MERIT RESEARCH JOURNALS
www.meritresearchjournals.org

Merit Research Journal of Medicine and Medical Sciences (ISSN: 2354-323X) Vol. 4(12) pp. xxx-xxx, December, 2016
Available online http://www.meritresearchjournals.org/mms/index.htm

Original Research Article

Docetaxel plus androgen deprivation therapy as first – line treatment in high volume metastatic hormone-sensitive prostate cancer

Rasha Abd El-Ghany Khedr* and Mohamed Fathy Sheta

Clinical Oncology Department Faculty of Medicine-Tanta University, Tanta, Egypt

***Corresponding Author's E-mail: Khedr_rasha@yahoo.com**
Tel.: 01227939561

Abstract

Addition of docetaxel to androgen deprivation therapy (ADT) as first –line treatment in high volume metastatic hormone-sensitive (hormone naïve) prostate cancer (mHSPC). The Sun sets on ADT alone in mHSPC after the results of CHAARTED trial and STAMPEDE trial, that showed significant improvement in overall survival after addition of docetaxel to ADT in comparison to ADT alone. From January 2012 to January 2014, 46 patients with newly diagnosed metastatic hormone sensitive prostate cancer with confirmed measurable high-volume metastatic disease, were enrolled Eligible. Patients received androgen-deprivation therapy (with a long-acting GnRH agonist (Goserelin acetate, 3.6 mg subcutaneously monthly) and an androgen antagonist (Flutamide®, 750 mg daily) plus docetaxel (at a dose of 75mg/m2 given as an intravenous infusion every 3 weeks × 6 cycles). The median follow up period was 49 months ± SE 4.905 Median progression free survival (PFS) was 28 months ± SE 1.787. The 2-year PFS rate was 58.6%. Median overall survival (OS) was 49 months ± SE 4.905. The 2-year OS rate was 85.9%. Docetaxel in addition to ADT should be considered SOC for men with newly diagnosed mHSPC.

Keywords: Androgen deprivation therapy, Docetaxel, Metastatic castration-resistant prostate cancer, Metastatic hormone-sensitive prostate cancer, Taxanes

INTRODUCTION

Regressions of metastatic prostate cancer were first documented in the 1940s and were achieved with surgical castration (Huggins and odges, 1941); subsequently, Androgen deprivation therapy (ADT) has been the standard initial treatment for metastatic hormone-sensitive prostate cancer (mHSPC) (Lam and Flaig, 2015).

Docetaxel was the fırst agent approved for metastatic castration-resistant prostate cancer (mCRPC) (Zielinski et al., 2013), with its US Food and Drug Administration (FDA) approval for use in mCRPC in 2004 (Tannock et al., 2004; Petrylak et al., 2004).

Ten years after the FDA approval for use in mCRPC, docetaxel has found another potential place in the treatment of prostate cancer (Murphy and Zargar, 2016). Results from the CHAARTED study of docetaxel plus ADT for the treatment of hormone-sensitive metastatic prostate cancer show significant improvement in overall survival for prostate, or any other metastatic epithelial cancer reported to date (Fizazi et al., 2015).

It is important to note that the GETUG-15 trial was conducted in a similar patient population, but without demonstrating a benefit to added docetaxel (Gravis et al., 2013).

STAMPEDE is a third trial that has recently reported results. The results of this trial confirmed the results of the CHAARTED trial and will change the standard of care for

newly diagnosed mHSPC. Regardless, not all patients are appropriate for chemotherapy, and not all patients will consent to chemotherapy. Noteworthy, patients presented with visceral metastasis or patients with four or more bony lesions, chemotherapy should be offered (Medical Press, 2015; James et al., 2015; James et al., 2015).

The full impact of early docetaxel therapy for mHSPC, especially in low-volume disease, is still to be determined, awaiting more mature data from both CHAARTED and STAMPEDE. The value of aggressive early chemotherapy in the modern context, where multiple other agents with proven OS benefits in mCRPC are now widely available, will also need to be assessed during long-term follow-up. In fact, the strongly positive results from CHAARTED and STAMPEDE set the stage for evaluating other CRPC therapies in earlier stages of disease. As these other agents move into the hormone-sensitive space, optimal sequence and duration of treatment will become even more of a challenge than it is now for CRPC (Gundem et al., 2015; Bobby et al., 2015).

Based on these data, we conducted a phase II single-institution study to evaluate the efficacy and toxicity of docetaxel plus ADT regimen as first-line therapy in patients with high volume hormone-sensitive metastatic prostate cancer.

Patients and Methods

Patient Eligibility Criteria

This phase II trial was conducted at the Clinical Oncology Department, Faculty of Medicine, Tanta University Hospitals from January 2012 to January 2014. Forty-six metastatic hormone-sensitive prostate cancer (mHSPC) patients with, confirmed measurable high-volume metastatic disease (the presence of visceral metastasis and/or 4 or more osseous metastases, with at least 1 being extra-axial) were enrolled.

Inclusion criteria include, chemotherapy, hormonal therapy and radiotherapy-naïve patients with their age ranged between 18 and 70 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; measurable high-volume metastatic disease; adequate bone marrow reserve (WBC count $\geq$3.5 x 10^9/L, ANC count $\geq$1.5 x10^9/L, platelets $\geq$100 x 10^9/L, and hemoglobin $\geq$10 g/dL), adequate renal function (measured creatinine clearance level $\geq$60 mL/min) and normal liver function (transaminases less than 2 x upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL).

Exclusion criteria include symptomatic heart failure, severe arrhythmia, peripheral neuropathy, prior chemotherapy or hormonal therapy, active infection, any other uncontrolled medical illness or other malignant diseases.

Design of the Study

This study is a prospective single-arm phase II single-institution study**.** The Ethics Committee in Faculty of Medicine, Tanta University, approved the protocol with informed consent from all patients included in the study before the initiation of any treatment.

Pretreatment Evaluation

Medical histories are recorded and all patients underwent physical examination, trans-rectal ultrasound, chest X-rays, routine laboratory studies, bone scan and contrast-enhanced abdominopelvic computed tomography (CT) scan.

Treatment Plan and Dose Modification

Eligible patients received androgen-deprivation therapy (with a long-acting GnRH agonist ([Goserelin acetate, 3.6 mg subcutaneously monthly] and an androgen antagonist [Flutamide®, 750 mg daily]) plus docetaxel (at a dose of 75mg/m2 given as an intravenous infusion every 3 weeks × 6 cycles). Patients without progressive disease (PD) or unacceptable toxicity continued treatment. Hydration, adequate anti-emetic therapy, and steroids were ensured for all patients. Growth factors (G-CSF) and antibiotics were administered in patients, based on clinical judgment. Decisions to adjust doses of chemotherapy, withhold therapy, or proceed on the schedule were made every 3 weeks.

Patient Assessment

Assessment of Clinical Benefit, Follow-up and Restaging

A tumor response assessment was performed after every three cycles of treatment. Pre- and on-treatment monitoring consisted of medical history, physical examination, trans-rectal ultrasound, abdomen, and pelvis ultrasound, bone scan, CT-scan of the chest, abdomen and pelvis, and PSA measurement. After completion of treatment, patients were evaluated by physical examination, chest radiography, and abdominopelvic CT every 3 - 4 months. Biopsy was rarely performed from new recurrent sites of the disease and was documented at the time of initial occurrence.

Assessment of Toxicity

Patients were evaluated using a directed history and physical examination every 3 weeks during treatment. The

Table 1. Patient and tumor characteristics of the 46 patients with mHSPC at baseline.

Patient Characteristics	**No.**	%
Age, years		
Median	63	
Range	36-69	
ECOG performance status		
0	8	17.4
1	28	60.9
2	10	21.7
Metastatic sites		
Bone	36	78.3
Liver	14	30.4
Lung	10	21.7
lymph node	8	17.4
Others	6	13.1
Number of sites involved		
1	30	65.2
2	10	21.7
≥3	6	13.1
Gleason score		
4-6	3	6.5
7	12	26.1
8-10	31	67.4
Prior prostatectomy		
Yes	10	21.7
No	36	78.3
Level of PSA, ng/ml		
Median	58	
Range	0.5 – 101 0.6	

- ECOG: - Eastern Cooperative Oncology Group
- PSA: - prostatic specific antigen

occurrence and nature of any adverse events were recorded. Toxicity grading was assessed to according to the common terminology criteria for adverse event (NCI-CTC, version 3.0) (NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2003).

Primary and Secondary Endpoints

The primary endpoint of the study was overall survival. Secondary end points were the progression-free survival, achieving a serum prostate-specific antigen (PSA) less than0.2 ng/mL at 6 and 12 months and toxicity. Disease progression was measured from the first dose of chemotherapy. Disease progression was defined as the appearance of new distant metastatic disease or increase in the size of previously present distant metastatic disease as determined by serial axial CT.

Statistical Analysis

Forty-six patients were recruited in the study between January 2012 and January 2014. The date of this analysis was March 2016.

Overall-survival (OS) rates were calculated from the start of androgen-deprivation therapy (ADT) plus docetaxel to the time of the last follow-up visit or death using the Kaplan-Meier method (Kaplan and Meier, 1958) with SPSS [Statistical package] (version 21.0). Progression-free survival was the time elapsed from the date of initiation of ADT plus docetaxel to the date of first evidence of disease progression or death in the absence of disease progression. Overall survival and progression-free survival were assessed by the Kaplan–Meier method (Kaplan and Meier, 1958) with statistical significance assessed by the log-rank test. Mean and standard deviation were estimates of quantitative data.

RESULTS

Patient characteristics

A total of 46 patients were enrolled in this phase II trial from January 2012 to January 2014 at Clinical Oncology Department, Tanta University Hospital. The characteristics of all eligible patients are listed in Table 1. Median age was 63 years (range, 36–69). Twenty-eight patients (60.8%) had performance status 1. More than half of the patients

Table 2. Serum PSA less than 0.2 ng/mL at 6 and 12 months after ADT plus docetaxel regimen in the management of the 46 patients with mHSPC

Evaluable patients	N=46	
	No.	%
Serum PSA less than 0.2 ng/mL at 6 months	12	26.1
Serum PSA less than 0.2 ng/mL at 12 months	10	21.7

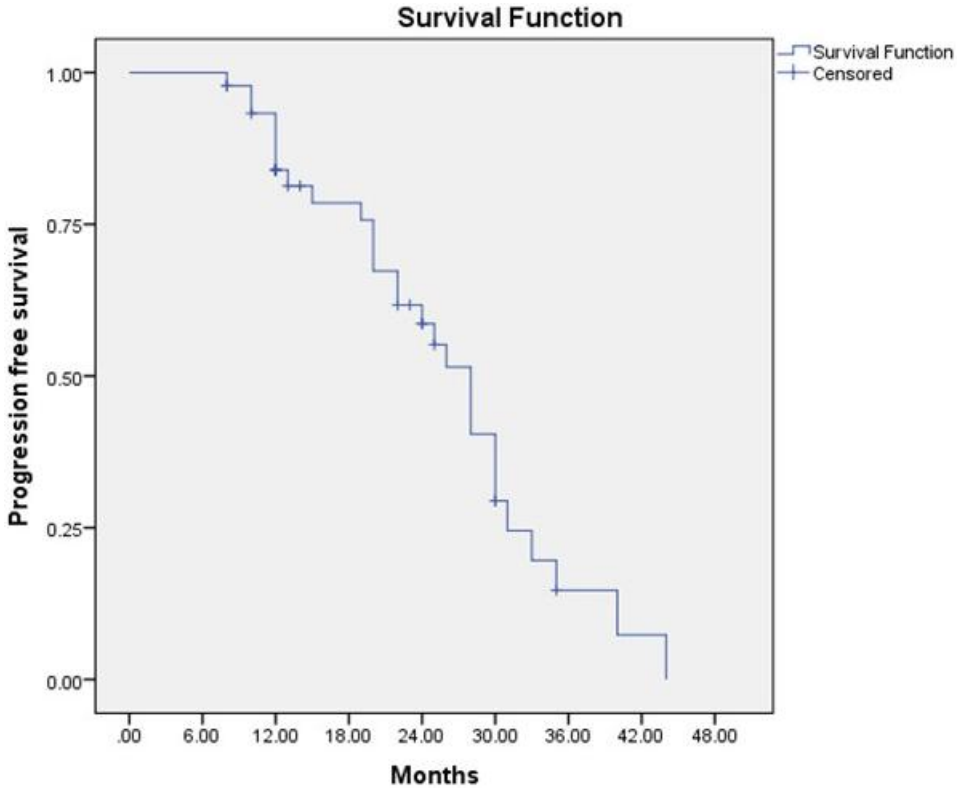

Figure 1. Kaplan–Meier curves for progression-free survival time in patients with mHSPC.

(65.2%) had a solitary involved site of metastases, with bone, liver, and lung being the most frequent sites of metastases. The median level of PSA was 58ng/ml.

Treatment Administration

A total of 189 chemotherapy cycles were administered. Patients were treated with a median number of 4 cycles of ADT plus docetaxel (range 3-6 cycles).

Activity of both drugs

Twelve patients (26.1%) achieved a serum prostate-specific antigen (PSA) less than 0.2 ng/mL at 6 months and 10 patients (21.7%) achieved a PSA level of less than 0.2 ng/mL at 12 months. (Table 2)

Survival

All our patients were followed up regularly as mentioned previously in patients and methods, with no one had lost follow-up in this study. The median follow-up period was 49 months ± SE 4.905.

Median progression-free survival (PFS) was 28 months ± SE 1.787 (Figure 1). The 2-year PFS rate was 58.6%.

Median overall survival (OS) was 49 months ± SE 4.905 (Figure 2). The 2-year OS rate was 85.9%.

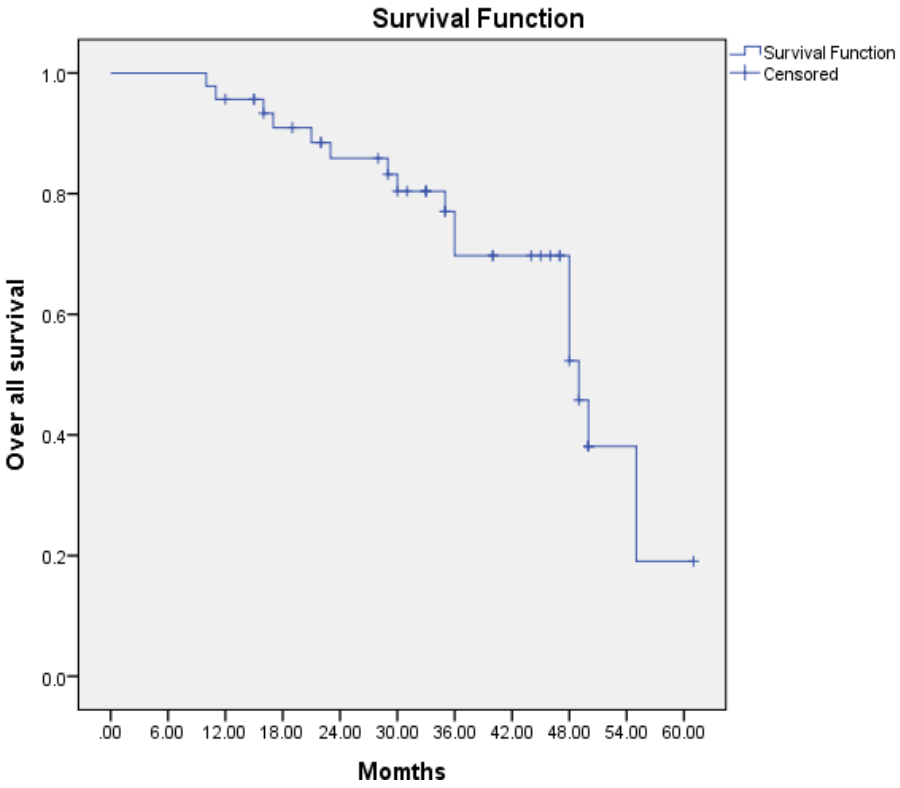

Figure 2. Kaplan–Meier curves for overall survival time in patients with mHSPC.

Table3. Grade 3&4 Hematologic and non-hematologic toxicity in 46 patients with mHSPC

	No.	%
Hematologic Toxicity		
Neutropenia	3	6.5
Febrile Neutropenia	2	4.3
Thrombocytopenia	1	2.2
Non-hematologic Toxicity		
Diarrhea	2	4.3
Nausea/vomiting	2	4.3
Paresthesia	1	2.2

Toxicity

To determine hematologic and non-hematologic toxicities (Table 3), patients were evaluated for adverse events and toxicity using the common terminology criteria for adverse event (NCI-CTC, version 3.0) (NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2003). Most common grade 3-4 hematological toxicities were neutropenia in 3 patients (6.5%), with two (4.3%), patients suffered from febrile neutropenia, and one patient (2.2%) developed grade 3-4 thrombocytopenia. Grade 3-4 diarrhea in 2 patients (4.3%), one patient (2.2%) developed grade 3-4 paresthesia, as well as nausea and vomiting in 2 patients (4.3%) were the most common Grade 3-4 non-hematological toxicity. Five patients (10.9%) had G-CSF support added during chemotherapy cycles. Six patients from 46 (13.1%) were hospitalized for treatment-related toxicity. The dose was modified in 6 patients from 46 (13.1%) in response to adverse events with 86.9% of all our patients completing 6 cycles without any dose modification required. There was no treatment-related death.

DISCUSSION

The upfront docetaxel administration plus ADT regimen has gained increased acceptance due to its efficacy as first-line therapy in patients with high-volume mHSPC, improving median OS with decreasing PSA level to less

than 0.2 ng per milliliter at 12 months over that achieved with ADT alone as reported in previous studies. The docetaxel plus ADT regimen was quite toxic. Considering the efficacy and toxicity, docetaxel plus ADT could be a viable option in selected patients with high-volume mHSPC.

Since long time, the standard of care for mHSPC has been androgen deprivation therapy (ADT). Docetaxel, was the first chemotherapeutic agent that demonstrated overall survival benefit in mCRPC based on the data collected from the TAX 327 and the Southwest Oncology Group (SWOG) S9916 clinical trials, (Lam and Flaig, 2015). Sweeney et al recently published the results of the Eastern Cooperative Oncology Group (ECOG) E3805 CHAARTED (Chemo-Hormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer) trial, which evaluated the addition of docetaxel to ADT for the first-line treatment of men with untreated mHSPC [16]. The results were overwhelmingly positive and are changing the treatment policy for selection of chemotherapy-eligible patients with metastatic prostate cancer.

We sought to document the use of docetaxel plus ADT and its efficacy and tolerance in metastatic extensive disease prostatic carcinoma patients treated at Clinical Oncology Department, Faculty of Medicine, Tanta University Hospital.

Several randomized clinical trials have recently tested the early addition of docetaxel to ADT in mHSPC to evaluate the combination of docetaxel and ADT. Exploratory subgroup analysis according to high-volume versus low-volume disease was performed. A systematic review of PubMed/Medline, Embase, and the proceedings of major international meetings was performed in June 2015 and updated in August 2015. Three trials were selected for inclusion. A total of 951 in docetaxel and ADT group were metastatic. In metastatic patients, overall survival benefit was observed after the addition of docetaxel (hazard ratio [HR]: 0.73; 95% confidence interval [CI], 0.60-0.90; p=0.002), with minor heterogeneity between these trials (Tucci et al., 2015).

In our study, 26.1% of patients achieved a serum PSA less than 0.2 ng/mL at 6 months and 21.7% of patients achieved a PSA level of less than 0.2 ng/mL at 12 months which was comparable to the results of the CHAARTED trial on docetaxel plus ADT, as the first regimen in patients with metastatic extensive disease prostatic carcinoma published in 2015, by Sweeney et al., (2015) (27.5% of patients achieved a serum PSA less than 0.2 ng/mL at 6 months and 22.7% of patients achieved a PSA level of less than 0.2 ng/mL at 12 months).

The estimated median OS in our study was 49 months, similar to the 49.2 months reported in Sweeney et al., (2015) study. However, our results were better than the results of an updated report with longer follow-up of the GETUG-AFU 15 trial (Gravis et al., 2015) which was presented at the 2015 Genitourinary Cancers Symposium, in patients with high-volume disease, median OS rate was 39 months in ADT plus docetaxel arm (Gravis et al., 2015), which suggests that this study had a different case mix than that in our study and Sweeney et al., (2015) study.

The median progression-free survival in our study was 28 months, comparable to 33 months in patients in phase III CHAARTED clinical trial (Sweeney et al., 2015), and higher than that published in 2015, by Fizazi et al., (2015), in 192 patients on the docetaxel plus ADT group with metastatic high-volume disease prostatic carcinoma (median progression-free survival was 15.2 months). National Comprehensive Cancer Network (NCCN), approved the use of docetaxel in mHSPC as a consequence of the strongly positive subgroup analysis favoring high-volume disease, and became the standard of care in United States for such patients (James et al., 2015).

In the STAMPEDE trial, 2962 men with high-risk, locally advanced or mHSPC who had started ADT were randomized to standard of care (SOC), which was at least 3 years of ADT; SOC plus docetaxel; SOC plus zoledronic acid; or SOC plus zoledronic acid and docetaxel. The median OS for all patients with M1 disease was 5.4 years in the ADT plus docetaxel arm versus 3.6 years in the ADT only arm (a difference of 1.8 years between groups compared with a 1.1 year difference in CHAARTED).the results of STAMPEDE trial seems to confirm the results the results of CHAARTED trial (10).

In our study, the most common grade 3-4 hematological toxicities were neutropenia in 3 patients (6.5%), with two (4.3%) patients suffered from febrile neutropenia, and one patient (2.2%) developed grade 3-4 thrombocytopenia. Grade 3-4 diarrhea in 2 patients (4.3%), one patient (2.2%) developed grade 3-4 paresthesia as well as nausea and vomiting in 2 patients (4.3%) were the most common grade 3-4 non-hematological toxicity. This was comparable to the proportion of patients in Sweeney et al [16] study, in the combination therapy arm, the rate of grade 3/4 febrile neutropenia was 6.2% and the rate of grade 3/4 infection with neutropenia was 2.3%, in addition, 1% experienced significant effects on sensory nerves, and 1% on motor nerves in addition to 2% grade 3 - 4 allergic reaction; grade 3 fatigue in 4%, grade 3 diarrhea in 1%, and stomatitis at a rate of 1%. A higher proportion of patients suffered from serious adverse events in GETUG-AFU 15 trial (Gravis et al., 2015) in the group given ADT plus docetaxel, more frequently neutropenia (21%), febrile neutropenia (3%), abnormal liver function tests (2%), and neutropenia with infection (1%).

In our study, the dose was modified in 6 patients from 46 (13.1%) in response to adverse events with 86.9% of all our patients completing 6 cycles without any dose modification required. Investigators at phase III CHAARTED clinical trial (Sweeney et al., 2015) observed that 86% of patients in the combination arm who started on ADT completed the prescribed 6 cycles of docetaxel,

with 74% of all patients in this arm didn't need any dose modification with completion of their 6 cycles without interruption (Sweeney et al., 2015). However, 21% of men in GETUG-AFU 15 trial (Gravis et al., 2015) in the group treated with ADT plus docetaxel discontinued treatment because of toxicity.

Consequently, there was no treatment-related death in our study. However, one of the 397 patients died as a result of treatment in the docetaxel plus ADT group in the Sweeney et al., (2015) study and four treatment-related deaths occurred in the ADT plus docetaxel group in GETUG-AFU 15 trial (Gravis et al., 2015). Thus, GETUG-AFU 15 trial showed unusually high toxicity reported, with 21% incidence of grade 3 neutropenia and four deaths in the group given ADT plus docetaxel; in addition, 21% of men who received docetaxel plus ADT discontinued treatment because of toxicity.

Based on its high efficacy in high-volume mHSPC, further studies are needed to explore the value of docetaxel plus ADT regimen in unresectable locally advanced prostatic tumors, together with radiation for a possible down-staging effect. Docetaxel plus ADT should be investigated also in adjuvant settings where patients can potentially accept more toxic effects. In addition, further prospective trials should evaluate how to adjust doses to ameliorate toxicity. Also, future prospective trials depending on further understanding of the tumor biology, targeting various growth factor signaling pathways, and development of new strategies, such as investigation of biomarkers that predict treatment response should be encouraged.

Conflict of Interests

All authors report no conflict of interests.

Authors' Contribution

All authors designed the study, analyzed the data, performed the statistical analysis, drafted the paper, contributed to patient treatment and follow-up and critically reviewed the paper.

Funding

We did not receive any funding for this research.

REFERENCES

Bobby C. Liaw, MD, and William K. Oh, MD (2015). Is Docetaxel Chemotherapy a New Standard of Care for Metastatic Hormone-Sensitive Prostate Cancer?. American Journal of Hematology / Oncology; 11(9):17-20.

Fizazi K, Jenkins C, Tannock IF (2015). Should Docetaxel Be Standard of Care for Patients with Metastatic Hormone-Sensitive Prostate Cancer? Pro and Contra. Ann Oncol; 260 (8): 1660–1667.

Gravis G, Boher JM, Joly F, Soulié M, Albiges L, Priou F, Latorzeff I, Delva R, Krakowski I, Laguerre B, Rolland F, Théodore C, Deplanque G, Ferrero JM, Culine S, Mourey L, Beuzeboc P, Habibian M, Oudard S, Fizazi K, GETUG (2015). Androgen deprivation therapy (ADT) plus docetaxel (D) versus ADT alone for hormone-naıve metastatic prostate cancer (PCa): long-term analysis of the GETUG-AFU 15 phase III trial. J Clin Oncol.; 33:(suppl 7; abstr 140).

Gravis G, Fizazi K, Joly F, Oudard S, Priou F, Esterni B, Latorzeff I, Delva R, Krakowski I, Laguerre B, Rolland F, Théodore C, Deplanque G, Ferrero JM, Pouessel D, Mourey L, Beuzeboc P, Zanetta S, Habibian M, Berdah JF, Dauba J, Baciuchka M, Platini C, Linassier C, Labourey JL, Machiels JP, El Kouri C, Ravaud A, Suc E, Eymard JC, Hasbini A, Bousquet G, Soulie M (2013). 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.; 14: 149-158.

Gundem G, Van Loo P, Kremeyer B, Alexandrov LB, Tubio JM, Papaemmanuil E, Brewer DS, Kallio HM, Högnäs G, Annala M, Kivinummi K, Goody V, Latimer C, O'Meara S, Dawson KJ, Isaacs W, Emmert-Buck MR, Nykter M, Foster C, Kote-Jarai Z, Easton D, Whitaker HC; ICGC Prostate UK Group, Neal DE, Cooper CS, Eeles RA, Visakorpi T, Campbell PJ, McDermott U, Wedge DC, Bova GS (2015). The evolutionary history of lethal metastatic prostate cancer. Nature; 520: 353-357.

Huggins C, Hodges CV (1941). Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res;1: 293-297.

James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, Hetherington J, Hoskin PJ, Jones RJ, Laing R, Lester JF, McLaren D, Parker CC, Parmar MK, Ritchie AW, Russell JM, Strebel RT, Thalmann GN, Mason MD, Sydes MR (2015). 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). Lancet. 2016 Mar 19;387(10024):1163-77. doi: 10.1016/S0140-6736(15)01037-5. Epub 2015 Dec 21.

James ND, Sydes MR, Clarke NW, Mason MD, Dearnaley DP, Spears MR, Ritchie AW, Parker CC, Russell JM, Attard G, de Bono J, Cross W, Jones RJ, Thalmann G, Amos C, Matheson D, Millman R, Alzouebi M, Beesley S, Birtle AJ, Brock S, Cathomas R, Chakraborti P, Chowdhury S, Cook A, Elliott T, Gale J, Gibbs S, Graham JD, Hetherington J, Hughes R, Laing R, McKinna F, McLaren DB, O'Sullivan JM, Parikh O, Peedell C, Protheroe A, Robinson AJ, Srihari N, Srinivasan R, Staffurth J, Sundar S, Tolan S, Tsang D, Wagstaff J, Parmar MK; STAMPEDE investigators (2015). 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 Mar 19;387(10024):1163-77. doi: 10.1016/S0140-6736(15)01037-5. Epub 2015 Dec 21.

Kaplan EL, Meier P (1958). Nonparametric estimation from incomplete observations. J Am Stat Assoc; 53: 457-81. DOI:10.1080/01621459.1958.10501452.

Lam ET, Flaig TW (2015). Upfront Chemotherapy for Metastatic Prostate Cancer. Oncology; 29 (12): 956–962.

Medical Press (2015). Adding chemotherapy to standard prostate cancer treatment may extend life expectancy. http:// medicalxpress.com/news/2015-05-adding-chemotherapy-standard-prostate-cancer.html. Accessed May 14

Murphy DG, Zargar H (2016). Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. European Urology; 69 (3). Published online: 01 March 2016.

NCI Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (2003). .http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. March 31,

Petrylak DP, Tangen CM, Hussain MH, Lara PN Jr, Jones JA, Taplin ME, Burch PA, Berry D, Moinpour C, Kohli M, Benson MC, Small EJ, Raghavan D, Crawford ED (2004). Docetaxel and estramustine

compared with mitoxantrone and prednisone for advanced refractory prostate cancer. N Engl J Med. 2004 Oct 7;351(15):1513-20. PMID: 15470214.

Sweeney CJ, Chen YH, Carducci M, Liu G, Jarrard DF, Eisenberger M, Wong YN, Hahn N, Kohli M, Cooney MM, Dreicer R, Vogelzang NJ, Picus J, Shevrin D, Hussain M, Garcia JA, DiPaola RS (2015). Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med. 2015 Aug 20;373(8):737-46. doi: 10.1056/NEJMoa1503747.PMID: 26244877.

Tannock IF1, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA, Eisenberger MA; TAX 327 Investigators (2004). Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med.; 351:1502-1512.

Tucci M, Bertaglia V, Vignani F, Buttigliero C, Fiori C, Porpiglia F, Scagliotti GV, Di Maio M (2015). Addition of Docetaxel to Androgen Deprivation Therapy for Patients with Hormone-sensitive Metastatic Prostate Cancer: A Systematic Review and Meta-analysis. Eur Urol. 2016 Apr;69(4):563-73. doi: 10.1016/j.eururo.2015.09.013. Review. PMID: 26422676

Zielinski RR, Tyldesley S, Chi KN (2013). Population-based impact on overall survival (OS) after the introduction of docetaxel as standard therapy for metastatic castration resistant prostate cancer (CRPC). J Clin Oncol.; 31(suppl 6; abstr 77)