Real World Evaluation of Upfront Docetaxel in Metastatic Castrate Sensitive Prostate Cancer

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Abstract

Background: Recent randomised phase III trials demonstrate survival benefit for the addition of upfront docetaxel to androgen deprivation therapy (ADT) in metastatic castrate sensitive prostate cancer (mCSPC). Following its implementation in routine care, this combined treatment strategy needs further evaluation in a real world setting.

Methods: A multicentre retrospective cohort study in the South East Health care region of Sweden was conducted. All patients given upfront docetaxel for mCSPC from July 2015 until December 2017 were included. Primary endpoint was progression free survival (PFS) at 12 months and secondary endpoints were PFS at 24 months, overall survival (OS), treatment intensity, adverse events, and unplanned hospitalisations. Exploratory analyses on potentially prognostic parameters were performed.

Results: 94 patients were eligible and formed the study cohort. PFS at 12 and 24 months were 75% (95% CI 66-84) and 58% (46-70). OS at 12 and 24 months were 93% (87-99) and 86% (76-96). 91% (n=86) initiated docetaxel according to the standard protocol of 75 mg/m2 every 3 weeks (6 cycles), whereas 9% (n=8) received a modified protocol of 50 mg/m2 every 2 weeks (9 cycles). The average overall dose intensity for those commencing standard treatment was 91%. Univariate cox regression analyses revealed that baseline PSA >180 vs <180 and presence vs absence of distant metastases were negative prognostic factors (HR 2.86, 95% CI 1.39-5.87, p =0.0041 and 3.36, 95% CI 1.03-10.96, p=0.045). Following multivariate analysis, the statistical significance remained for PSA (2.51, CI 1.21-5.19, p =0.013) but not for metastatic status (2.60, 95% CI 0.78-8.65, p=0.12). Febrile neutropenia was recorded in 21% (n=20) and 26% (n=24) had at least one episode of unplanned hospitalisation under and up to 30 days after the treatment course.

Conclusions: The outcome and safety profile of upfront docetaxel in addition to androgen deprivation therapy in metastatic castrate sensitive prostate cancer appear similar in real world and randomised controlled populations. Further implementation of this treatment strategy is encouraged.

Background

Prostate cancer (PC) is the second most common malignancy in men. In 2018, more than 1.2 million new cases were reported worldwide which corresponds to about 7% of all cancers [1]. In Sweden, the annual incidence is about 10,500, with a median age of onset of 68 years [2] While the 5-year overall survival (for all stages combined) is continuously improving and now exceeds 90%, the prognosis for patients presenting with upfront metastases remains less optimistic, with expected overall survival in the range of 30–36 months and 5-year survival about 30% [3–9].

The majority of patients with newly diagnosed mPC will initially respond to androgen deprivation therapy (ADT) and are classified as castrate sensitive (mCSPC). Following months to years of ADT, the disease will however become resistant to ADT and thus defined as metastatic castrate refractory prostate cancer (mCRPC). In mCRPC, palliative chemotherapy with docetaxel may offer temporarily relief but survival

benefits are usually limited to a few months [4]. However, two recent multicentre trials demonstrated a considerable benefit for docetaxel when this drug was introduced early, i.e. in the initial castrate sensitive phase of the disease [10, 11].

In the CHAARTED study, 790 men were randomised to six cycles of docetaxel plus ADT vs ADT alone. Patients were stratified according to high (visceral metastases or ≥ 4 bone lesions with ≥ 1 beyond the vertebral bodies and pelvis) or low-volume disease. Median overall survival (OS) was 58 months for men treated with ADT plus docetaxel and 44 months for ADT alone. In men with high volume disease, the additive effect of docetaxel was even better with a median OS benefit of 17 months (49 vs 32 months) [11].

STAMPEDE was a multi-armed, multistage trial that included 2962 men with both metastatic and non-metastatic PC. Stratified randomisation (2:1:1:1) allocated men to standard of care (SOC); ADT with or without radiotherapy, SOC plus docetaxel, SOC plus zoledronic acid, and SOC plus docetaxel plus zoledronic acid. Sixty-one percent had distant metastatic and 15% had node positive disease. The remaining 24% presented with non-metastatic high risk locally advanced disease (T3/4, PSA ≥ 40 ng/ml, and/or Gleason score 8–10). In the STAMPEDE trial, median OS was improved by 10 months for SOC plus docetaxel compared with SOC alone (81 vs 71 months). For the group with metastatic disease the OS benefit was 15 months for SOC plus docetaxel vs SOC alone (60 vs 45 months) [10, 12, 13].

A smaller French study, GETUG-AFU 15, including around 400 patients that were randomised to receive ADT alone or ADT plus docetaxel [14], could not confirm the findings of CHAARTED and STAMPEDE. The French study did not reveal any statistically significant survival benefit with upfront docetaxel treatment (median OS 59 months in the ADT plus docetaxel group vs 54 months in the ADT alone group). The different outcomes of the various trials may depend on discrepancies of study populations. In the STAMPEDE and CHAARTED trials, the median PSA levels were almost twice as high as the median PSA reported in the GETUG-15 population. This indicates that the disease stage was generally more advanced in the former cohorts compared to the latter. Whereas 66% in CHAARTED were reported to have high volume of metastases, only 48% were classified as such in GETUG-15. Differences were also observed in Gleason Score (GS) with a GS ≥ 8 reported for nearly 61 % of the population in CHAARTED and 74% in STAMPEDE compared to 55% in the GETUG-15 [10, 11, 14]. Together, these findings suggest that the CHAARTED and STAMPEDE trials included patients with worse prognosis than the subjects enrolled in the GETUG-15 study.

Based on the promising results of STAMPEDE and CHAARTED, the addition of docetaxel to ADT in early mCSPC was introduced in the Swedish national guidelines for PC in 2015. To be eligible for this therapy, patients should be in good general condition and without significant comorbidities [15]. The eligibility conditions were adopted from the reported characteristics of the STAMPEDE and CHAARTED populations.

Since its introduction in routine care, it remains largely unknown to what extent the outcomes observed in the STAMPEDE and CHAARTED trials are evident in patients treated outside the frame of a randomised

controlled trial. The present study was therefore designed to assess the real world outcome and safety of early docetaxel treatment for patients with mCSPC. To fully reflect the real world situation with patients of all ages and with or without concomitant comorbidities, all consecutive patients who received this treatment in the South East health care region of Sweden since 2015 were included.

Methods

A retrospective multicentre cohort study of all men diagnosed with primary mCSPC in the South East health care region of Sweden was designed. This region covers approximately 1.1 million citizens and include the oncology departments of Linköping, Jönköping and Kalmar. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethics Review board in Linköping, Region Östergötland, Sweden (diary number 2018/3–31). Based on the retrospective and noninterventional nature of the study, and the absence of publication of individual data, the Regional Ethics Review board in Linköping, Region Östergötland, Sweden (diary number 2018/3–31) did not consider it possible or necessary to obtain written informed consent.

Inclusion criteria were as follows: Male sex, age of 18 years or older, evidence of newly diagnosed mCSPC between July 2015 and December 2017 (ICD-10 code C61.x), defied as either node positive (N+) and/or distant metastatic (M+) disease, and administration of at least one cycle of upfront docetaxel chemotherapy in addition to ADT. Exclusion criteria were recurrent disease, castrate refractory disease, and patient's refusal to undergo ADT.

The Swedish Cancer Registry (SCR) was used to identify eligible patients (https://www.socialstyrelsen.se/statistik-och-data/register/alla-register/cancerregistret/). Reporting to the SCR is mandatory, and the registry achieves over 95% coverage for all malignant tumours. The CSAM Cytodos software system (CSAM Health AS, Oslo, Norway), a software being used for the prescription and administration of chemotherapy at all participating centres, was used to identify those treated with docetaxel.

Medical records were reviewed and data were registered in a standardised case report form where patient and tumour characteristics, baseline biochemistry, performance status according to Eastern Cooperative Oncology Group (ECOG), treatment regimens, toxicity parameters, PSA levels, relapse, and vital status were recorded. Patient and tumour characteristics were recorded according to the TMN classification (8th edition by Union for International Cancer Control [UICC] 2017), GS according to International Society of Urological Pathology (ISUP) 2014, and histology according to WHO 2004.

The patients included had received docetaxel according to any of two different regimens; either by intravenous infusion every three weeks at doses of 75mg/m² for a total of six cycles (according to the CHAARTED and STAMPEDE treatment protocols) or at a dose of 50 mg/m² in two weeks cycles for a total of nine cycles according to local guidelines. The latter was used by one site for patients whom, for any reason and at the treating oncologist's discretion, were deemed unfit to receive the 75mg/m² regimen.

Bone marrow toxicity was evaluated by blood cell counts beside other standard biochemical parameters prior to each dose. In general, treatment response was evaluated with PSA levels at day 18–20 in every cycle and, for most patients, with X-ray computed tomography at the end of the sixth cycle (or at the ninth cycle of the 50 mg/m2 two weeks cycles).

Primary endpoint was progression free survival (PFS) at 12 months. PFS was defined as time to biochemical progression in accordance with the CHAARTED protocol, where a serologic increase of the PSA level of more than 50% above nadir, reached after initiation of ADT and with two consecutive increases at least two weeks apart, clinical progression due to increasing symptoms, or deterioration or disease progression according to RECIST 1.0 were considered progression. If PSA nadir was less than 2 µg/l, a minimum increase of more than 2 µg/l was required [10, 11]. In addition, an alternative definition of progression according to the Swedish national guidelines, which stipulate serologic increase ≥ 25% from lowest PSA value after start of latest given treatment (and a minimum absolute increase of ≥ 2 µg/l), worsening of clinical symptoms, or radiological disease progression according to RECIST 1.0, was similarly applied[15].

Secondary endpoints were PFS at 24 months, overall survival (OS), treatment intensity including dose reductions, premature termination and protocol modifications, and safety of docetaxel treatment in terms of registered bone marrow toxicity and unplanned hospitalisations under and within 30 days after the last docetaxel treatment cycle. Patients were followed until death or May 18th 2018, whatever occurred first.

Statistical analysis:

All statistical analyses were carried out in the per protocol population, defined as all patients that received at least one dose of docetaxel. Patient characteristics and tumour and treatment data were reported as number and percentage for categorical variables and median and range for continuous variables. PFS at 12 and 24 months were estimated according to the CHAARTED [11] and the Swedish national guidelines [15] definitions of progressive disease, respectively. Median PFS and OS for the whole cohort and subgroups defined by age over and under median [68], PSA over and under median [180], comorbidities, and presence or absence of distant metastases, were estimated using Kaplan-Meier survival analyses and the significance of the differences in estimates of median survival was calculated using log rank test. Cox regression analysis with 95% confidence interval was used to evaluate hazard ratios for the same subgroups. P-values below 0.05 were considered statistically significant. Analyses were performed using IBM SPSS statistics software (IBM, version 25).

Results

Patients and baseline characteristics

A total of 94 patients with primary mCSPC treated with docetaxel and ADT were identified. Baseline characteristics are displayed in Table 1. For comparison, published data from CHAARTED [11] and

STAMPEDE [10] are similarly displayed in Table 1. Median age was 68 years (range 49–79). Comorbidities were present in 53% (n = 50) of which hypertension was the most prevalent. Regarding ECOG PS, data were only available in 64 (70%) of the cases. Among those, an overwhelming majority were ECOG PS 0–1 (n = 61, 95%). Median PSA at diagnosis was 180 (range 2-7367). Clinical TNM staging was recorded in 84 (90%) of the subjects, with T3N1M1 being the most common staging. Of those with distant metastases, bone metastases were most prevalent (n = 74, 79%) followed by lymph node metastases (n = 54, 57%). Most tumours (n = 60, 64%) were classified as GS 8–10.

Treatment data

While 82 (87%) of the patients received a combination of gonadotropin releasing hormone (GnRH) and a non-steroidal antiandrogen as castration method, nine (10%) were treated with GnRH alone and three (3%) were surgically orchidectomised. The median time from start of ADT until start of docetaxel was 63 days (range 8-400). The median duration of ADT was 331 days (range 5-1038) (Table 2). Seventy seven patients (82%) received docetaxel according to the 75 mg/m^2 every six weeks schedule and eight (8%) received docetaxel according to the modified schedule of 50 mg/m2 every two weeks.

Of those 77 patients commencing the 75 mg/m2 regimen, 63 (81 %) completed all 6 cycles. The mean administered dose (of 75 mg/m2 full dose) was 91%, corresponding to 139 mg docetaxel (Table 2).

Of those eight patients commencing the 50 mg/ m^2 schedule, four (50%) completed all 9 planned cycles. For this regime, the mean administered dose was 83% of full dose, corresponding to 86 mg docetaxel.

Nine patients started with the 75 mg/m2 schedule but switched to the 50 mg/m2 regimen during treatment. In this subgroup of patients, all nine fulfilled the expected 6 cycles.

In total, 33 (35%) underwent at least one dose reduction, 13 (14%) had a dose escalation, and 47 (50%) received the prescribed dose during the whole treatment period (Table 2).

Progression free and overall survival

PFS and OS in the entire cohort are displayed in Figs. 1 and 2. PFS at 12 months, in the total cohort of 94 patients, were 75% (95% CI 66%-84%) or 71% (95% CI 61%-81%) depending on whether the definition of CHAARTED/STAMPEDE or the Swedish national guidelines was employed. The corresponding proportions at 24 months were 58% (95% CI 46%-70%) and 55% (95% CI 43%-67%) (Table 2). OS at 12 and 24 months were 93% (95% CI 87%-99%) and 86% (95% CI 76%-96%). Median PFS and median OS were not reached by the data cut-off date. At time of analysis, 65 patients had evidence of disease (69%) and 14 had died (15%) (Table 1).The best response at end of docetaxel treatment was complete response (CR) for six subjects (6%), partial response (PR) (n = 50, 53%), stable disease (SD) (n = 15, 16%), and progressive disease (PD) (n = 11, 12%). Twelve (13%) of the patients were non-evaluable (NE) for PFS (Table 2). Median follow-up was 20 months.

Univariate and multivariate regression analyses of progression free and overall survival in subgroups

Cox regression analyses were performed to compare PFS and OS in the following subgroups: Age older than 68 years vs 68 years or younger, PSA higher than 180 µg/L vs less than 180 µg/L, comorbidities (yes/no) and absence of distant metastases vs presence of any distant metastases. For continuous variables (age and PSA), patients were dichotomised according to below or above the median value of the respective parameter. Univariate cox regression analyses revealed that baseline PSA higher than 180 and presence of distant metastases were negative prognostic factors (HR 2.86, 95% CI 1.39–5.87, p = 0.0041 and 3.36, 95% CI 1.03–10.96, p = 0.045). Following multivariate analysis, the statistical significance remained for PSA (2.51, CI 1.21–5.19, p = 0.013) but not for metastatic status (2.60, 95% CI 0.78–8.65, p = 0.12) (Table 3a). Similar and statistically significant findings on baseline PSA and PFS were evident when the Swedish national guidelines criteria for progressive disease were employed (Table 3b).

Safety

Table 4 displays registered side effects and bone marrow toxicity according to the National Cancer Institute Common Terminology Criteria for adverse Events (CTCAE version 4). Most strikingly, 20 (21%) of the patients experienced febrile neutropenia and 24 (26%) had at least one episode of unplanned hospitalisation under and up to 30 days after the docetaxel treatment course. Other reported adverse events, as well as reasons for early termination of the treatment, are presented in detail in Table 4.

Discussion

This population-based study explored the outcome and safety of combined upfront docetaxel and ADT in mCSPC in a real world cohort including the first 94 patients undergoing this treatment strategy in the South East Health Care Region of Sweden, reporting outcome and safety measures similar to previous findings in pivotal randomised controlled trials on the topic [10, 11] .

In the last few years, treatment of mCSPC with upfront docetaxel in addition to ADT has been widely implemented in the routine care in Sweden and elsewhere. This significant change of practice was mainly based on the results of two major randomised controlled trials CHAARTED and STAMPEDE [10, 11]. Whereas the results of these trials were extraordinary promising, less has been known about the outcome and safety of this treatment in a real world context, i.e. amongst patients who are treated outside the frame of a randomised controlled trial.

The present cohort displayed a PFS rate (based on the CHAARTED/STAMPEDE definition of progressive disease) of 75% and 58% at 12 and 24 months, respectively, closely corresponding to the outcomes displayed in the CHAARTED and STAMPEDE publications [10, 11]. Similarly, the present OS estimates at 12 and 24 months of 93% and 86% mirror the Kaplan-Meier curves of the two trial populations. Taken together, this indicates that the value of upfront docetaxel added to ADT in mCSPC appear similar in randomised controlled populations and this Swedish real world cohort.

There are some similarities and some differences between the present real world population and the patient populations of CHAARTED and STAMPEDE. In the present cohort the patients were slightly older with a median of 68 years compared to a median of 64 (CHAARTED) and 65 (STAMPEDE) in the randomised controlled trials. The vast majority of all patients (95–99%) in the real world cohort as well as the phase III trial populations presented with ECOG PS 0–1. On the other hand, baseline PSA levels were considerably higher in the real world cohort (median 180) compared to the controlled trial populations which displayed median PSA levels of 51 (CHAARTED) and 70 (STAMPEDE), potentially reflecting a higher disease burden in the real world cohort at the start of the treatment. Notably, patients with PSA above median had a significantly higher risk of progressive disease, which was reflected in univariate as well as multivariable regression analyses (Figs. 2a and 2b).

Further, the extent of metastatic disease appeared different in the two phase III trials and this real world cohort. The STAMPEDE trial reported that 61% of the total study population had metastatic disease and the CHAARTED trial, which only included patients with evidence of metastatic disease, reported 65% with high volume disease (these latter numbers were not available from the STAMPEDE publication). In this real world cohort, 80% had evidence of distant metastases while 20 % had non-distant metastases only. While metastatic burden was a negative prognostic factor in univariate regression analysis of the present cohort, the statistical significance did not remain following multivariable analysis.

Completion of all planned cycles was reported in 86% of the CHAARTED and 76% of the STAMPEDE trial populations. Similar figures were seen in the present cohort as 81% completed the entire treatment course and 35% (n = 33) underwent dose reductions. Notably, eight (8%) received a modified 50 mg/m2 every two weeks schedule from start, and nine (10%) converted from standard 75 mg/m2 every three weeks to this modified 50 mg/m2 protocol (switch). There is currently little evidence for this 50 mg/m2 protocol in mCSPC, and the deviation from standard of care probably reflects an eagerness to provide the treatment to frail and/or comorbid patients who otherwise would be considered not eligible for docetaxel. The low number of patients in this subgroup together with the finding that only 50% of the patients who began with 50 mg/m2 were able to fulfil all planned cycles mean that the efficacy and safety for this adapted treatment schedule remain unproven.

Safety data of the present study reveal that 21% of the patients experienced febrile neutropenia and, in total, 26% had at least one episode of unplanned hospitalisation under or shortly after the docetaxel treatment course. While only 4% had their treatments prematurely terminated due to febrile neutropenia, these findings still emphasises that the docetaxel 75 mg/m2 every three weeks regimen is a considerably toxic treatment. This might be particularly important when upfront docetaxel is considered for older and/or frail patients, who would not been eligible for the STAMPEDE and CHAARTED trials.

To our knowledge, this is the first study that systematically reports the real world outcome of upfront docetaxel in a Scandinavian context. Other real world studies, conducted in other countries and/or ethnical groups, largely corroborate our findings; Lavoie et al assessed the clinical effectiveness of upfront docetaxel in a Canadian setting, showing a similar outcome and safety data to ours with 12

months OS of 91% and 26% experiencing a grade 3–4 febrile neutropenia [16], and comparable outcomes were also reported in a German study [17] and in Northern American non-white populations[18]

The main strengths of the present study include the truly real world setup, covering all eligible patients in a reasonably large geographical region. As there are no non-governmental healthcare providers offering cancer chemotherapy in the South East Region in Sweden, every patient that was given the therapy and met the inclusion criteria were included. Another additional value is that the Swedish health care is generally available and publicly funded. This means that all individuals regardless of socio-economic status are offered similar treatment and follow-up programs.

The study's main weakness mirrors its main strength: the retrospective inclusion and the, to some extent, different treatments regimes prescribed make it more difficult to define the efficacy and the toxicity of the treatment schedule evaluated in the STAMPEDE and CHAARTED trials. The limited sample size means that subgroup analyses should be considered exploratory and their results should be interpreted with care.

Conclusions

This study provides additional evidence on the efficacy and safety of upfront docetaxel in a real world context of mCSPC. Progression free and overall survival appear similar in real world and randomised controlled trial settings. Febrile neutropenia remains a frequent and severe adverse event, and unplanned hospitalisations are common in patients undergoing this treatment. High baseline PSA indicates worse prognosis. In conclusion, the present results supports the implementation of upfront docetaxel plus ADT as part of the standard of care treatment strategy in mCSPC.

List Of Abbreviations

ADT androgen deprivation therapy

CR complete response

ECOG Eastern Cooperative Oncology Group

GnRH gonadotropin releasing hormone

GS Gleason Score

mCRPC metastatic castrate refractory prostate cancer

mCSPC metastatic castrate sensitive prostate cancer

mPC metastatic prostate cancer

NE non-evaluable

PR partial response

PS performance status

PD progression of disease

PC prostate cancer

SD stable disease

SOC standard of care

Declarations

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Availability of data and materials

The datasets used in the current study are available from the corresponding

author on request.

Authors’ contributions

JI, HG, EÅL and NOE designed the study. JI acquired the patient data with the help of DP, LP and MA at the respective sites. JI, HG, JR and NOE analysed the data. JI, HG and NOE drafted the first version of the manuscript. All authors were involved in the methodology and investigation and all read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethics Review board in Linköping, Region Östergötland, Sweden (diary number 2018/3-31). Based on the retrospective and noninterventional nature of the study, and the absence of publication of individual data, the Regional Ethics Review board in Linköping, Region Östergötland, Sweden (diary number 2018/3-31) did not consider it possible or necessary to obtain written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. 2018;68(6):394-424.
2. Socialstyrelsen. Cancer i siffror 2018. In: Socialstyrelsens artikelnummer: 2018-6-10. 2018.
3. Petrylak DP, Tangen CM, Hussain MH, Lara PN, Jr., Jones JA, Taplin ME, Burch PA, Berry D, Moinpour C, Kohli M *et al*. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004;351(15):1513-1520.
4. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Theodore C, James ND, Turesson I *et al*. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-1512.
5. Maximum androgen blockade in advanced prostate cancer: an overview of 22 randomised trials with 3283 deaths in 5710 patients. Prostate Cancer Trialists' Collaborative Group. Lancet. 1995;346(8970):265-269.
6. Dearnaley DP, Sydes MR, Mason MD, Stott M, Powell CS, Robinson AC, Thompson PM, Moffat LE, Naylor SL, Parmar MK *et al*. A double-blind, placebo-controlled, randomized trial of oral sodium clodronate for metastatic prostate cancer (MRC PR05 Trial). J Natl Cancer Inst. 2003;95(17):1300-1311.
7. Tangen CM, Hussain MH, Higano CS, Eisenberger MA, Small EJ, Wilding G, Donnelly BJ, Schelhammer PF, Crawford ED, Vogelzang NJ *et al*. Improved overall survival trends of men with newly diagnosed M1 prostate cancer: a SWOG phase III trial experience (S8494, S8894 and S9346). The Journal of urology. 2012;188(4):1164-1169.

8. Aus G, Robinson D, Rosell J, Sandblom G, Varenhorst E, South-East Region Prostate Cancer G. Survival in prostate carcinoma–outcomes from a prospective, population-based cohort of 8887 men with up to 15 years of follow-up: results from three countries in the population-based National Prostate Cancer Registry of Sweden. Cancer. 2005;103(5):943-951.
9. James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, Hetherington J, Hoskin PJ, Jones RJ, Laing R *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). European urology. 2015;67(6):1028-1038.
10. James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, Ritchie AW, Parker CC, Russell JM, Attard G *et al*. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016;387(10024):1163-1177.
11. Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, Wong YN, Hahn N, Kohli M, Cooney MM *et al*. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015;373(8):737-746.
12. van Soest RJ, de Wit R. Irrefutable evidence for the use of docetaxel in newly diagnosed metastatic prostate cancer: results from the STAMPEDE and CHAARTED trials. BMC medicine. 2015;13:304.
13. Puente J, Grande E, Medina A, Maroto P, Lainez N, Arranz JA. Docetaxel in prostate cancer: a familiar face as the new standard in a hormone-sensitive setting. Therapeutic advances in medical oncology. 2017;9(5):307-318.
14. Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, Latorzeff I, Delva R, Krakowski I, Laguerre B *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. The Lancet Oncology. 2013;14(2):149-158.
15. Uppsala-Örebro Rc. Nationellt vårdprogram för prostatacancer. In., vol. version 4.0; 2018.
16. Lavoie JM, Zou K, Khalaf D, Eigl BJ, Kollmannsberger CK, Vergidis J, Noonan K, Zulfiqar M, Finch D, Chi KN. Clinical effectiveness of docetaxel for castration-sensitive prostate cancer in a real-world population-based analysis. Prostate. 2019;79(3):281-287.
17. Mager R, Savko O, Böhm K, Thomas A, Dotzauer R, Borgmann H, Jäger W, Thomas C, Haferkamp A, Höfner T *et al*. Comparative assessment of docetaxel for safety and efficacy between hormone-sensitive and castration-resistant metastatic prostate cancer. Urologic oncology. 2019;37(12):999-1005.
18. Pathak S, Thekkekara R, Yadav U, Ahmed AT, Yim B, Lad TE, Mullane M, Batra KK, Aronow WS, Psutka SP. Efficacy of Upfront Docetaxel With Androgen Deprivation Therapy for Castration-Sensitive Metastatic Prostate Cancer Among Minority Patients. American journal of therapeutics. 2020.

Tables

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Figures

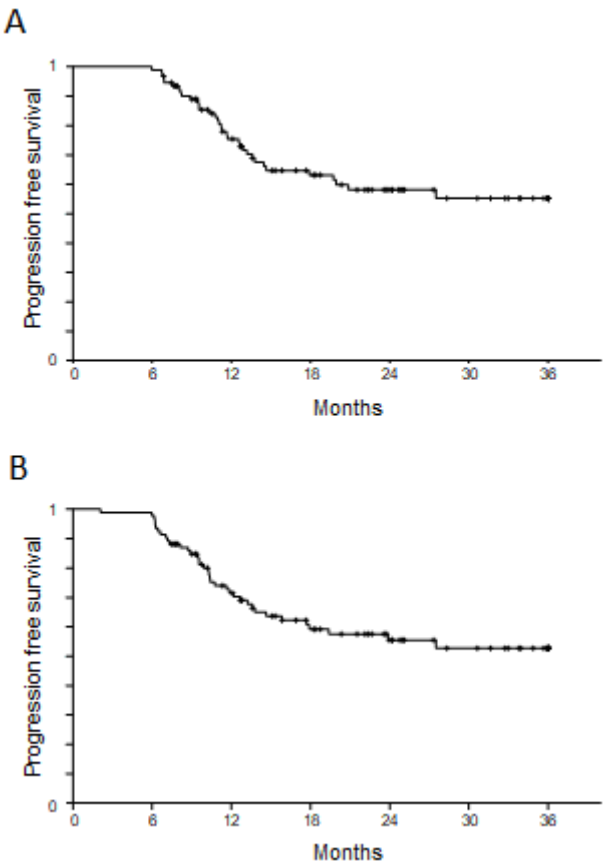

Figure 1

PFS according to A) CHAARTED and STAMPEDE and B) according to Swedish national guidelines. Time from date of diagnosis to last follow-up/death. Censored at 36 months.

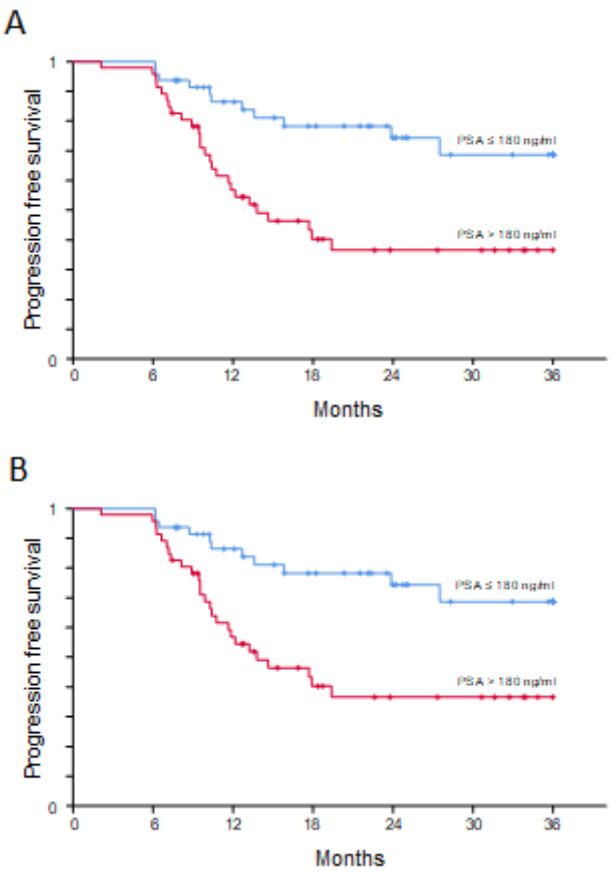

Figure 2

PFS for PSA over/under median according to A) CHAARTED and STAMPEDE (Log-rank: p=0.0027) and B) according to the Swedish national guidelines (Log-rank: p=0.0018). Time from date of diagnosis to last follow-up/death. Censored at 36 months.

Supplementary Files

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