of homogeneity of treatment effects among HVD and LVD subgroups did not reveal a significant difference between the estimated HRs in the two subgroups ($p = 0.40$) (Supplementary Table 2).

Patients with metastatic disease after failure of local treatment (28%) had a significantly longer median OS than those with metastases at diagnosis (72%) at 83.1 mo (95% CI, 68.6–NR) versus 46.5 mo (95% CI, 40.5–54.6)

Table 1 – Characteristics of the patients ($n = 385$)

	ADT ($n = 193$)	ADT plus D ($n = 192$)
Age, yr, median (IQR)	64.0 (58.0–70.0)	63.0 (57.0–68.2)
ECOG performance status, *n* (%)		
0	176 (96)	181 (99)
1–2	7 (4)	2 (1)
Gleason score, *n* (%)		
<7	78 (41)	84 (45)
≥8	113 (59)	103 (55)
Metastases after treatment for local disease, *n* (%)	46 (24)	62 (33)
Metastases at diagnosis, *n* (%)	144 (76)	128 (67)
PSA, ng/ml, median (IQR)	25.8 (5.0–126)	26.7 (5.0–106)
Alkaline phosphatase, *n* (%)		
Normal	113 (61)	106 (57)
Elevated	71 (39)	79 (43)
Bone metastases, *n* (%)	156 (81)	155 (81)
Visceral metastases, *n* (%)	23 (12)	28 (15)
Four or more bone metastases with one or more beyond pelvis or spine, *n* (%)	95 (49)	82 (43)
Low-volume disease (%)	102 (53)	100 (52)
High-volume disease (%)	91 (47)	92 (48)

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; IQR = interquartile range; PSA = prostate-specific antigen.

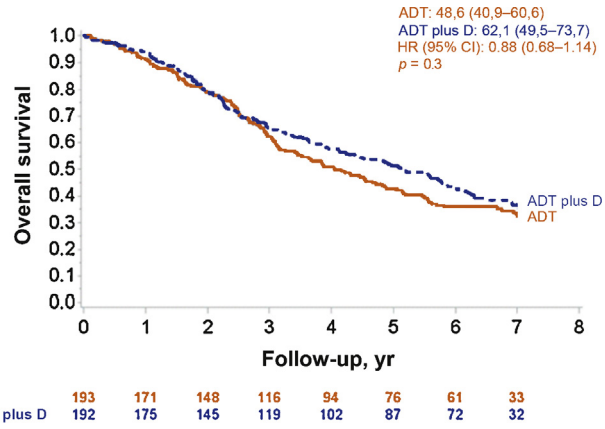

Fig. 1 – Overall survival in the overall population. ADT = androgen-deprivation therapy; CI = confidence interval; D = docetaxel; HR = hazard ratio.

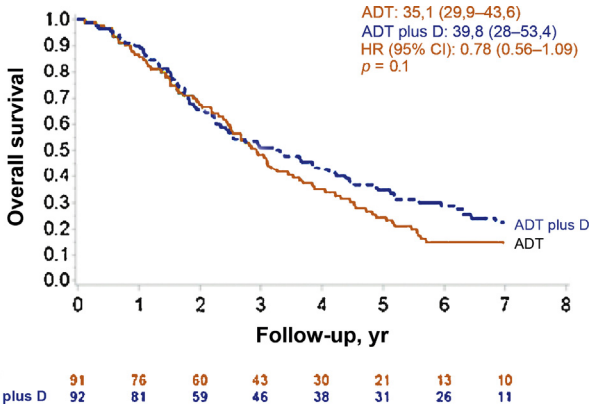

Fig. 2 – Overall survival for patients with high-volume disease. ADT = androgen-deprivation therapy; CI = confidence interval; D = docetaxel; HR = hazard ratio.

Table 2 – Survival data in the GETUG-AFU 15 and CHAARTED studies by treatment arm and metastatic burden

Median follow-up, mo	GETUG-AFU 15 83.9			CHAARTED [15] 28.9		
	All patients *n* = 385	HVD *n* = 183	LVD *n* = 202	All patients *n* = 790	HVD *n* = 513	LVD *n* = 277
ADT, mo	48.6	35.1	83.4	44.0	32.2	NR
ADT plus D, mo	62.1	39.8	NR	57.6	49.2	NR
HR	0.88	0.78	1.02	0.61	0.6	0.6
95% CI	0.68–1.14	0.56–1.09	0.67–1.55	0.47–0.80	0.45–0.81	0.32–1.13
p value	0.3	0.14	0.9	<0.001	<0.001	0.11

ADT = androgen deprivation therapy; CI = confidence interval; HR = hazard ratio; HVD = high-volume disease, LVD = low-volume disease; NR = not reached.

(HR: 1.57 [95% CI, 1.09–2.26]; $p = 0.015$). In patients with metastases at diagnosis, median OS was 11.1 mo longer in the ADT plus D arm compared with the ADT arm, without a statistically significant difference, at 52.6 mo (95% CI, 43.3–66.8) versus 41.5 mo (95% CI, 36.3–54.5) (HR: 0.93 [95% CI, 0.69–1.25]; $p = 0.6$). For patients with metastases after failure of local treatment, median OS was not reached (95% CI, 69.5–NR) in the ADT plus D arm and was 69.8 mo (95% CI, 62.2–NR) in the ADT arm (HR: 0.83 [95% CI, 0.47–1.47]; $p = 0.5$) (Supplementary Table 2).

Four treatment-related deaths occurred during the course of chemotherapy in the ADT plus D arm including two neutropenia-related deaths (both in the HVD subgroup).

3.2. *Biochemical and radiographic progression-free survival*

The bPFS was significantly longer for patients randomized in the ADT plus D arm in the overall population at 22.9 mo (95% CI, 19.5–28.4) versus 12.9 mo (95% CI, 11.9–17.7) (HR: 0.67 [95% CI, 0.54–0.84]; $p < 0.001$) (Fig. 4) and in the HVD group at 15.2 mo (95% CI, 12.0–21.2) versus 9.2 mo (95% CI, 8.3–12.2) (HR: 0.58 [95% CI, 0.42–0.79]; $p < 0.001$) but not in the LVD group at 40.9 mo (95% CI, 28.4–65.2) versus 22.4 mo (95% CI, 16.8–35.5) (HR: 0.79 [95% CI, 0.57–1.10]; $p = 0.16$). Similarly, rPFS was significantly longer for patients randomized in the ADT plus D arm in the overall population

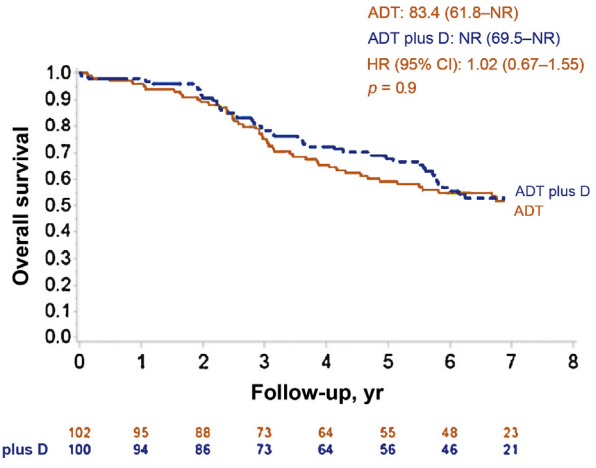

Fig. 3 – Overall survival for patients with low-volume disease. ADT = androgen-deprivation therapy; CI = confidence interval; D = docetaxel; HR = hazard ratio; NR = not reached.

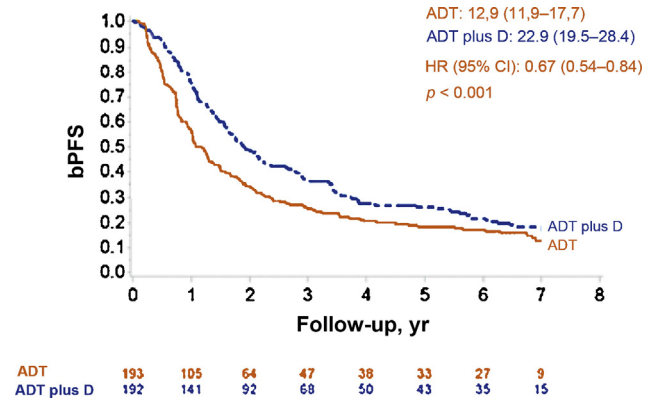

Fig. 4 – Biochemical progression-free survival for the overall population. ADT = androgen-deprivation therapy; bPFS = biochemical progression-free survival; CI = confidence interval; D = docetaxel; HR = hazard ratio.

at 22.9 mo (95% CI, 20.5–31.4) versus 15.3 mo (95% CI, 12.4–19.8) (HR: 0.69 [95% CI, 0.55–0.87]; $p = 0.002$) and in the HVD subgroup at 15.9 mo (95% CI, 12.9–22.0) versus 9.7 mo (95% CI, 9.0–13.6) (HR: 0.61 [95% CI, 0.44–0.83]; $p = 0.002$) but not in the LVD group at 41.0 mo (95% CI, 28.4–69.3) versus 23.2 mo (95% CI, 18.4–38.6) (HR: 0.81 [95% CI, 0.57–1.14]; $p = 0.23$).

Median time to subsequent treatment was longer in the ADT plus D arm: 28.1 mo (95% CI, 0.6–189) versus 18.5 mo (95% CI, 2.9–179.8). In the ADT arm, 127 of 149 patients (85%) treated for progressive disease received D (91% in the HVD and 78% in the LVD subgroup). Other treatments administered after progression were abiraterone acetate (36 and 33 in the ADT and ADT plus D arm, respectively), cabazitaxel (15 and 16 patients, respectively), and enzalutamide (12 and 15 patients, respectively).

4. Discussion

The role of D in the management of mNCPC is still a matter of active debate [20]. The benefit–risk ratio might be negative in some patients who will have a long-lasting nonprogressive, hormone-sensitive disease, whereas in others, early chemotherapy would target less androgen receptor pathway–mediated clones right away and avoid rapid progression toward a state in which the patient would

be too frail to receive chemotherapy. This latest intuitive argument is supported by two recent phase 3 trials, CHAARTED [14,15] and STAMPEDE [21]. In the CHAARTED study, D added to ADT yielded a statistically significant reduction in the risk of death of 39% (HR: 0.61; $p < 0.001$) (Table 2), with a 17-mo OS improvement in the HVD subgroup. These findings were recently corroborated by the results of the STAMPEDE study presented at the American Society of Clinical Oncology meeting in 2015 [22].

Following the results of the CHAARTED study, we distinguished between patients with high and low metastatic extent.

After a median follow-up of almost 7 yr, OS was not statistically different in the two arms in our study, despite a 13-mo longer OS with D. Subgroup analyses estimated a 20% reduction in the risk of death in HVD patients and no difference in mortality HRs in LVD patients.

Of the 202 patients enrolled in the HVD subgroup, 147 died. According to the study design, 146 deaths observed were sufficient to detect a true reduction in the risk of death of 38%. Nevertheless, the lack of significance in this particular subgroup can be attributed to a lack of power due to a less pronounced effect than that observed in the CHAARTED and STAMPEDE trials, and strong departures from proportional hazards assumptions between treatment arms. In the LVD subgroup, only 95 patients died. The comparison of survival between the two randomized treatment arms in this particular subgroup is clearly underpowered. The estimated conditional power to detect a true reduction in the risk of death of 38% after 146 deaths, as planned per protocol, given the current results in LVD patients (current $p = 0.9$), is 13% and below the 20% standard threshold used to stop a trial for futility reasons [23]. The lack of difference between treatments observed in LVD patients (HR: 1.02) suggests that early D administration in LVD patients is medically futile. According to Schmoor et al [24], the estimated powers in our study to detect a differential effect of 38% (HR: 0.62 in HVD vs 1.00 in LVD) or 20% (HR: 0.62–0.80 in HVD vs 1.00 in LVD) are 45% and 14%, respectively. This confirms that failure to reject a differential treatment effect between HVD and LVD patients ($p = 0.4$) can be attributed to a lack of power.

Discrepancies between the GETUG-AFU15 and the CHAARTED studies cannot be explained by treatment exposure because patients received a median number of eight and six cycles of D, respectively. Other hypotheses can be proposed. First, the CHAARTED study included twice as many patients as ours, leading to possible insufficient power of our study to demonstrate a benefit of chemotherapy, as discussed earlier.

Second, patients in the CHAARTED trial, who had worse prognosis diseases, were perhaps more likely to gain benefits from chemotherapy: 64% and 66% had HVD in the ADT and ADT plus D arms, respectively, versus 47% and 48%, respectively, in our study. Eastern Cooperative Oncology Group performance status was 1–2 in 30.5% of patients versus 2.3% in the GETUG-AFU15 trial; high Gleason score (8–10) was found in 61% of patients versus 57% in our study, and median PSA was approximately twice higher. These differences can partly explain the higher OS in our ADT control group (medians: 48.6 vs 44.0 mo).

Third, in our study, as in the CHAARTED study, bPFS and rPFS were significantly improved in the ADT plus D arm. Improved progression-free survival without improvement of OS raises the question of treatments administered beyond progression. In the CHAARTED trial, besides D that some patients received beyond progression (48% of patients with progressive disease in the ADT arm and 22.7% in the ADT plus D arm), those in the ADT plus D arm received numerically more frequently drugs that were previously shown to improve OS than patients in the ADT alone arm: cabazitaxel (23.9% and 12.9%), abiraterone and/or enzalutamide (44.1% and 36.2%), and sipuleucel-T (9.2% and 6.6%). Taken together, this indicates that patients in the experimental arm received active drugs more frequently, including D at randomization, but also other active drugs beyond progression, than patients in the control arm. In the GETUG-AFU15 study, in contrast, the vast majority of patients (79%) in the ADT arm received so-called salvage D within a median time of 18.5 mo (95% CI, 2.9–179) indicating that this trial was more a trial of early versus delayed D. Moreover, in contrast to CHAARTED, other active treatments (abiraterone, enzalutamide, and cabazitaxel) received beyond progression were well balanced between arms.

In the STAMPEDE trial, patients are randomized to research arms, assessing various strategies, or to a control arm, namely ADT alone in metastatic patients. Data from 917 metastatic patients included in the control arm were recently published [21]. Median OS was 42.1 mo and median failure-free survival was 11.2 mo. In multivariate analysis, the presence of bone metastases, regardless of soft tissue metastases, was among factors associated with poor failure-free survival and OS. The number and distribution of bone metastases was not specified. Survival data were recently presented with a statistically significant 27% reduction in the risk of death in the D plus ADT arm (HR: 0.73 [95% CI, 0.59–0.89]; $p = 0.002$) [22]. Median OS was 43 mo (95% CI, 24–88) in the ADT arm and 65 mo (95% CI, 27–NR) in the ADT plus D arm. Of note, in the STAMPEDE study, most patients were metastatic at presentation, whereas in the CHAARTED and GETUG-AFU15 trials, patients initially treated for local disease could be included. In our study, this represented 28% of cases, and these patients had a significantly longer survival (83.1 vs 46.5 mo; HR: 1.57 [95% CI, 1.09–2.26]; $p = 0.015$). But no significant difference in OS was observed between treatment arms (ADT plus D vs ADT) between patients with de novo and secondary metastatic diseases.

Data from CHAARTED and STAMPEDE trials suggest a benefit in OS for patients with metastatic PCa who receive upfront D, and we believe that their results do not contradict ours, even if our trial could not show statistically significant OS improvement, likely for methodological and environmental reasons (patients' characteristics and management). Other trials will provide information on the use of D in even earlier stages of the disease [22,25]. For instance, in the GETUG 12 trial, patients with high-risk localized PCa were randomized to ADT plus D and estramustine or ADT

alone [26]. Results indicate that D-based chemotherapy is associated with improved relapse-free survival in high-risk localized PCa [27]. A longer follow-up of this trial and other ongoing similar studies will be required to assess whether this benefit translates into improved metastasis-free survival and, ultimately, OS.

The main limitation of our study is that data on metastatic burden were collected retrospectively. The study was not initially designed to show the benefits of chemotherapy in specific subgroups of patients, and our sample size is clearly too small to detect a differential treatment effect between HVD and LVD patients.

5. Conclusions

This retrospective analysis of OS by tumor volume in mNCPC patients enrolled in the GETUG-AFU15 randomized study showed a nonsignificant survival improvement in the D arm in the HVD subgroup. This absence of statistical significance is due to a lack of power because the study was not initially designed for subgroup analysis. Thus these apparently contradictory results actually support the conclusion drawn by the CHAARTED study with longer survival in the subgroup of patients with HVD. Despite the lack of statistical evidence in the GETUG-AFU15, we conclude that early D should be systematically considered in newly diagnosed metastatic patients in case of high metastatic burden while this attitude remains questionable in those with a low metastatic burden. It might be interesting to pool the data of patients with LVD from the GETUG-AFU15 and CHAARTED studies to increase the number of patients and draw more conclusive results in this population.

Author contributions: Gwenaelle Gravis had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Appendix A. Supplementary data

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References

[1] Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2007;25:1596–605.
[2] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med 2004;351:1502–12.
[3] Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med 2004;351:1513–20.
[4] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med 2012;367:1187–97.
[5] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet 2010;376:1147–54.
[6] Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2012;13:983–92.
[7] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. N Engl J Med 2010;363:411–22.
[8] Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol 2015;16:152–60.
[9] Crawford ED, Eisenberger MA, McLeod DG, et al. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. N Engl J Med 1989;321:419–24.

[10] Hussain M, Tangen CM, Berry DL, et al. Intermittent versus continuous androgen deprivation in prostate cancer. N Engl J Med 2013;368:1314–25.
[11] Millikan RE, Wen S, Pagliaro LC, et al. Phase III trial of androgen ablation with or without three cycles of systemic chemotherapy for advanced prostate cancer. J Clin Oncol 2008;26:5936–42.
[12] Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998;339:1036–42.
[13] Gravis G, Fizazi K, Joly F, et al. Androgen-deprivation therapy alone or with docetaxel in non-castrate metastatic prostate cancer (GETUG-AFU 15): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:149–58.
[14] Sweeney C, Chen Y-H, Carducci MA, et al. Impact on overall survival (OS) with chemohormonal therapy versus hormonal therapy for hormone-sensitive newly metastatic prostate cancer (mPrCa): an ECOG-led phase III randomized trial [abstract LBA2]. J Clin Oncol 2014;5s(Suppl).
[15] Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015; 373:737–46.
[16] Glass TR, Tangen CM, Crawford ED, Thompson I. Metastatic carcinoma of the prostate: identifying prognostic groups using recursive partitioning. J Urol 2003;169:164–9.
[17] Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol 1999;17:3461–7.
[18] Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205–16.
[19] Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. Biometrics 1983;39:499–503.
[20] Fizazi K, Jenkins C, Tannock IF. Should docetaxel be standard of care for patients with metastatic hormone-sensitive prostate cancer? Pro and contra. Ann Oncol 2015;26:1660–7.
[21] James ND, Spears MR, Clarke NW, et al. Survival with newly diagnosed metastatic prostate cancer in the "docetaxel era": data from 917 patients in the control arm of the STAMPEDE trial (MRC PR08, CRUK/06/019). Eur Urol 2015;67:1028–38.
[22] James ND, Sydes MR, Mason MD, et al. Docetaxel and/or zoledronic acid for hormone-naïve prostate cancer: first overall survival results from STAMPEDE (NCT00268476) [abstract 5001]. J Clin Oncol 2015;33(Suppl).
[23] Demets DL. Futility approaches to interim monitoring by data monitoring committees. Clin Trials 2006;3:522–9.
[24] Schmoor C, Sauerbrei W, Schumacher M. Sample size considerations for the evaluation of prognostic factors in survival analysis. Stat Med 2000;19:441–52.
[25] Sandler HM, Hu C, Rosenthal SA, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521) [abstract LBA5002]. J Clin Oncol 2015;33(Suppl).
[26] Fizazi K, Lesaunier F, Delva R, et al. A phase III trial of docetaxel-estramustine in high-risk localised prostate cancer: a planned analysis of response, toxicity and quality of life in the GETUG 12 trial. Eur J Cancer 2012;48:209–17.
[27] Fizazi K, Faivre L, Lesaunier F, et al. Androgen deprivation therapy plus docetaxel and estramustine versus androgen deprivation therapy alone for high risk localised prostate cancer (GETUG 12): a phase 3 randomised controlled trial. Lancet Oncol 2015;16: 787–94.