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Addition of docetaxel to androgen deprivation therapy for patients with hormone-sensitive, metastatic prostate cancer: a systematic review and meta-analysis.

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Abstract

Context: Several randomized clinical trials (RCTs) have recently tested the early addition of docetaxel to androgen deprivation therapy (ADT) in hormone-sensitive, metastatic prostate cancer.

Objective: To perform a systematic review and meta-analysis of RCTs evaluating the combination of docetaxel and ADT in hormone-sensitive, metastatic prostate cancer. Primary endpoint was overall survival (OS). Secondary endpoint was progression-free survival. Exploratory subgroup analysis according to high-volume vs. low-volume disease was performed.

Evidence acquisition: A systematic review of PubMed/Medline, Embase, and proceedings of main International meetings was performed in June 2015 and updated in August 2015. Three trials were selected for inclusion.

Evidence synthesis: Overall, 2951 patients were included in the 3 trials. Two trials enrolled only metastatic patients, while in the third trial 61% were metastatic: overall, metastatic patients were 2262 (951 docetaxel+ADT, 1311 ADT alone). Most patients had a good performance status. In metastatic patients, the addition of docetaxel was associated with improved OS (hazard ratio [HR] 0.73, 95%CI 0.60–0.90, p=0.002), with non significant heterogeneity among the 3 trials. Considering the whole study population (2951 patients), addition of docetaxel was associated with a similar OS improvement (HR 0.74, 95%CI 0.61–0.91, p=0.003). Although with limited statistical power, no significant interaction was demonstrated between the addition of docetaxel and the high or low volume of disease (p=0.5). The addition of docetaxel was associated with improvement in progression-free survival (metastatic patients: HR 0.63, 95%CI 0.57–0.70, p<0.001).

Conclusions: This meta-analysis shows a significant OS benefit from concomitant administration of docetaxel and ADT in patients with metastatic, hormone-sensitive prostate cancer.

Patient summary: We synthesized the evidence available about the early administration of docetaxel in patients starting hormonal treatment for metastatic prostate cancer. Based on results of this meta-analysis, we believe that the combination of chemotherapy and hormonal treatment should be considered in fit patients.

Introduction

Prostate cancer is the second most frequently diagnosed cancer in men and is the second leading cause of cancer death in male patients in United States and Europe [1]. Although localized prostate cancer may be successfully treated with radical prostatectomy and external beam radiation, many patients will subsequently develop metastatic disease [2]. In addition, in the United States, the proportion of patients presenting with advanced stage at first diagnosis of prostate cancer is 4-5% for distant disease and 10-12% for regional disease [3]. Androgen deprivation therapy (ADT) by medical or surgical castration is the mainstay of treatment for locally advanced and metastatic prostate cancer, because androgen receptor (AR) pathway plays a key role in the development and progression of prostate cancer cells [4]. Although ADT is able to induce biochemical and clinical response in more than 90% of patients, after a median of 24-36 months patients experience progression to castration-resistant prostate cancer (CRPC), despite persisting low testosterone levels [5].

Until very recently, chemotherapy with docetaxel has been the only effective treatment for CRPC patients. In detail, the randomized clinical trial (RCT) TAX327 demonstrated that docetaxel plus prednisone prolonged overall survival (OS) compared to mitoxantrone plus prednisone [6]. Another RCT, the SWOG-9916 study, also demonstrated that the treatment with docetaxel, estramustine and dexamethasone increased median OS by two months compared to mitoxantrone and prednisone [7]. Based on these results, docetaxel was the first cytotoxic drug to demonstrate an improvement in OS in prostate cancer. More recently, several new agents, able to modify the natural history of disease, have been introduced in clinical practice. Results from phase III trials have demonstrated the efficacy of two new-generation hormonal therapies (abiraterone [8] and enzalutamide [9]), an immunotherapy (sipuleucel-T [10]), a new

microtubule-targeting chemotherapy (cabazitaxel [11]) and an alpha-emitter (radium 223 [12]), all able to prolong OS.

Nowadays, progression of CRPC is known to be due to the onset of a number of resistance mechanism induced by the selective pressure of endocrine therapy [13-18]. Castration is able to induce clonal selection and subsequent growth of androgen-independent cellular clones [19]. Hormone-sensitive prostate cancer should be considered a heterogeneous disease, characterized by the coexistence of both AR-positive and AR-negative tumor cells.

In this biological context, patients with hormone-sensitive prostate cancer may benefit of chemotherapy in association with endocrine therapy, targeting also AR-negative cells and delaying the development of resistance mechanisms. In the “pre-docetaxel” era, several RCTs investigated the combination of endocrine therapy with other cytotoxic drugs in hormone-sensitive prostate cancer patients, but none of these studies showed a significant and convincing advantage [20,21]. In the last two years, the results of three different clinical trials (GETUG-AFU 15 [22], CHAARTED – E3805 [23] and STAMPEDE [24]), that investigated the combination of docetaxel and ADT in hormone sensitive disease, have been made available to scientific community.

The aim of this systematic review is to conduct a meta-analysis of RCTs that evaluated the combination of docetaxel with ADT vs. ADT alone, in hormone-sensitive metastatic prostate cancer, in order to assess the impact of this therapeutic option in terms of overall survival.

Evidence acquisition

Identification of eligible trials

Full protocol of the review is available on request from the corresponding author. Search was performed in June 2015 and updated in August 2015, to identify all randomized trials testing the addition of docetaxel to ADT in patients with hormone-naive metastatic prostate cancer. Literature search was performed using PubMed, EMBASE, Medline, Cochrane Library. The following key-words were used: *(prostate cancer) AND docetaxel AND (random*)*. References of the selected articles were also checked to identify further eligible trials. Furthermore, proceedings of the main International meetings (American Society of Clinical Oncology [ASCO] annual meeting, ASCO Genitourinary symposium, European Society of Medical Oncology, European Association of Urology), were searched from 2010 onwards for relevant abstracts. Trials enrolling both patients with metastatic disease and patients without metastases were eligible (details about subgroups were collected as specified below). Trials enrolling only patients without metastases [25,26] were excluded. When more than one report was available describing results of the same trial, the most recent information (corresponding to a longer follow-up and a higher number of events) was considered in the analysis.

Data collection and study quality

For each eligible trial, the following data were collected, if available:

- main inclusion criteria: age, performance status, stage, Gleason score, prostate-specific antigen (PSA) at randomization, presence of visceral metastases, volume(high vs. low) of metastatic disease, previous treatments;
- details of study treatment: type of ADT allowed, schedule and number of cycles of docetaxel planned in experimental arm, timing of docetaxel start compared to ADT

initiation in experimental arm, number of docetaxel cycles actually administered (median, range), proportion of patients completing planned docetaxel cycles, proportion of patients needing dose reduction of docetaxel;

- study design: primary endpoint, study hypothesis;
- patients' enrolment and follow-up: date of start and date of end of accrual; number of patients assigned to experimental arm (docetaxel + ADT), number of patients assigned to control arm (ADT alone), median follow-up;
- Overall survival [OS]: number of deaths in each arm, median OS, hazard ratio with 95% confidence interval, p value, details of subgroup analysis of metastatic patients (for trials enrolling both M0 and M1 patients), details of subgroup analysis in "high-volume" patients and "low-volume" patients;
- Progression-free survival [PFS]: number of events in each arm, median PFS, hazard ratio with 95% confidence interval, p value, details of subgroup analysis of metastatic patients (for trials enrolling both M0 and M1 patients).

For each study, the quality of the randomization process was evaluated based on the information available in the publication [22, 23] or in the study protocol [24].

Statistical Methods

After data were abstracted, analysis was performed the Review Manager (RevMan 5.3) software. In all the trials included, efficacy data were analysed from all randomly assigned patients on an intention-to-treat basis. Primary endpoint of the meta-analysis was overall survival. Secondary endpoint was biochemical progression-free survival (bPFS). Definition of bPFS was different in the three trials and is reported in **Supplemental table A1**.

For both overall survival and bPFS, summary measure was hazard ratio (with 95% confidence interval). A random-effects model was applied. Statistical heterogeneity between studies was examined using the χ^2 test and the I^2 statistic.

Main analysis was performed considering the 3 comparisons of docetaxel + ADT vs. ADT alone. In one trial [24], a further experimental arm was reported, testing the addition of docetaxel + zoledronic acid to ADT alone. Since the addition of zoledronic acid alone did not show any significant efficacy compared to ADT, we decided to perform an exploratory analysis adding also this comparison to the analysis of docetaxel. However, since that trial used the same control arm for the two comparisons (docetaxel + ADT vs. ADT alone, and docetaxel + zoledronic acid + ADT vs. ADT alone), the weight of each comparison was reduced according to a correction factor equal to the number of events actually observed in the trial, divided by the number of events taken into account in the analysis (where the control arm was counted twice). This correction resulted in a prudential increase in the width of the confidence interval for the estimated hazard ratio of each comparison.

For overall survival, the subgroup analysis of patients according to disease volume ("high-volume" vs "low-volume") was available for two of the three trials [27,23]. In both trials, "high-volume" disease was defined as the presence of at least 4 bone lesions and at least 1 lesion in any bone beyond the spine / pelvis, or the presence of visceral metastasis. Patients without these conditions were classified as "low-volume". No subgroup analysis of progression-free survival according to disease volume was available.

Role of funding source

There was no funding source for this review. All authors had full access to all the data and the corresponding author (MDM) had final responsibility for the decision to submit for publication.

Evidence synthesis

Characteristics and quality of the trials

The selection process of trials eligible for the meta-analysis is reported in **Supplemental Figure 1**. In the search updated in August 2015, out of the 466 papers published *in extenso*, 464 were excluded, while two (GETUG-AFU 15 and CHAARTED – E3805) were found eligible for inclusion [22, 23]. One further eligible trial (STAMPEDE) was found searching the proceedings of the main International meetings [24]. Furthermore, an updated report of the already published GETUG-AFU 15 trial, with longer follow-up and a higher number of events for analysis, was available [27].

Main characteristics of the three available trials are described in **Table 1**. In all the trials, patients assigned to experimental arm received docetaxel 75 mg/m^2, for a maximum of 6 [23,24] or 9 cycles [22]. The maximum interval since ADT start allowed to start docetaxel ranged from 2 to 4 months: in the GETUG-AFU 15 trial about half of the patients had started ADT within 15 days of enrolment [22]; in the CHAARTED – E3805 trial, median time from ADT to randomization was slightly higher than 1 month in both arms [23].

According to description available in the publication for 2 trials [22,23] and in the study protocol for the third trial [24], quality of randomization process was judged adequate in all the 3 trials.

Patients' characteristics

Overall, 2951 patients were included in the 3 trials included in the meta-analysis, 1181 (40%) assigned to docetaxel + ADT, and 1770 (60%) assigned to ADT alone (**Table 2**). Main characteristics of the 2951 patients are described in **Table 2**. Patients were enrolled between October 2004 and March 2013. Median age was 63-65 years, and most

of the patients had a good performance status. Two of the trials [22,23] enrolled only metastatic patients, while in the STAMPEDE trial [24] metastatic patients were 61% of total study population: overall, metastatic patients were 2262 (951 docetaxel+ADT, 1311 ADT alone). Patients with metastatic disease at diagnosis were 71% in the GETUG-AFU 15 trial and 73% in the CHAARTED – E3805 trial; 94% of patients enrolled in the STAMPEDE trial had not received previous local therapy. Patients with high-volume disease were 48% in the GETUG-AFU 15 trial, and 65% in the CHAARTED – E3805 trial; this information was not available in the STAMPEDE trial.

Treatment compliance and toxicity

Median number of docetaxel cycles actually administered was 8 in the GETUG-AFU 15 trial [22], 6 in the CHAARTED – E3805 [23] and 6 in the STAMPEDE trial [24]. Proportion of patients completing the planned number of cycles was 48% in the GETUG-AFU 15 trial (9 planned cycles), 86% in the CHAARTED – E3805 trial (6 planned cycles) and 76% in the STAMPEDE trial (6 planned cycles). Proportion of patients needing dose reduction was 11% in the GETUG-AFU 15 trial and 26% in the CHAARTED –E3805 trial, while this information was not available in the report of the STAMPEDE trial.

The most common adverse events reported with the addition of docetaxel were haematologic toxicity (anemia, thrombocytopenia, neutropenia), fatigue, gastro-intestinal toxicity (nausea, vomiting, constipation, diarrhea), alopecia, sensory neuropathy, stomatitis/mucositis, nail changes and peripheral edema. In all the 3 trials, the addition of docetaxel was associated to higher incidence of febrile neutropenia: 8%, 6% and 12% in the GETUG-AFU 15, in the CHAARTED – E3805 and in the STAMPEDE trial, versus 0%, not reported and 1% with ADT alone in the 3 trials respectively.

Overall survival

Number of events and OS data reported in each trial are summarized in **Table 3**. Overall, 916 deaths were recorded for the main comparison (docetaxel + ADT vs. ADT alone) in metastatic patients. As shown in **Figure 1 (panel A)**, the addition of docetaxel to ADT in metastatic patients was associated with a statistically significant benefit in overall survival (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.60 – 0.90, p = 0.002). There was no evidence of statistically significant heterogeneity among the three trials (p = 0.15, I^2 = 48%). In the whole study population, including also the minority of non-metastatic patients (**Figure 1, panel B)**, the addition of docetaxel to ADT was associated with a similar, statistically significant benefit in overall survival (HR 0.74, 95% CI 0.61 – 0.91, p = 0.003). Very similar results were obtained in the exploratory analysis including also the docetaxel + zoledronic acid arm of the STAMPEDE trial: HR 0.74 (95%CI 0.63 – 0.88, p<0.001) considering only metastatic patients (**Figure 1, panel C**), HR 0.76 (95%CI 0.64 – 0.89, p=0.001) in all patients (**Figure 1, panel D**).

Subgroup analysis was performed for metastatic patients with “high-volume” and “low-volume” disease enrolled in the GETUG-AFU 15 and in the CHAARTED – E3805 trial (**Figure 2**). The test for difference of efficacy among the two subgroups did not demonstrate a statistically significant interaction (p=0.5). Hazard ratio for the addition of docetaxel to ADT was 0.67 (95% CI 0.51 – 0.88) in patients with “high-volume” disease and 0.80 (95% CI 0.49 – 1.32) in patients with “low-volume” disease.

Progression-free survival

As shown in **Figure 3 (panel A)**, the addition of docetaxel to ADT in metastatic patients was associated with a statistically significant benefit in progression-free survival (HR 0.63, 95% CI 0.57 – 0.70, p < 0.001), without significant heterogeneity among the three trials (p = 0.7, I^2 = 0%). The same benefit was shown considering the whole study population, including the minority of patients without metastates (HR 0.63, 95% CI 0.57 –

0.70, p < 0.001) (**Figure 3, panel B).** Very similar results were obtained in the exploratory analysis including also the docetaxel + zoledronic acid arm of the STAMPEDE trial: HR 0.63 (95%CI 0.56 – 0.70, p<0.001) in metastatic patients (**Figure 3, panel C**), HR 0.63 (95%CI 0.57 – 0.70, p<0.001) in all patients (**Figure 3, panel D**).

Conclusions.

This meta-analysis shows that the addition of docetaxel to ADT in patients with metastatic, hormone-sensitive prostate cancer is associated with a significant improvement in overall survival and progression-free survival.

A quantitative synthesis of the evidence currently available about this treatment strategy can be really helpful for clinical decisions, because three recent, different phase III trials (GETUG-AFU-15 [22,27], CHAARTED – E3805 [23], STAMPEDE [24]) tested the activity of docetaxel in combination with endocrine therapy in the “early” setting of hormone-sensitive prostate cancer. To the best of our knowledge, there are no other trials conducted with docetaxel in the same setting, and this meta-analysis represents the synthesis of all the evidence produced to date. Notably, in GETUG-AFU-15 trial, the first trial to be published, the concomitant administration of docetaxel with ADT versus ADT alone did not show a significant impact in terms of OS [22, 27]. On the contrary, CHAARTED – E3805 trial showed a significant OS improvement for ADT plus docetaxel [28], adding fuel to the scientific debate about the opportunity of this therapeutic option in hormone-sensitive prostate cancer patients. In our meta-analysis, that also included the recent results of the “third- comer”, the STAMPEDE trial [24], the addition of docetaxel to ADT in metastatic patients was associated with a statistically significant increase in overall survival, with a moderate, non significant heterogeneity among the three available RCTs. Of note, the absence of statistical heterogeneity increases the validity of the result, allowing a global, unambiguous interpretation of all the evidence available. Of course, a meta-analysis based on individual patient data (IPD) would represent the best synthesis of evidence, allowing for data checking, updated follow-up compared to publications, calculation and comparison of times to events, and for investigation of treatment heterogeneity in subgroups [29]. However, in the absence of IPD meta-analysis, a meta-

analysis based on abstracted data can be considered an acceptable surrogate, allowing a timely synthesis of all the available trials.

The efficacy showed by docetaxel in combination with ADT in hormone-sensitive patients is not surprising due to strong biological basis. Recent evidences show that one of the mechanisms responsible for progression from hormone-sensitive to castration-resistant phase of disease is the clonal selection and proliferation of pre-existing AR-independent cells, able to survive in a low androgen levels environment [19]. Therefore it is reasonable to assume that, since its onset, prostate cancer is a heterogeneous disease where coexist AR-positive and AR-negative cells [19, 30]. Both these cellular clones are likely involved in progression to castration-resistant disease [19]. Docetaxel administration concurrent to ADT in hormone-sensitive prostate cancer patients allows to inhibit the growth of the pre-existing AR-insensitive clones, killing these cells earlier when they are still a small number and before the development of multiple escape mechanisms. Moreover, preclinical data show that the adaptive response to ADT by prostate cancer cells is mediated by both ligand-dependent AR activation and ligand-independent AR activation and by mechanisms of progression bypassing AR signaling [19,31]. Taxanes are able to interfere with several steps of these resistance mechanisms. Emerging preclinical data demonstrated that taxanes could inhibit AR signaling pathway [32]. In fact, these cytotoxic drugs interfere with polymerization of microtubules, blocking AR nuclear translocation and AR-induced gene expression [32,33]. Therefore docetaxel could act synergistically with endocrine therapy, because it impairs AR activity [32,33]. Additionally, chemotherapy may also kill cells that escape ADT through activation of AR-independent survival pathways [34].

From a clinical point of view, there are several potential advantages in administering chemotherapy to metastatic prostate cancer patients in an early phase of disease. In the hormone-sensitive setting, patients are, on average, in better clinical conditions compared

to castration-resistant setting, due to lower burden of disease. Consequently, they are able to better tolerate chemotherapy and to maintain adequate drug dose intensity. Moreover, a greater number of patients is eligible for chemotherapy; in the castration-resistant setting, on the contrary, a relevant number of patients cannot receive chemotherapy, due to worsening of performance status and clinical conditions.

Our meta-analysis shows an improvement in OS that is not only statistically significant, but also clinically relevant. The addition of docetaxel to ADT is associated with a 27% reduction in the risk of death of metastatic patients (Hazard Ratio 0.73), and the reduction in the risk of death is as high as 33% in patients with high-volume disease (Hazard Ratio 0.67). In absolute terms, such a benefit is rarely obtained in the setting of advanced solid tumors: difference in median OS for metastatic patients was more than 13 months in the CHAARTED – E3805 trial [23], and 18 months in the STAMPEDE trial [24]. Much smaller benefits have been often judged sufficient to change clinical practice in metastatic prostate cancer, as well as in other settings. However, we recognize that a careful selection of patients to be treated with up-front docetaxel is essential for a favorable benefit / risk ratio. Subgroup data of the CHAARTED trial had suggested that the benefit associated with concomitant administration of docetaxel with ADT, at least in early analysis, was more pronounced in patients with “high-volume” disease than in patients with “low-volume” disease [28, 23]. Definition of “high-volume” disease follows previous robust data showing that, in patients with hormone-sensitive disease, the presence of extensive disease (visceral metastases or appendicular skeletal involvement) is related to a worse prognosis [35-37]. In both the CHAARTED – E3805 (based on a prospective definition) and the GETUG-AFU 15 (based on a retrospective assessment), “high-volume” disease was defined as the presence of visceral metastases or the presence of at least 4 bone lesions, with 1 or more lesions in any bone beyond the spine / pelvis. However, based on subgroup data available for those 2 trials [23, 27], we performed an exploratory

analysis of treatment efficacy according to disease volume: although the statistical test for interaction is characterized by a limited statistical power, we did not demonstrate a significant interaction between disease volume and treatment efficacy. Importantly, this absence of significant interaction does not allow to state that the addition of docetaxel to ADT is not effective in patients with low-volume metastatic disease. A longer follow-up with a higher number of events in these latter patients, together with the availability of this subgroup analysis also in the STAMPEDE trial, could increase the statistical power of the analysis. With the currently available evidence, however, no definitive statement can be made about the interaction between docetaxel efficacy and disease volume.

With the exception of a subgroup of patients eligible for the STAMPEDE trial, the majority of patients included in the 3 trials had metastatic disease. Other trials have tested the efficacy of the addition of docetaxel to androgen deprivation therapy in patients with high-risk, localized prostate cancer [25,26]. However, the definition of the role of docetaxel in patients with high-risk, localized prostate cancer is beyond the scope of this meta-analysis.

Of course, particular attention should be given to toxicity associated with combination treatment. In the experimental arm of GETUG-AFU 15 study, four treatment-related deaths were reported (one due to febrile neutropenia, one neutropenia with infection, one multiorgan failure, and one pulmonary embolism), compared to no treatment-related deaths with ADT alone [22]. In CHAARTED – E3805 trial, only one treatment-related death (sudden death) occurred in combination arm [23]. Although these numbers, overall considered, are quite reassuring, it is well known that patients enrolled in clinical trials are selected compared to all patients treated in daily clinical practice, in terms of age, performance status, comorbidities. For instance, patients older than 70 years are a relevant proportion of those treated in clinical practice, but were quite under-represented in

the 3 trials. In the CHAARTED trial, subgroup analysis according to age supports docetaxel efficacy also in elderly patients, but they represented only 23% of total study population [23]. Although a potential explanation is that the age of metastatic presentation of patients eligible for these 3 trials could be younger than the whole population of patients with new diagnosis of earlier stage prostate cancer, we believe that the main reason for the under-representation of elderly patients in the trials included in this meta-analysis is the selection bias, because patients had to be fit enough to receive chemotherapy with docetaxel [38]. In any case, chemotherapy toxicity is often worse in the “real world” population, compared with the toxicity reported in clinical trials. Therefore, clinicians must properly take into account some relevant clinical factors (performance status, concomitant diseases) before considering the addition of docetaxel to ADT, in order to reduce the risk of severe toxicity, that could negatively affect quality of life and, in worst cases, survival.

In conclusion, our meta-analysis clearly shows a significant impact on overall survival with the concomitant administration of docetaxel and androgen-deprivation treatment in patients with metastatic, hormone-sensitive prostate cancer patients. Considering the absence of heterogeneity among the available trials, and the balance between magnitude of efficacy and risk of toxicity, combination of chemotherapy and hormonal treatment should be reasonably offered to patients with metastatic disease, if judged eligible for chemotherapy. Higher statistical power would be needed to better understand the interaction, if any, between the efficacy of docetaxel and the volume of disease.

Figure legends.

Figure 1. Forest plots of hazard ratios for overall survival from three randomized trials of docetaxel added to androgen-deprivation therapy (ADT), compared with ADT alone, in patients with advanced, hormone-sensitive prostate cancer. Pooled HRs were computed using random-effect models. The bars indicate 95% confidence intervals (CI). Panel A (only metastatic patients) and panel B (all randomized patients) consider only comparisons between docetaxel + ADT vs. ADT alone. Panel C (only metastatic patients) and panel D (all randomized patients) show a sensitivity analysis considering also the comparison of docetaxel + zoledronic acid + ADT vs. ADT alone in the STAMPEDE trial.

Figure 2. Forest plots of hazard ratios for overall survival (subgroup analysis according to disease volume: patients with “high-volume” disease and patients with “low-volume” disease) in two randomized trials of docetaxel added to androgen-deprivation therapy (ADT), compared with ADT alone, in patients with metastatic, hormone-sensitive prostate cancer. Pooled HRs were computed using random-effect models. The bars indicate 95% confidence intervals (CI). Definition of “high-volume” disease and “low-volume” disease is detailed in the text.

Figure 3. Forest plots of hazard ratios for biochemical progression-free survival from three randomized trials of docetaxel added to androgen-deprivation therapy (ADT), compared with ADT alone, in patients with advanced, hormone-sensitive prostate cancer. Pooled HRs were computed using random-effect models. The bars indicate 95% confidence intervals (CI). Panel A (only metastatic patients) and panel B (all randomized patients) consider only comparisons between docetaxel + ADT vs. ADT alone. Panel C (only

418 metastatic patients) and panel D (all randomized patients) show a sensitivity analysis
419 considering also the comparison of docetaxel + zoledronic acid + ADT vs. ADT alone in
420 the STAMPEDE trial.
421
422 **Supplemental Figure 1.** Selection process of randomized trials eligible for inclusion in
423 the meta-analysis.

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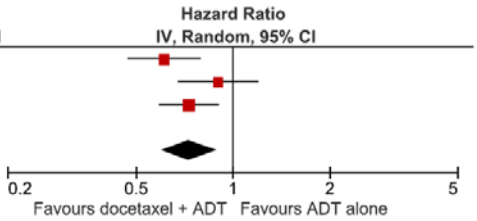
A

Outcome: overall survival (only metastatic patients)

Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
CHAARTED	-0.4943	0.133	397	393	32.1%	0.61 [0.47, 0.79]
GETUG-AFU 15	-0.1054	0.1468	192	193	28.8%	0.90 [0.67, 1.20]
STAMPEDE Docetaxel	-0.3147	0.1086	362	725	39.1%	0.73 [0.59, 0.90]
Total (95% CI)			**951**	**1311**	**100.0%**	**0.73 [0.60, 0.90]**

Heterogeneity: Tau² = 0.02; Chi² = 3.86, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 3.03 (P = 0.002)

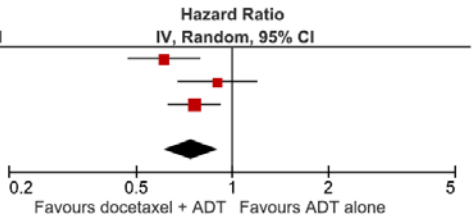


B

Outcome: overall survival (all randomized patients)

Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
CHAARTED	-0.4943	0.133	397	393	30.8%	0.61 [0.47, 0.79]
GETUG-AFU 15	-0.1054	0.1468	192	193	27.5%	0.90 [0.67, 1.20]
STAMPEDE Docetaxel	-0.2744	0.0957	592	1184	41.7%	0.76 [0.63, 0.92]
Total (95% CI)			**1181**	**1770**	**100.0%**	**0.74 [0.61, 0.91]**

Heterogeneity: Tau² = 0.01; Chi² = 3.96, df = 2 (P = 0.14); I² = 49%
Test for overall effect: Z = 2.95 (P = 0.003)



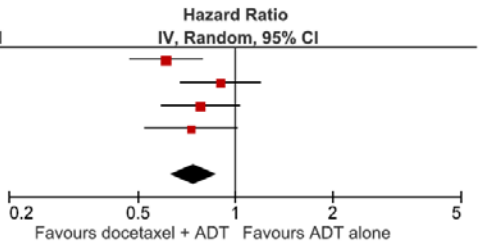
C

Outcome: overall survival (only metastatic patients)

Sensitivity analysis including the docetaxel + zoledronic acid arm

Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
CHAARTED	-0.4943	0.133	397	393	28.8%	0.61 [0.47, 0.79]
GETUG-AFU 15	-0.1054	0.1468	192	193	25.0%	0.90 [0.67, 1.20]
STAMPEDE Doc + Zol	-0.2485	0.1437	365	725	25.8%	0.78 [0.59, 1.03]
STAMPEDE Docetaxel	-0.3147	0.1678	362	725	20.4%	0.73 [0.53, 1.01]
Total (95% CI)			**1316**	**2036**	**100.0%**	**0.74 [0.63, 0.88]**

Heterogeneity: Tau² = 0.01; Chi² = 4.03, df = 3 (P = 0.26); I² = 26%
Test for overall effect: Z = 3.49 (P = 0.0005)



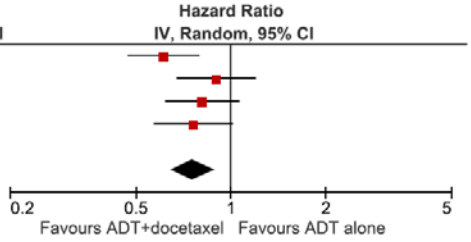
D

Outcome: overall survival (all randomized patients)

Sensitivity analysis including the docetaxel + zoledronic acid arm

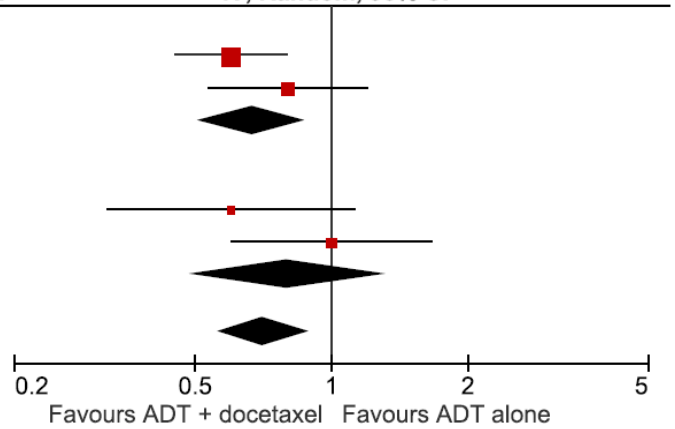
Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
CHAARTED	-0.4943	0.133	397	393	27.1%	0.61 [0.47, 0.79]
GETUG-AFU 15	-0.1054	0.1468	192	193	23.6%	0.90 [0.67, 1.20]
STAMPEDE Doc + Zol	-0.2107	0.1374	593	1184	25.9%	0.81 [0.62, 1.06]
STAMPEDE Docetaxel	-0.2744	0.1473	592	1184	23.5%	0.76 [0.57, 1.01]
Total (95% CI)			**1774**	**2954**	**100.0%**	**0.76 [0.64, 0.89]**

Heterogeneity: Tau² = 0.01; Chi² = 4.27, df = 3 (P = 0.23); I² = 30%
Test for overall effect: Z = 3.30 (P = 0.0010)



Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
1.11.1 High volume						
CHAARTED	-0.5108	0.1468	263	250	43.8%	0.60 [0.45, 0.80]
GETUG-AFU 15	-0.2231	0.2069	92	91	26.2%	0.80 [0.53, 1.20]
Subtotal (95% CI)			**355**	**341**	**70.0%**	**0.67 [0.51, 0.88]**
1.11.2 Low volume						
CHAARTED	-0.5108	0.3207	134	143	12.3%	0.60 [0.32, 1.12]
GETUG-AFU 15	0	0.2606	100	102	17.7%	1.00 [0.60, 1.67]
Subtotal (95% CI)			**234**	**245**	**30.0%**	**0.80 [0.49, 1.32]**
Total (95% CI)			**589**	**586**	**100.0%**	**0.71 [0.56, 0.89]**

Heterogeneity: Tau² = 0.01; Chi² = 3.62, df = 3 (P = 0.31); I² = 17%
Test for overall effect: Z = 2.93 (P = 0.003)
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%

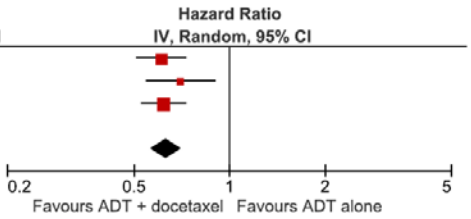


A

Outcome: progression-free survival (only metastatic patients)

Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
CHAARTED	-0.4943	0.0914	397	393	36.9%	0.61 [0.51, 0.73]
GETUG-AFU 15	-0.3567	0.1282	192	193	18.7%	0.70 [0.54, 0.90]
STAMPEDE Docetaxel	-0.478	0.0833	362	725	44.4%	0.62 [0.53, 0.73]
Total (95% CI)			**951**	**1311**	**100.0%**	**0.63 [0.57, 0.70]**

Heterogeneity: Tau² = 0.00; Chi² = 0.84, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 8.31 (P < 0.00001)

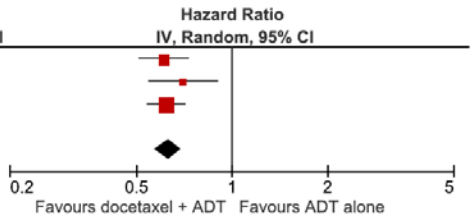


B

Outcome: progression-free survival (all randomized patients)

Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
CHAARTED	-0.4943	0.0914	397	393	31.4%	0.61 [0.51, 0.73]
GETUG-AFU 15	-0.3567	0.1282	192	193	15.9%	0.70 [0.54, 0.90]
STAMPEDE Docetaxel	-0.478	0.0705	592	1184	52.7%	0.62 [0.54, 0.71]
Total (95% CI)			**1181**	**1770**	**100.0%**	**0.63 [0.57, 0.70]**

Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 9.06 (P < 0.00001)



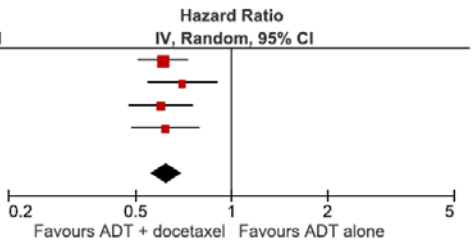
C

Outcome: progression-free survival (only metastatic patients)

Sensitivity analysis including the docetaxel + zoledronic acid arm

Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
CHAARTED	-0.4943	0.0914	397	393	37.6%	0.61 [0.51, 0.73]
GETUG-AFU 15	-0.3567	0.1282	192	193	19.1%	0.70 [0.54, 0.90]
STAMPEDE Doc + Zol	-0.5108	0.1173	365	725	22.9%	0.60 [0.48, 0.76]
STAMPEDE Docetaxel	-0.478	0.1243	362	725	20.4%	0.62 [0.49, 0.79]
Total (95% CI)			**1316**	**2036**	**100.0%**	**0.63 [0.56, 0.70]**

Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 8.35 (P < 0.00001)



D

Outcome: progression-free survival (all randomized patients)

Sensitivity analysis including the docetaxel + zoledronic acid arm

Study or Subgroup	log[Hazard Ratio]	SE	Docetaxel + ADT Total	ADT alone Total	Weight	Hazard Ratio IV, Random, 95% CI
CHAARTED	-0.4943	0.0914	397	393	33.2%	0.61 [0.51, 0.73]
GETUG-AFU 15	-0.3567	0.1282	192	193	16.9%	0.70 [0.54, 0.90]
STAMPEDE Doc + Zol	-0.478	0.1059	593	1184	24.8%	0.62 [0.50, 0.76]
STAMPEDE Docetaxel	-0.478	0.1052	592	1184	25.1%	0.62 [0.50, 0.76]
Total (95% CI)			**1774**	**2954**	**100.0%**	**0.63 [0.57, 0.70]**

Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 3 (P = 0.84); I² = 0%
Test for overall effect: Z = 8.78 (P < 0.00001)

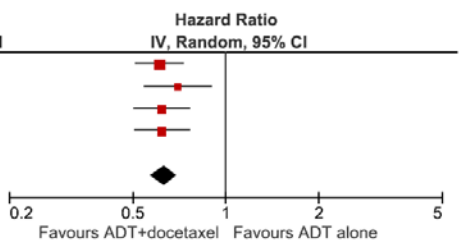


Table 1. Characteristics of the 3 trials included in the meta-analysis

	GETUG-AFU 15 [22,27]	CHAARTED – E3805 [23]	STAMPEDE [24]
Main inclusion criteria			
Age	Older than 18. No upper limit declared in the methods.	Both younger than 70 and older than 70 were eligible (stratification criteria).	Not specified.
Performance status	Karnofsky >= 70	ECOG 0-2 (2 only if due to prostate cancer) (0-1 vs 2 stratification criteria)	WHO 0-2
Stage	Metastatic prostate cancer (High-volume vs low-volume assessed retrospectively)	Metastatic prostate cancer (High-volume vs low-volume stratification criteria)*	Prostate cancer if metastatic, node-positive or >=2 among: • Stage T3/T4 • PSA>=40ng/ml • Gleason 8-10
Previous treatment	Previous chemotherapy for metastatic disease was not allowed. In the neoadjuvant and adjuvant settings or in the context of isolated PSA increase, previous chemotherapy or ADT, or both, were allowed, with the condition that the treatment had been discontinued at least 12 months before inclusion in the study.	No prior docetaxel was allowed. Adjuvant ADT was allowed, but <24 months (<=12 months vs >12 months stratification criteria) and interval between end of adjuvant treatment and progression > 12 months.	Prior chemotherapy was not allowed. Long-term anti-androgen therapy was not allowed. Short periods of prior anti-androgens to cover tumour flare were allowed. Adjuvant or neo-adjuvant hormone therapy had to be completed at least 12 months before the trial, and duration of therapy had to be no longer than 12 months.

(table continues in next page)

Table 1. (continued)

	GETUG+AFU 15 [22,26]	CHAARTED – E3805 [23]	STAMPEDE [24]
Treatment			
ADT (both arms)	Orchiectomy or LHRH agonists, alone or combined with non-steroidal antiandrogens	Medical or surgical castration. Use of a nonsteroidal antiandrogen at the time of initiation of therapy was at the discretion of the investigator..	LHRH analogues or LHRH antagonists, or bilateral orchidectomy according to local practice
Docetaxel (experimental arm)	Docetaxel (75 mg/m^2 i.v. day 1 q3w); up to 9 cycles. Standard corticosteroids premedication, no daily prednisone.	Docetaxel (75 mg/m^2 i.v. day 1 q3w); up to 6 cycles. Standard dexamethasone premedication, no daily prednisone.	Docetaxel (75 mg/m^2 i.v. day 1 q3w); up to 6 cycles. Standard dexamethasone premedication, daily prednisolone 10 mg.
Timing of treatment	Docetaxel within 2 months of ADT start.	Docetaxel within 4 months of ADTstart.	Randomization within 12 weeks of ADT start.
Study design			
Primary endpoint	Overall survival	Overall survival	Overall survival
Hypothesis	Increase in 3-yr OS from 50% to 65%	33% increase in median OS (from 33 to 44 months in high-volume, from 67 to 89 months in low-volume)	25% increase in overall survival.
Patients' enrollment and follow-up			
Accrual start	October 2004	July 2006	October 2005
Accrual stop	December 2008	November 2012	March 2013
Number of patients			
ADT alone	193	393	1184

ADT + docetaxel	192	397	592
ADT + docetaxel + zoledronic acid			593
Median follow-up	82.9 months	28,9 months	n.a.

ADT: androgen-deprivation treatment; ECOG: Eastern Cooperative Oncology Group; WHO: World Health Organization; PSA: prostate-specific antigen; LHRH: luteinizing hormone – releasing hormone; OS: overall survival; n.a.: not available.

**after amendment. In the initial protocol version, only high-volume patients were eligible.*

Table 2. Main characteristics of enrolled patients

	GETUG-AFU 15 [22,27]	CHAARTED – E3805 [23]	STAMPEDE [24] (whole trial*)
Age	ADT alone: Median 64 years (IQR 58-70)	ADT alone: Median 63 years (range 39-91)	Median 65 years (range 40-84)
	ADT +docetaxel: Median 63 years (IQR 57-68)	ADT + docetaxel: Median 64 years (range 36-88)	
Performance status	ADT alone: Median Karnofsky 100% (IQR range 90%-100%)	ADT alone: ECOG 0: 69% ECOG 1: 29% ECOG 2: 1.5%	WHO PS0: 76% WHO PS1: 21% WHO PS2: 1%
	ADT+ docetaxel: Median Karnofsky 100% (IQR 90%-100%)	ADT + docetaxel: ECOG 0: 70% ECOG 1: 29% ECOG 2: 1.5%	
Gleason score	ADT alone (unknown 2/193): Gleason 2-6: 7% Gleason 7: 34% Gleason 8-10: 59%	ADT alone (unknown 46/393): Gleason 4-6: 6% Gleason 7: 24% Gleason 8-10: 70%	n.a.
	ADT+ docetaxel (unknown 5/192): Gleason 2-6: 10% Gleason 7: 35% Gleason 8-10: 55%	ADT + docetaxel (unknown 39/393): Gleason 4-6: 6% Gleason 7: 27% Gleason 8-10: 67%	
PSA at randomization	ADT alone: Median 26 (IQR 5 – 127)	ADT alone: Median 52.1 (range 0.1 – 8056.0)	n.a.
	ADT+ docetaxel: Median 27 (IQR 5 – 106)	ADT + docetaxel: Median 50.9 (range 0.2 – 8540.1)	
Stage	ADT alone: 100% metastatic	ADT alone: 100% metastatic	61% Metastatic 15% Node positive M0 24% N0 M0
	ADT + docetaxel: 100% metastatic	ADT + docetaxel: 100% metastatic	

Metastatic at diagnosis	ADT alone: 67%	ADT alone: 73% had not received prior local therapy	94% of randomized patients had not received previous local therapy
	ADT + docetaxel: 76%	ADT + docetaxel: 73% had not received prior local therapy	
Presence of visceral metastases	ADT alone: 11% lung 2% liver	ADT alone: 17%	n.a.
	ADT + docetaxel: 11% lung 5% liver	ADT + docetaxel: 14%	
Volume of metastatic disease	ADT alone: 52% low-volume 48% high-volume	ADT alone: 36% low-volume 64% high-volume	n.a.
	ADT + docetaxel: 53% low-volume 47% high-volume	ADT + docetaxel: 34% low-volume 66% high-volume	

IQR: interquartile range; ADT: androgen- deprivation treatment; PS: performance status; PSA: prostate specific antigen; M0: absence of distant metastases; N0: absence of nodal metastases; n.a.: not applicable.

**details by arm are not provided*

Table 3. Overall survival data reported in each single trial.

	GETUG-AFU 15 [22,27]	CHAARTED – E3805 [23]	STAMPEDE [24]	
			All patients	Metastatic patients
Number of patients				
ADT alone	193	393	1184	725
ADT + docetaxel	192	397	592	362
ADT + docetaxel + zoledronic acid			593	365
Number of events				
ADT alone	212 (both arms)	136	405	343
ADT + docetaxel		101	165	134
ADT + docetaxel + zoledronic acid			181	152
Median OS				
ADT alone	46.5 months	44.0 months	67 months	43 months
ADT + docetaxel	60.9 months	57.6 months	77 months	65 months
ADT + docetaxel + zoledronic acid			72 months	n.a.
Hazard Ratio (95% confidence interval)				
ADT + docetaxel vs. ADT alone	0.9 (0.7 – 1.2), p=0.4	0.61 (0.47 – 0.80), P<0.001	0.76 (0.63 – 0.91), p=0.003	0.73 (0.59 – 0.89), p=0.002
ADT + docetaxel + zoledronic acid vs. ADT alone			0.81 (0.68 – 0.97), p=0.02	0.78 (0.65 – 0.95), p=n.a.

ADT: androgen-deprivation treatment; n.a.: not available.

Supplementary Table A1. Definition of biochemical progression-free survival

GETUG-AFU 15 [22]	CHAARTED – E3805 [23]	Stampede [24]
Time to PSA progression, clinical progression or death. Biochemical progression was defined with the PSA Working Group definition: 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 of at least 25% above the nadir and of at least 5 ng/mL.	Time to castration-resistant prostate cancer: time until documented clinical or serologic progression with a testosterone level of less than 50 ng per deciliter (or source documentation of medical castration or surgical castration). Disease progression on imaging was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0. Serologic progression was defined as an increase in the PSA level of more than 50% above the nadir reached after the initiation of ADT, with two consecutive increases at least 2 weeks apart. The date of a first recorded increase of more than 50% above the nadir was deemed the date of progression. If the nadir level was less than 2 ng per milliliter, a minimum increase of more than 2 ng per milliliter was required.	Failure-free survival: First event among PSA failure, local failure, lymph node failure, distant metastases, prostate cancer death. PSA failure definition: If PSA fall >= 50%: • 24 week nadir + 50% and • >4 ng/ml If PSA fall < 50%: • Failure at t=0

PSA: prostate-specific antigen; ADT: androgen deprivation therapy.