EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2019
EMA/647024/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/WS1550

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Taxotere	docetaxel	EMEA/H/C/000073/WS1550/0131
Docetaxel Zentiva	docetaxel	EMEA/H/C/000808/WS1550/0058

Worksharing applicant (WSA): Aventis Pharma S.A.

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AdEER: adverse event expedited reporting system

ADT: androgen-deprivation therapy

CI: confidence interval

CP: clinical progression

CRPC: castration-resistant prostate cancer

ECOG: Eastern Cooperative Oncology Group

FACT-P: Functional Assessment of Cancer Therapy-Prostate

FDA: Food and Drug Administration

FFS: failure-free survival

FPM: flexible parametric model

HR: hazard ratio

HT: hormone therapy

HVD: high volume of disease

ITT: intention-to-treat

LHRH: luteinizing hormone releasing hormone

LVD: low volume of disease

MAMS: multi-arm-multi-stage

mHSPC: metastatic hormone-sensitive prostate cancer

MRC: Medical Research Council

NR: not reached

NSAID: non-steroidal anti-inflammatory drug

OS: overall survival

PFS: progression-free survival

PSA: prostate specific antigen

QoL: Quality of Life

RCT: randomized clinical trial

RT: radiotherapy

SD: standard deviation

SOC: standard of care

SRE: skeletal-related event

WHO: World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Aventis Pharma S.A. submitted to the European Medicines Agency on 13 March 2019 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of patients with metastatic hormone-sensitive prostate cancer in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone, for Taxotere and Docetaxel Zentiva; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP version 1.0 has also been submitted. In addition, the Worksharing applicant took the opportunity to update information on the local representatives in the Package Leaflet.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Rapportuer: Alexandre Moreau Co-Rapporteur: Janet Koenig

Timetable	Actual dates
Submission date	13 March 2019
Start of procedure:	30 March 2019
CHMP Co-Rapporteur Assessment Report	3 June 2019
CHMP Rapporteur Assessment Report	28 May 2019
PRAC Rapporteur Assessment Report	29 May 2019
PRAC members comments	5 June 2019
Updated PRAC Rapporteur Assessment Report	6 June 2019
PRAC Outcome	14 June 2019
CHMP members comments	17 June 2019
Updated CHMP Rapporteur(s) (Joint) Assessment Report	21 June 2019
Request for supplementary information (RSI)	27 June 2019
PRAC Rapporteur Assessment Report	27 August 2019
CHMP Rapporteur Assessment Report	11 September 2019
PRAC Outcome	5 September 2019
CHMP members comments	9 September 2019
Updated CHMP Rapporteur Assessment Report	11 September 2019
Opinion	19 September 2019

2. Scientific discussion

2.1. Introduction

Docetaxel is available as intravenous formulations for infusion and is currently approved in the United States, Europe, and in more than 130 other countries worldwide for the treatment of breast cancer, non-small cell lung cancer, gastric cancer, prostate cancer (castration-resistant setting), and head and neck cancer. In Japan, Taxotere is registered for the treatment of breast, non-small cell lung, gastric, oesophagus, endometrial, ovarian, head and neck cancer, and prostate cancer (castration-resistant setting).

The Applicant has submitted an application for an extension of indication: Taxotere/Docetaxel Zentiva in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone, is indicated for the treatment of patients with metastatic hormone-sensitive prostate cancer.

This is a literature-based submission from the studies STAMPEDE, CHAARTED and GETUG-AFU15 conducted under the sponsorship of the Medical Research Council (MRC), the Eastern Cooperative Oncology Group (ECOG), and Unicancer, respectively, and independently from the Applicant. It was agreed in advance with the Applicant that the Clinical Study Reports (CSRs) originating from the academic groups who conducted the studies would be acceptable for submission. The relevant CSRs were included within the variation.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

The amount predicted for all indications in the next years in the European member states is evaluated at a maximum of 165.4 kg/year. Maximum annual consumption was calculated by multiplying the patient population with metastatic prostate cancer (193,400) by the maximum daily dose (142.5 mg) by 6 days of treatment per patient = 165.4 kg/yr.

where:

Metastatic prostate cancer incidence = total 2018 EU population with prostate cancer = 449,761 men multiplied by the highest reported percentage of metastatic prostate cancer in the reported in EU epidemiology data = 43% = 193,400 men and maximum daily dose = 75 mg/m2 x 1.9 m2 (avg. adult male) = 142.5 mg. Following EMA guidance, the PECsurfacewater is the ratio of the maximum annual quantity marketed (165.4 Kg/yr) to the total estimated quantity of water consumption in Europe (i.e. 512.6 million inhabitants of Europe in 2018 (10) x 200 L x 365 days) and the EMA ERA Guidance dilution factor of 10. The PECsurfacewater would therefore be the following:

$165.4 / ((512.6 \times 10^6) \times 200 \times 365 \times 10) = 4.42\ 10^{-7}$ mg/L = $4.42\ 10^{-4}$ µg/L

Under these conditions, the PECsurfacewater is 4.42×10^{-4} µg/L.

As PEC<0.01 µg/L, Phase II environmental fate and effect analysis is not required.

2.2.2. Conclusion on the non-clinical aspects

An ERA has been submitted which is acceptable. The calculated PEC is well overestimated considering the short duration of treatment by parenteral route. Docetaxel is used in small quantities under strict medical supervision in hospitals which ensures confinement of the product and prevents significant environmental exposure.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

Type of study	- Study identifier - Location of study report - Coordinating Investigator and center - Number of centers	- Objectives of study - Study design and type of control	Test products: - Formulation - Dosage regimen - Route of administration	Reference therapy: - Formulation - Dosage regimen - Route of administration	Number of subjects - Total[a, b, c] - Gender[b] (M) - Race[b] (C/B/A/O) - Age[a] mean ± SD (range) - Treatment group[b]	Healthy subjects or diagnosis of patients	Duration of treatment	Study status Type of report
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication								
Efficacy, Safety	[STAMPEDE][d] - Section 5.3.5.1 - Prof. Nicholas D James, CRUK Institute for Cancer Studies, University of Birmingham (Birmingham, UK) - 111 centers	- To assess the effects of adding different agents, both as single agents and in combinations, to hormone therapy - Randomized, multi-arm, multi-stage, active control trial with a seamless phase 2/3 design	**Docetaxel + corticosteroid** - Solution for injection (vials) - 75 mg/m²/day on Day 1 of every 3 week cycle for up to 6 cycles, plus prednisolone (or prednisone) 5 mg twice daily each day of each cycle - Intravenous **ADT (one of the following) ± Radiotherapy** - LHRH agonists/analogues, LHRH antagonists, or bilateral orchiectomy - Dosage: according to local practice - Administration: according to local practice	**ADT (one of the following) ± Radiotherapy** - LHRH agonists/analogues, LHRH antagonists, or bilateral orchiectomy - Dosage: according to local practice - Administration: according to local practice	- 1776/1752/454 (Completion status only reported for the docetaxel + ADT arm) - 1752 - Race not reported - 65 years ± NR (40-81), docetaxel + ADT arm; 65 years ± NR (41-82), ADT-only arm - Docetaxel + ADT group: 545; ADT-only group: 1207	Men with histologically confirmed prostate adenocarcinoma and one of the following: high-risk newly diagnosed non-metastatic node-negative disease, newly diagnosed metastatic or node-positive disease, or relapsing disease previously treated with radical surgery or radiotherapy.	For docetaxel, treatment continued until progression for a maximum of 6 cycles.	Complete Full CSR (Primary Analysis Report)
Efficacy, Safety	[CHAARTED] - Section 5.3.5.1 - Christopher Sweeney, Dana-Farber Cancer Institute (Boston, MA; USA) - 83 centers	- Primary: To evaluate the ability of early chemotherapy to improve overall survival in men commencing androgen deprivation for metastatic prostate cancer - Randomized, open-label phase III study; active control (ADT)	**Docetaxel** - Solution for injection (vials) - 75 mg/m²/day on Day 1 of every 3 week cycle for up to 6 cycles - Intravenous **ADT (one of the following)** **LHRH agonist or antagonist therapy** - Any LHRH analogue approved by US FDA could be used. - Dosage: per manufacturer instruction. - Administration: per manufacturer instruction. **Surgical castration**	**ADT (one of the following)** **LHRH agonist or antagonist therapy** - Any LHRH analogue approved by US FDA could be used. - Dosage: per manufacturer instruction. - Administration: per manufacturer instruction. **Surgical castration**	- 790/782/335 (Completion status only reported for the docetaxel + ADT arm) - 782 - 674/76/8/32 - 64 years ± NR (36-88 years), docetaxel + ADT arm; 63 years ± NR (36-91 years), ADT-only arm. -Docetaxel + ADT arm: 390; ADT-only arm: 392	Men with histologically or cytologically confirmed prostate cancer and metastatic disease.	For docetaxel, treatment continued until progression for a maximum of 6 cycles.	Complete Full CSR
Efficacy, Safety	[GETUG-AFU15] - Section 5.3.5.1 - Dr Gwenaelle Gravis, Paoli-Calmettes Institute (Marseille, France) - 30 centers	- Primary: Compare the 3-year overall survival (OS) of metastatic prostate cancers patients treated with first-line chemotherapy (docetaxel) + ADT to those treated only with ADT. - Randomized, open-label phase III study; active control (ADT)	**Docetaxel** - Solution for injection (vials) - 75 mg/m²/day on Day 1 of every 3 week cycle (continued if the tumor responded or was stable) for a maximum of 9 cycles - Intravenous **ADT (one of the following)** **LHRH agonist (Zoladex®)** - To be started less than 2 months before start of chemotherapy, or at the same time as chemotherapy; to be continued until androgen resistance developed. No further dose regimen details are provided in the CSR. - Intravenous **CAB:LHRH agonist + peripheral antiandrogen (Zoladex + Anandron®)** Specific details are not provided in the CSR. **Surgical castration**	**ADT (one of the following)** **LHRH agonist (Zoladex®)** - To be continued until androgen resistance developed. No further dose regimen details are provided in the CSR. - Intravenous **CAB:LHRH agonist + peripheral antiandrogen (Zoladex + Anandron®)** Specific details are not provided in the CSR. **Surgical castration**	- 385/375/89 (Completion status only reported for the docetaxel + ADT arm) - 375 - Race NR - Docetaxel + ADT arm: 62.7 ±7.5 years; ADT-only arm: 63.4 ± 8.1 years. Ranges NR. - Docetaxel + ADT arm: 189; ADT-only arm: 186	Men with histologically proven prostatic adenocarcinoma and measurable or assessable metastatic disease.	For docetaxel, treatment continued until progression for a maximum of 9 cycles.	Complete Full CSR

a Randomized.
b Treated patients who underwent adverse event assessment.
c Completed study drug.
d For STAMPEDE, only information for ADT (active control) and docetaxel + ADT treatment groups are presented here since the other treatment groups are not relevant for this submission.
Abbreviations: A, Asian; ADT, androgen deprivation therapy; B, Black; C, Caucasian; CAB, complete androgen blockade; CRUK, Cancer Research UK; CSR, clinical study report; LHRH, luteinizing hormone releasing hormone; M, male; NR, not reported; O, other; OS, overall survival; PSA, prostate specific antigen; SD, standard deviation

2.3.2. Pharmacokinetics

No new PK data have been submitted in this application, which is considered acceptable.

2.3.3. Pharmacodynamics

No new PD data have been submitted in this application, which is considered acceptable.

2.4. Clinical efficacy

The purpose of the provided data is to support a proposed docetaxel label expansion to include the treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT), with or without prednisone or prednisolone. These data are based primarily upon the following three randomized clinical trials (RCTs):

- STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy (1)
- CHAARTED-E3805: ChemoHormonal therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer (2)
- GETUG-AFU15: Hormone Therapy and Docetaxel or Hormone Therapy Alone in Treating Patients with Metastatic Prostate Cancer (3)

These studies were conducted under the sponsorship of the Medical Research Council (MRC), the Eastern Cooperative Oncology Group (ECOG), and Unicancer, respectively, independently of Sanofi.

Each study compared the combination of docetaxel and ADT versus ADT in hormone-sensitive disease, and the results of these trials led to the implementation of the recommendation to use docetaxel plus ADT in metastatic hormone-sensitive prostate cancer patients with level of evidence 1, within several academic and institutional guidelines (eg, the European Society for Medical Oncology [ESMO], and European Association of Urology [EAU] Guidelines).

The efficacy analysis is primarily based on the STAMPEDE study. CHAARTED and GETUG-AFU15 are supplemental studies.

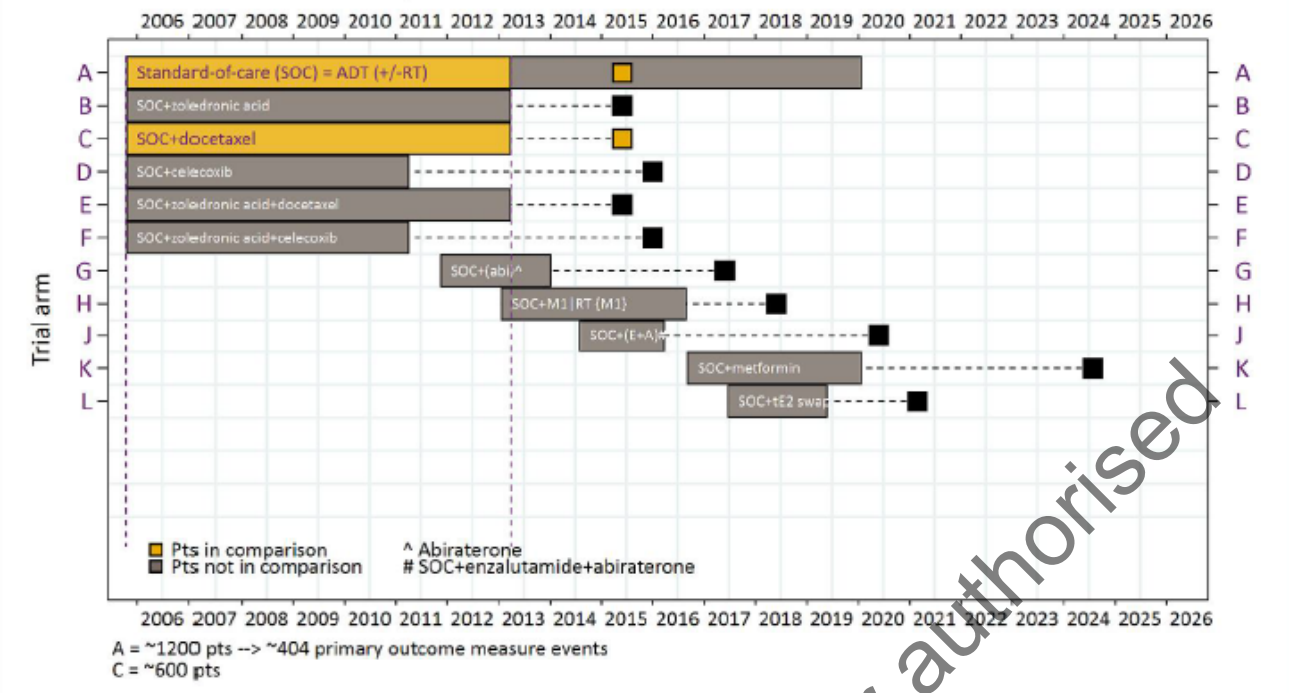
The data are also supplemented with a meta-analysis of the three studies.

2.4.1. Main study - STAMPEDE

STAMPEDE: an international, open-label, adaptive, multicenter, controlled, multi-arm-multi-stage (MAMS), randomized study with a seamless phase 2/3 design comparing the efficacy (OS as primary endpoint) and safety of adding new agents (either in monotherapy or in combination) to ADT versus ADT alone in patients with hormone-naïve high risk locally advanced or metastatic prostate cancer who were commencing first line long term hormone therapy.

Methods

The "docetaxel comparison" was one of the five original comparisons which assessed the effects of adding different treatments (assessed as single agents and in combinations) to the standard of care (SOC) treatment (ADT and radiotherapy [RT] for certain patients). The five original comparisons were made using (i) a bisphosphonate, zoledronic acid; (ii) docetaxel; and (iii) a cyclooxygenase-2 (Cox-2) inhibitor, celecoxib. Further investigation approaches have since been included in the study, using the following treatments: (iv) a selective CYP-17 inhibitor, abiraterone; (v) RT to the prostate for newly-diagnosed metastatic disease; (vi) an androgen receptor signaling inhibitor, enzalutamide; and (vii) metformin. For purposes of this submission, only data for the "docetaxel comparison" (the docetaxel + ADT treatment arm compared to ADT-only treatment arm) are presented.



Patients in arms A and C were included in the "docetaxel comparison" (shown in yellow in the Figure).

Abbreviations: ADT, androgen deprivation therapy; RT, radiotherapy; SOC, standard of care.

Study participants

Main Inclusion Criteria:

Inclusion Criteria Participants must fulfil both of the criteria in Section 1 or at least one criterion in Section 2 or at least one criterion in Section 3 of the protocol. Additionally, all patients must fulfil the criteria in Section 4.

1. High-Risk Newly-Diagnosed Non-Metastatic Node-Negative Disease

Both:

- At least two of: T category T3/4, PSA≥40ng/ml or Gleason sum score 8-10
- Intention to treat with radical radiotherapy (unless there is a contra-indication; exemption can be sought in advance of consent, after discussion with CTU)

OR

2. Newly-Diagnosed Metastatic Or Node-Positive Disease

At least one of:

- Stage T_any N+ M0
- Stage T_any Nany M+

OR

3. Previously Radically Treated, Now Relapsing (Prior Radical Surgery And/or Radiotherapy)

At least one of

- PSA ≥4ng/ml and rising with doubling time less than 6 months
- PSA ≥20ng/ml

- N+
- M+

AND

4. For All Patients

- Histologically confirmed prostate adenocarcinoma

- Intention to treat with long-term androgen deprivation therapy

- Treating clinician and patient should have decided if docetaxel is to be part of the standard-of-care prior to randomisation

- Fit for all protocol treatment1 and follow-up, WHO performance status 0-22

- Have completed the appropriate investigations prior to randomisation

- Adequate haematological function: neutrophil count >1.5x109/l and platelets >100x109/l

- Adequate renal function, defined as GFR >30ml/min/1.73m2

Main Exclusion Criteria:

1. Prior systemic therapy for locally-advanced or metastatic prostate cancer except as listed above

2. Metastatic brain disease or leptomeningeal disease

3. Abnormal liver functions consisting of any of the following:

- Serum bilirubin ≥1.5 x ULN (except for patients with Gilbert's disease, for whom the upper limit of serum bilirubin is 51.3 μ mol/l or 3mg/dl)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥2.5 x ULN

4. Any other previous or current malignant disease which, in the judgement of the responsible clinician, is likely to interfere with STAMPEDE treatment or assessment

5. Any surgery (e.g. TURP) performed within the past 4 weeks

6. Participant with significant cardiovascular disease, including:

- Severe/unstable angina
- Myocardial infarction less than 6 months prior to randomisation
    - Arterial thrombotic events less than 6 months prior to randomisation
    - Clinically significant cardiac failure requiring treatment, defined as New York Heart Association (NYHA) class II or above1
    - Cerebrovascular disease (e.g. stroke or transient ischaemic episode) less than 6 months prior to randomisation
    - Or any other significant cardiovascular disease that in the investigator's opinion means the participant is unfit for any of the study treatments.

7. Prior chemotherapy for prostate cancer2

8. Prior exposure to long-term hormone therapy before randomisation

9. Prior exposure to systemic treatment for prostate cancer (excluding ADT or participants receiving abiraterone as part of SOC)

Treatments

Docetaxel was administered at a dose of 75 mg/m² repeated every 3 weeks for a maximum of 6 consecutive 21-day treatment cycles. In addition, prednisolone 5 mg twice daily was administered for the duration of the chemotherapy (each day of each treatment cycle) in the docetaxel + ADT treatment arm. Dexamethasone was given pre- and post-docetaxel infusion to suppress allergic reactions.

In all treatment arms, ADT consisted of luteinizing hormone releasing hormone (LHRH) agonists or LHRH antagonists for an intended duration of at least 2 years, or bilateral orchidectomy, according to the local practice at the investigational sites. Use of anti-androgens was recommended in the short term for the patients commencing LHRH agonists to prevent tumor "flare". Patients may have begun hormonal therapy prior to randomization, but it was not to have commenced more than 12 weeks (84 days) prior to randomization.

Objectives

The "docetaxel comparison," like all of the "original comparisons," was conducted in five stages: a Pilot Phase, Activity Stages 1 to 3, and Efficacy Stage 4. For the intermediate Activity Stages 1-3, patients were recruited to the research arm(s) until the approximate target number of failure-free survival (FFS) events were observed in the control arm patients for that comparison, with evidence of activity required for a research arm to proceed to further recruitment in each stage. Efficacy Stage 4 for the original research comparisons, which continued recruitment through all interim activity stages, was triggered by observing around 403 deaths in the control arm (SOC).

The study had the primary objective of demonstrating an overall survival benefit of the experimental arm, docetaxel +ADT, over ADT-only treatment.

The secondary objectives were aimed at assessing treatment failure, clinical progression (local progression, lymph node progression, distant metastases) and biochemical progression (PSA failure).

Outcomes/endpoints

The primary endpoint was overall survival, defined as time from randomisation to death due to any cause or date last known alive.

The study's main secondary outcome measure was failure-free survival (FFS).

FFS was defined as time from randomization to first evidence of at least one of the following:

- Biochemical failure: rise in PSA of 50% above the within-24-week nadir and above 4 ng/mL and confirmed by retest or treatment
- Progression either locally, in lymph nodes, or in distant metastases
- Skeletal-related event (SRE): when reported alone as the first failure, the SRE was queried with the site and coded as a FFS-failure when it was a confirmed progression
- Death from prostate cancer

Sample size

There was no formal overall sample size target. For the efficacy assessment of OS, it was assumed that there would be a slightly higher proportion of non-metastatic than metastatic patients, resulting in 2 years' median failure-free survival and in a median OS between 4 and 5 years, and a targeted relative improvement of 25% (HR 0.75) in both failure-free survival and OS for each comparator group with control.

The efficacy analysis of each pairwise comparison against control (eg, docetaxel + ADT versus ADT-only) for OS required around 403 deaths in the control arm for 90% power and a one-sided α level of 2.5% (corresponding to a two-sided α level of 5%), accounting for three intermediate analyses on failure-free survival. A total of 1776 patients were randomized to receive docetaxel + ADT or ADT-only, of whom 592 were allocated to receive docetaxel + ADT treatment and 1184 to ADT-only treatment.

Randomisation

Randomization was done centrally, using the method of minimization, stratifying for hospital, age at randomization, presence of metastases, planned use of radiotherapy, World Health Organization (WHO) performance status, planned hormone therapy, and regular use of aspirin or another nonsteroidal anti-inflammatory drug (NSAID). Patients were allocated in a 2:1 ratio to receive ADT or docetaxel + ADT. Although the STAMPEDE study utilized a MAMS design and included additional treatment arms, for the purpose of this submission only the docetaxel + ADT and ADT only treatment arms are relevant.

Blinding (masking)

The study was open label.

Statistical methods

Standard survival analysis methods were used to analyse time-to-event data. Cox proportional hazards regression models were used to estimate hazard ratios, adjusted for stratification factors (except hospital and planned hormone therapy), and stratified by time periods defined by addition of a new research group or end in recruitment to an ongoing research group. Adjusted p-values were calculated from the likelihood ratio test to compare event-time distributions between the two treatment groups.

Flexible parametric models were constructed with 4 degrees of freedom for each of the baseline hazard function and time-dependent effect, and adjusted for stratification factors and time periods. Medians and 5-year estimates were made using the Kaplan-Meier method, and using the flexible parametric model (FPM) fitted to the data. The proportional hazards assumption was tested; restricted mean survival time was used in the presence of non-proportionality. Fine and Gray regression models were used for competing risk analysis of prostate-cancer specific survival. Prespecified analyses looked at consistency of treatment effect within stratification factors, over time period, and also by metastasis status, categorized Gleason score (≤ 7, 8+, unknown), recurrent disease, and prostate-specific antigen values before hormone therapy. All tests were two-sided, with confidence intervals given at the 95% level.

The underlying assumptions of the Cox proportional hazard model were checked by a non-proportionality test. There is no evidence of a non-proportional hazards ($p = 0.874$ where a small p-value suggests evidence of non-proportionality); therefore, the adjusted Cox estimates take primacy for this comparison.

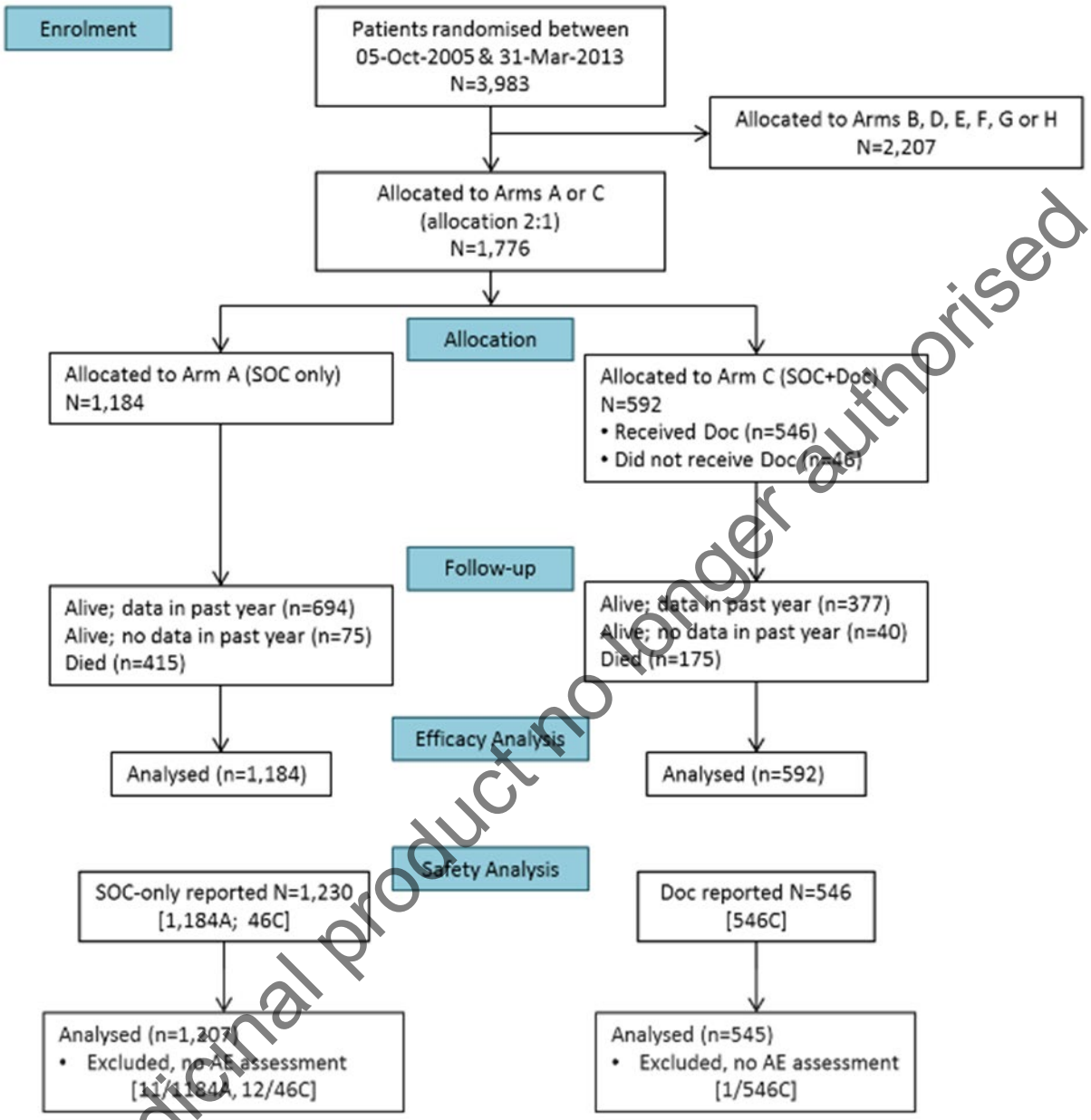
Several sensitivity analyses showed the consistency of the treatment effect on OS and the robustness of the results.

An unadjusted Cox model test was performed on survival data as a sensitivity analysis.

A multivariate flexible parametric model time-fixed estimates was performed as a sensitivity analysis using the stratification factors (except center and method of hormones) as covariates, and stratified by trial period. A multivariate Cox model adjusted on stratification factors (except center and method of hormones) and time-varying WHO-PS and stratified by trial period was also performed as a sensitivity analysis.

Results

Participant flow



Note: "Alive; data in past year" relates to the year prior to the data administrative cutpoint and gives detail of the number of patients for whom data had been received within that time.

Recruitment

The docetaxel comparison in STAMPEDE was conducted at 100 sites in the UK and Switzerland under the sponsorship of the MRC and was coordinated by MRC Clinical Trial Unit in London. Between 15 October 2005 and 31 March 2013, 1776 patients were randomized to the ADT-only and docetaxel + ADT treatment arms of the STAMPEDE RCT; 1184 and 592 patients were assigned to the ADT-only and docetaxel + ADT treatment arms, respectively. The study was completed (last patient completed in docetaxel arm) in July 2018.

Conduct of the study

The latest Trial Protocol Version is 8.0.

There were 9 protocol amendments in total:

Version 1.0 (May 2004)

Version 1.1 (May 2005)

Version 2.0 (Jun 2005)

Version 3.0 (Jul 2006)

Version 4.0 (Dec 2007)

Version 5.0 (Aug 2008)

Version 6.0 (Jul 2009)

Version 7.0 (Jul 2011)

Version 7.1 (Jul 2011)

Baseline data

A total of 1086 patients (61%) had metastatic disease (M1) at entry, while 690 patients (39%) had non-metastatic disease (M0). Most patients were newly diagnosed (1681; 95%), 1037 of whom (58%) had metastatic disease at entry. The median age was 65 years for both treatment arms, the median PSA values were 64 ng/mL and 63 ng/mL for the ADT-only and docetaxel + ADT arms, respectively, and 1238 patients (70%) had Gleason sum scores of 8-10.

Table 2: Baseline characteristics at randomisation (by treatment arm)

	A SOC		C SOC+Doc	
	N	%	N	%
WHO performance status				
0: Normal activity without restriction	922	78%	461	78%
1: Strenuous activity restricted	250	21%	127	21%
2: Up and about >50% of waking hrs	12	1%	4	1%
Missing	*0*	*n/a*	*0*	*n/a*
Age at randomisation (years)				
Median (IQR)	65 (60-70)		65 (61-71)	
Min-Max	41-82		40-81	
Missing	*0*	*n/a*	*0*	*n/a*
PSA at randomisation (ng/ml)				
Median (IQR)	67 (23-200)		70 (27-181)	
Min-Max	0-15747		1-9999	
Missing	*0*	*n/a*	*0*	*n/a*
Ln(PSA) at randomisation (ng/ml)				
Median (IQR)	4 (3-5)		4 (3-5)	
Min-Max	-2; 10		0; 9	
Missing	*0*	*n/a*	*0*	*n/a*
Time from diagnosis to randomisation (days)				
Median (IQR)	75 (54-99)		76 (56-99)	
Min-Max	0-4070		3-5033	
Missing	*5*	*n/a*	*7*	*n/a*
Pain from PCa at randomisation				
Absent	984	85%	490	84%
Present	179	15%	96	16%
Missing	*21*	*n/a*	*6*	*n/a*
Reported grouping by site				
N0M0, new	256	22%	131	22%
N+M0, new	171	14%	86	15%
M1, new	690	58%	347	59%
Local treatment, now relapsing	67	6%	28	5%
Missing	*0*	*n/a*	*0*	*n/a*
T-stage at randomisation				
T0	7	1%	2	0%
T1	21	2%	0	0%
T2	113	10%	60	10%
T3	756	64%	390	66%
T4	211	18%	105	18%
TX	76	6%	35	6%
Missing	*0*	*n/a*	*0*	*n/a*
N-stage at randomisation				
N0	522	44%	260	44%
N+	594	50%	298	50%
NX	68	6%	34	6%
Missing	*0*	*n/a*	*0*	*n/a*
Any metastases at randomisation				
No	460	39%	230	39%
Yes	724	61%	362	61%
Missing	*0*	*n/a*	*0*	*n/a*
Bone metastases at randomisation				
No	550	46%	285	48%
Yes	634	54%	307	52%
Missing	*0*	*n/a*	*0*	*n/a*
Liver metastases at randomisation				
No	1169	99%	586	99%
Yes	15	1%	6	1%
Missing	*0*	*n/a*	*0*	*n/a*
Lung metastases at randomisation				
No	1151	97%	579	98%
Yes	33	3%	13	2%
Missing	*0*	*n/a*	*0*	*n/a*
Nodal metastases at randomisation				
No	964	81%	490	83%
Yes	220	19%	102	17%
Missing	*0*	*n/a*	*0*	*n/a*
Other metastases at randomisation				
No	1138	96%	567	96%
Yes	46	4%	25	4%
Missing	*0*	*n/a*	*0*	*n/a*
Total	**1184**	**100%**	**592**	**100%**

Numbers analysed

Table 3: Censoring information by treatment arm - OS – STAMPEDE

		ADT	Docetaxel + ADT
Patients randomized		1184	592
Number of patients without death reported at administrative cut-point		769 (65%)	417 (70%)
Number of patients stopped follow-up early		20	16
Reason for censoring	Censored at randomization	0 (0%)	1 (0%)
	Alive in past 12 months	694 (90%)	377 (90%)
	Alive longer ago than 12 months	75 (10%)	39 (10%)
Time from last contact to administrative cut-point (m)	Median	3.4	3.7
	Mean	5.9	6.2
	Min-Max	0-96.8	0-108.5
Time from last contact to administrative cut-point	0-2 months	249 (32%)	121 (29%)
	2-6 months	346 (45%)	185 (44%)
	>6 months	174 (23%)	111 (27%)

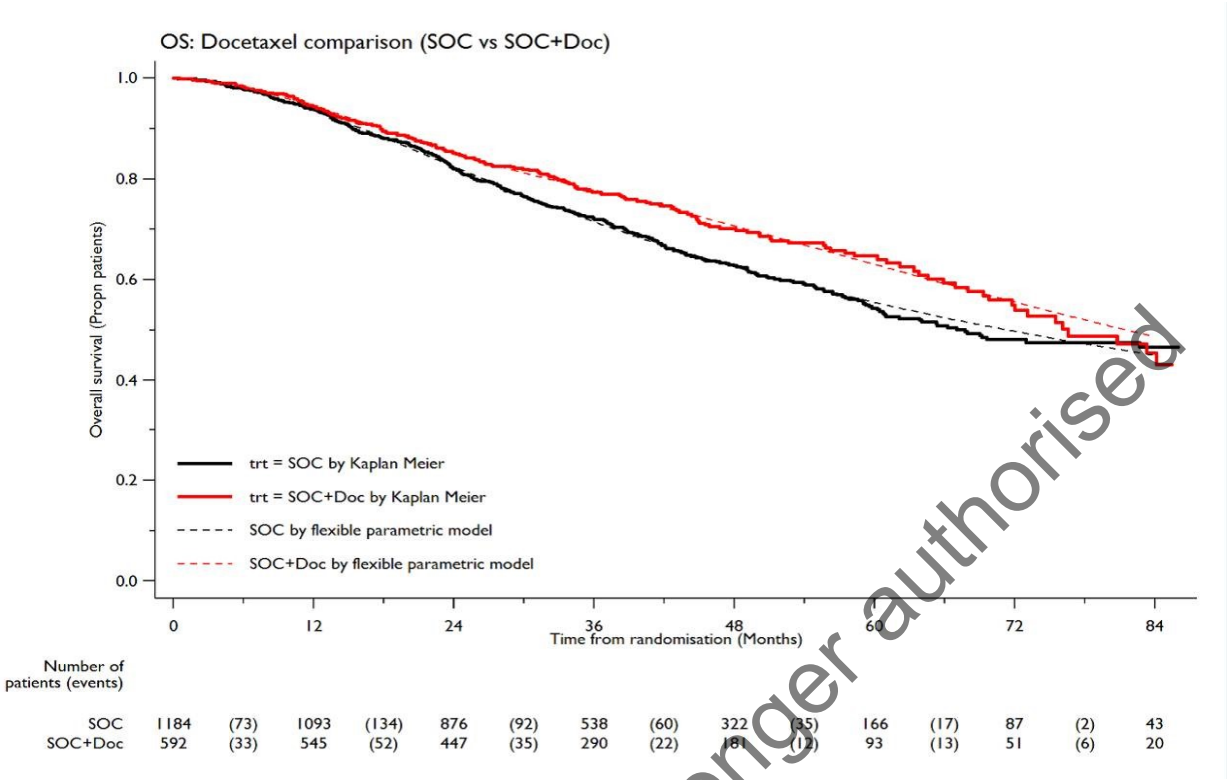
Outcomes and estimation

- Primary efficacy endpoint: Overall Survival

The analysis of OS was based on a total of 175 deaths (29.6%) in the docetaxel + ADT group and 415 deaths (34.8%) in the ADT-only group.

Median survival was 77 months (95% CI: 70-NR) and 68 months (95% CI: 60-91) in the docetaxel + ADT and ADT-only groups, respectively (HR 0.78, 95% CI: 0.66-0.93; p = 0.006). The 5-year survival was 65% and 54% in the docetaxel + ADT and ADT-only groups, respectively.

Figure 1:Kaplan-Meier overall survival (all patients) - STAMPEDE



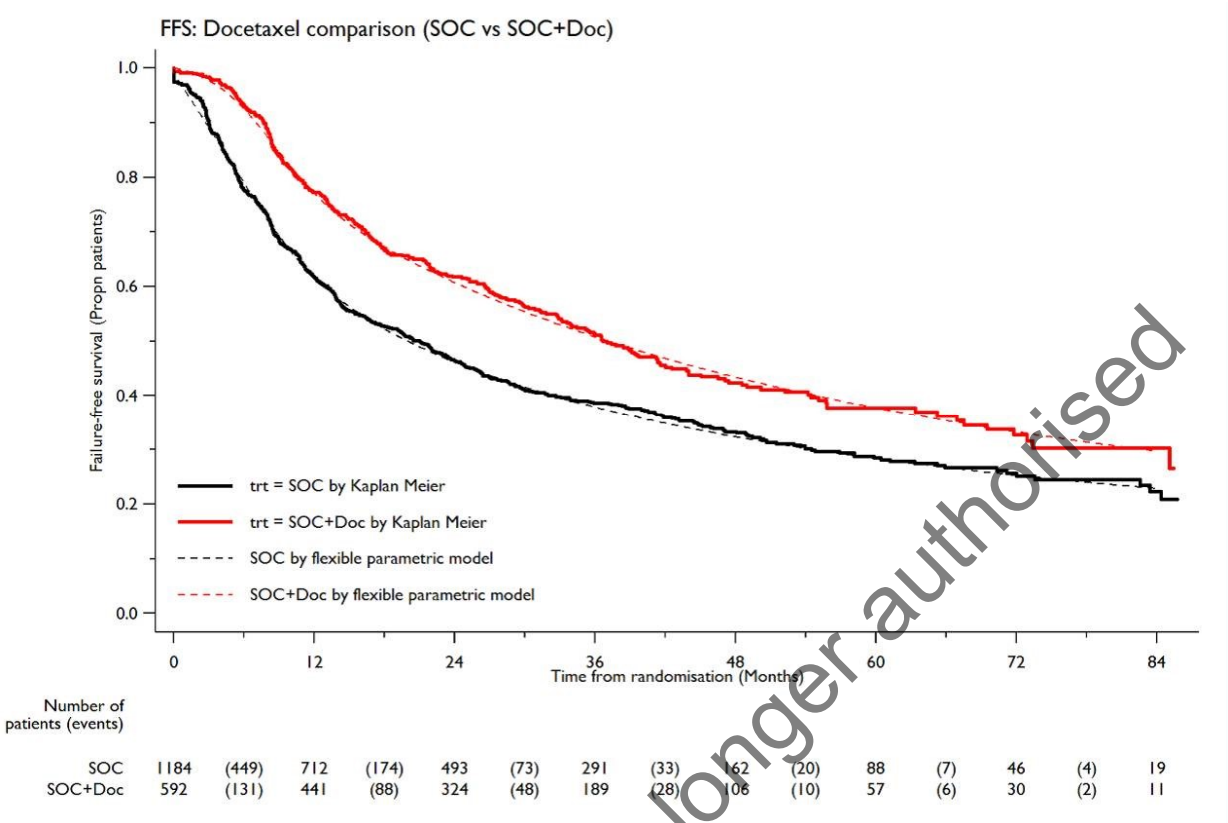
Abbreviations: Doc, docetaxel; OS, overall survival; SOC, standard of care (ie, ADT)

Overall, 1186 patients were without event at the cut-off date (65% in the ADT-only group and 70% in the docetaxel + ADT group). In both groups, 90% of patients (694 patients in the ADTonly group and 377 patients in the docetaxel + ADT group) were alive in the past 12 months.

- Secondary efficacy endpoint: Failure-free Survival

A total of 315 (53%) and 761 (64%) patients reported a FFS event in the docetaxel + ADT and ADT-only groups, respectively. Median FFS was 37 months (95% CI: 33-42) and 21 months (95% CI: 18-23) in the docetaxel + ADT and ADT-only groups, respectively (HR 0.61, 95% CI: 0.53-0.70; p = 0.413 x10-13). The 5-year FFS was 38% and 28% in the docetaxel + ADT and ADT-only groups, respectively.

Figure 2: FFS (all patients) - STAMPEDE



Abbreviations: Doc, docetaxel; FFS, failure-free survival; FPM, flexible parametric model; SOC, standard of care (ie, ADT); trt, treatment.

FFS was defined by several contributing event types. The events leading to FFS are described in the following table:

Table 1: Worst component of first reported event among patients experiencing FFS - STAMPEDE

Contributing event	ADT (N=761) n (%)	Doc + ADT (N=315) n (%)
Prostate cancer-related death	9 (1)	11 (4)
Distant metastases	88 (12)	38 (12)
Lymph node progression	15 (2)	3 (1)
Skeletal-related event	3 (0)	1 (0)
Local progression	17 (2)	12 (4)
PSA failure	629 (83)	250 (79)

Abbreviations: ADT, androgen deprivation therapy; Doc, docetaxel; PSA, prostate-specific antigen.

Table 2: Censoring information by treatment arm - FFS - STAMPEDE

		ADT	Docetaxel + ADT
Patients randomized		1184	592
Number of patients without FFS event at administrative cut-point		423 (36%)	277 (47%)
Time for censoring			
	Censored at randomization	0 (0%)	1 (0%)
	Censored at last follow-up	423 (100%)	276 (100%)
Time from last contact to administrative cut-point (m)			
	Median	3.4	3.9
	Mean (SD)	7.5 (13.2)	8.6 (14.7)
	Min-Max	0-96.8	0-108.5
Time from last contact to administrative cut-point			
	0-12 weeks	172 (41%)	105 (38%)
	12 weeks to 6 months	146 (35%)	91 (33%)
	6 months to 12 months	54 (13%)	43 (16%)
	>12 months	51 (12%)	38 (14%)

Abbreviations: ADT, androgen deprivation therapy; FFS, failure-free survival; SD, standard deviation

Time to skeletal-related events, there were a total 112 patients (19%) and 328 patients (28%) in the docetaxel + ADT and ADT-only groups, respectively, who reported a SRE. Median time to SRE was 106 months in the ADT-only group, but was not reached in the docetaxel + ADT group, (HR 0.60, 95% CI: 0.48-0.74; p = 0.127 $x10^{-5}$) and the 5-year SRE-free rate was 75% and 66% in the docetaxel + ADT and ADT-only groups, respectively. SREs were primarily due to bone pain (77% and 81% in the docetaxel + ADT and ADT-only groups, respectively).

Time to PSA failure, there were a total 277 patients (47%) and 698 patients (59%) in the docetaxel + ADT and ADT-only groups, respectively, who reported a PSA failure event. Median time to PSA failure was 43 months and 24 months in the docetaxel + ADT and ADT-only groups, respectively (HR 0.59, 95% CI: 0.52-0.68; p = 0.34 $x10^{-13}$). The 5-year PSA failure was 43% and 32% in the docetaxel + ADT and ADT-only groups, respectively.

Time to Progression-free survival (PFS), there were a total 229 patients (39%) and 561 patients (47%) in the docetaxel + ADT and ADT-only groups, respectively, who reported a PFS event. Median PFS was 67 months and 46 months in the docetaxel + ADT and ADT-only groups, respectively (HR 0.70, 95% CI: 0.60-0.81; p = 0.25 x10-5). The 5-year PFS was 53% and 49% in the docetaxel + ADT and ADT-only groups, respectively.

Time to cause-specific death, at the time of analysis there were a total of 175 and 415 deaths in the docetaxel + ADT and ADT-only treatment arms, respectively; 82% and 84% of these were due to prostate cancer, respectively. The median time to death due to prostate cancer was 102 months and 91 months in the docetaxel + ADT and ADT-only groups, respectively. An adjusted competing risks regression for prostate cancer-specific survival showed an advantage of docetaxel + ADT over ADT-only treatment (subHR 0.79, 95% CI: 0.65-0.96; p = 0.019). There was no difference between the two groups in the competing risks regression for non-prostate cancer-specific survival (subHR 0.94, 95% CI: 0.62-1.43; p = 0.782).

Ancillary analyses

Subgroup analyses - metastatic disease

This analysis is the one supporting the claimed indication.

Overall Survival

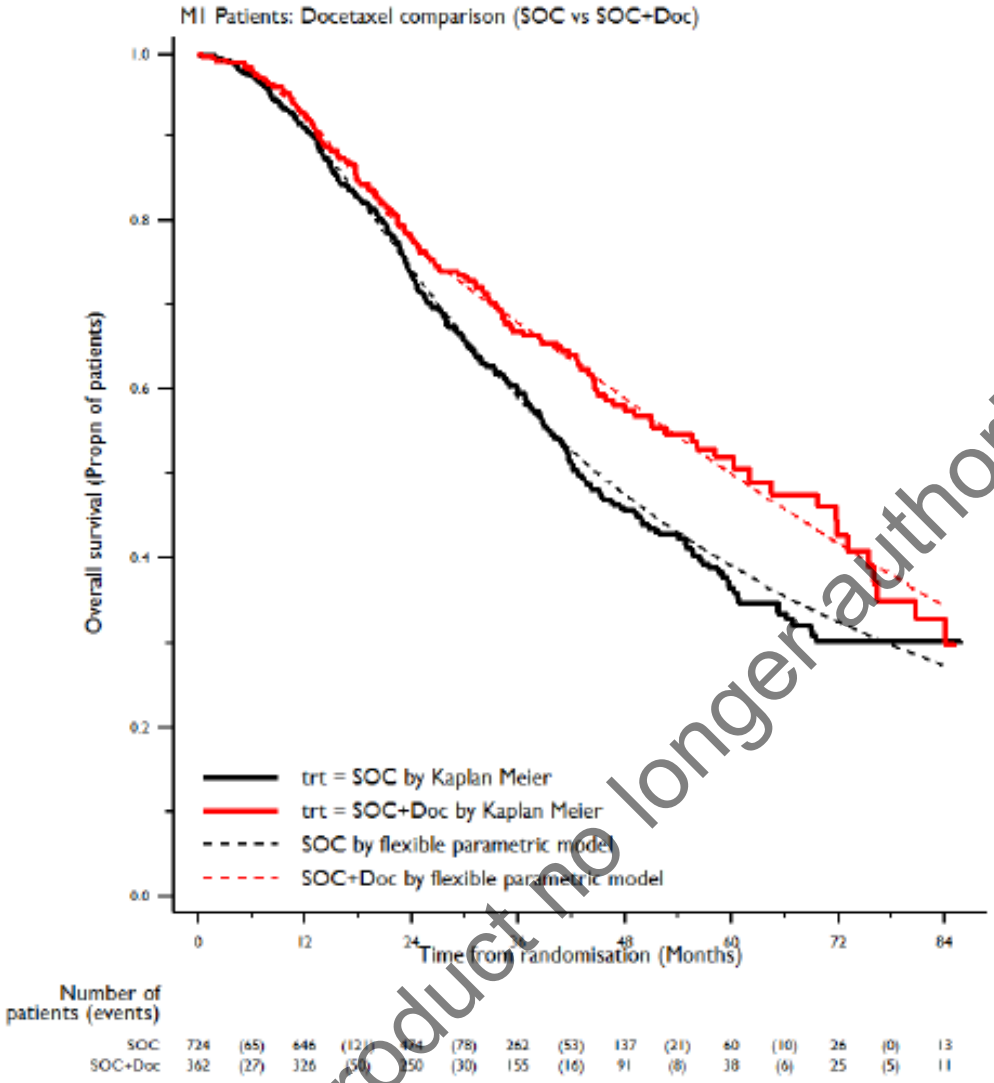
The median follow-up (FU) time at the cutoff date for the primary analyses was 3.5 years. There were 144 and 350 deaths among patients with metastatic disease (M1) in the docetaxel + ADT and ADT-only arms, respectively. Among these M1 patients, in a pre-planned subset analysis for the docetaxel + ADT group compared to the ADT-only group, the median survival was 62 months (95% CI: 51-73) and 43 months (95% CI: 40-48) in the docetaxel + ADT and ADT-only groups, respectively (HR 0.76, 95% CI: 0.62-0.92; p = 0.005) (below table). The 5-year survival was 52% and 37% in the docetaxel + ADT and ADT-only groups, respectively, among the patients with metastatic disease.

Table: OS results in M1 from STAMPEDE trial (median FU time of 3.5 years).

	Docetaxel + SOC	SOC
Number of metastatic prostate cancer patients	362	724
Median overall survival (months)	62	43
95% CI	51-73	40-48
Adjusted hazard ratio	0.76	
95% CI	(0.62-0.92)	
p-value[a]	0.005	

[a] p-value calculated from the likelihood ratio test and adjusted for all stratification factors (except center and planned hormone therapy) and stratified by trial period

Figure 3: Kaplan-Meier overall survival (metastatic patients) - STAMPEDE



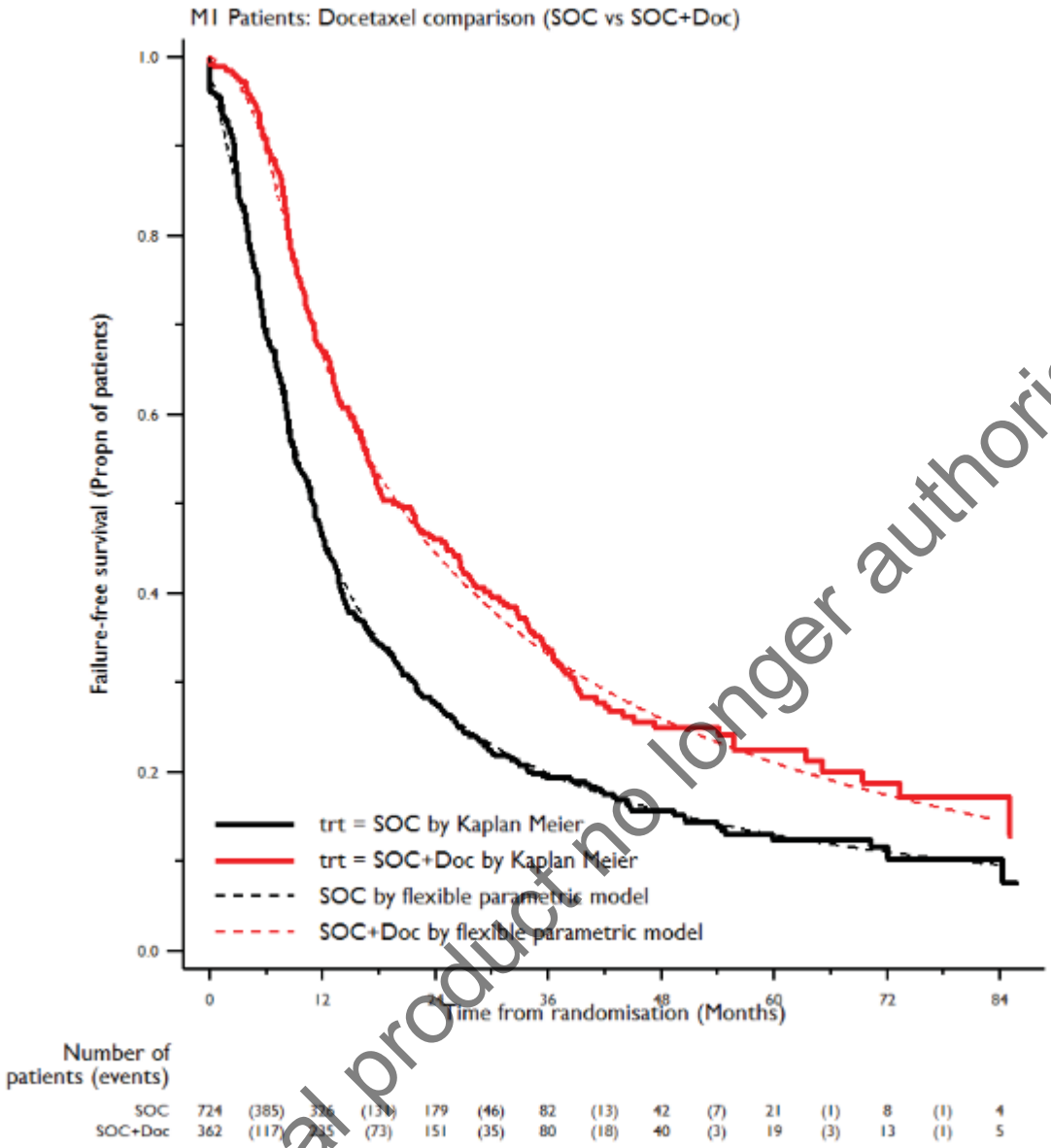
Abbreviations: Doc, docetaxel; SOC, standard of care (ie, ADT); trt, treatment.

Failure-Free Survival

Table 3: HR and 95% CI by metastatic status at randomisation

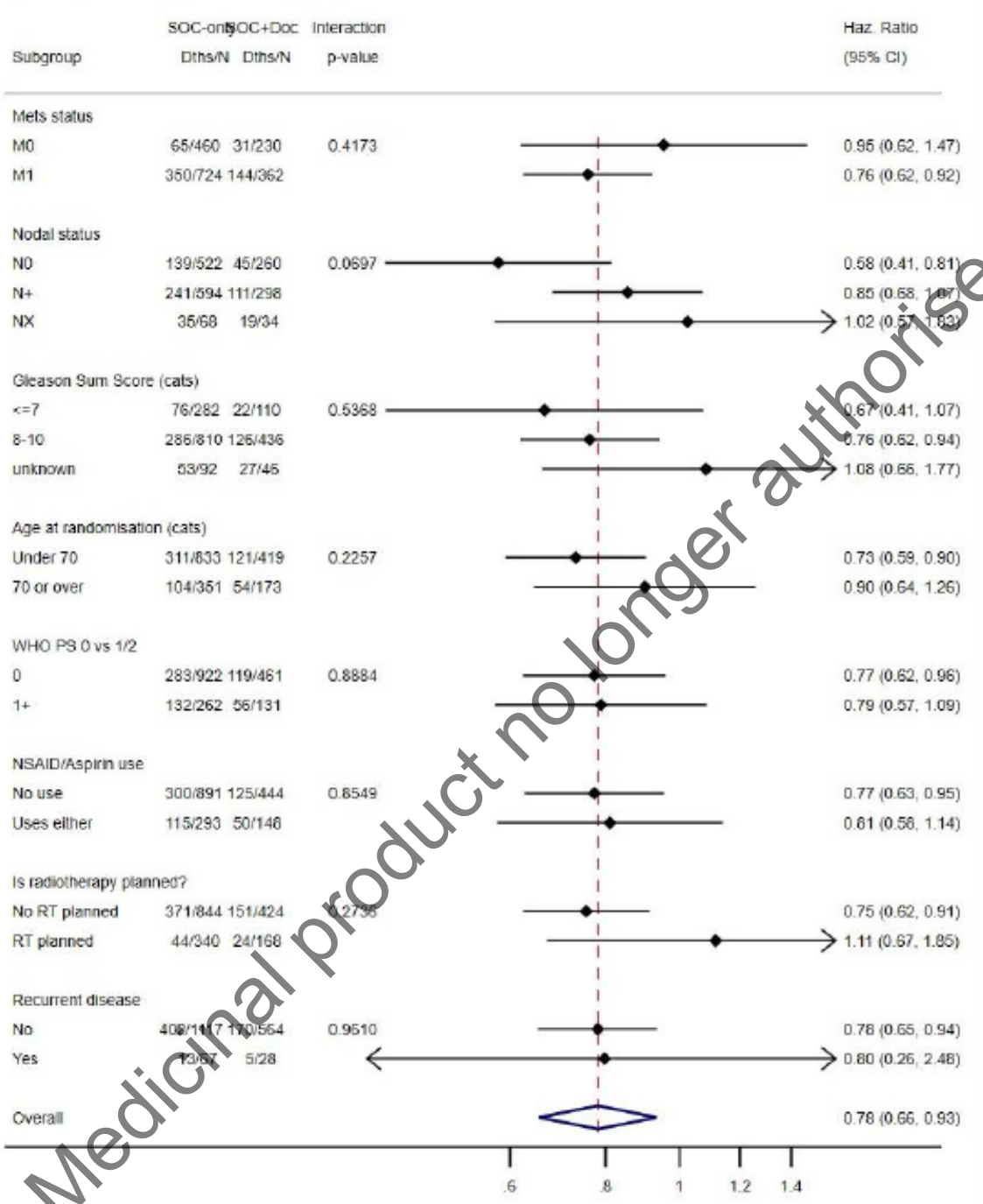
Research Arm	Mets status	Adjusted HR*	95% CI	p-value**	Events (ctrl)	Events (res)	Non PH test *** p-value	Trt/Mets interaction p-value
C: SOC+Doc	M0	0.60	0.45-0.80	$0.283x10^{-3}$	176	63	0.1463	0.898
	M1	0.61	0.53-0.71	$0.283x10^{-10}$	585	252	0.0001	

Figure 4: Failure-Free Survival for metastatic patients - STAMPEDE



Other subgroups analyses

Figure 5: Forest plots of treatment effect on OS by subgroup - STAMPEDE



Abbreviations: CI, confidence interval; Doc, docetaxel; NSAID, non-steroidal anti-inflammatory drug; PS, performance score; RT, radiotherapy; SOC, standard of care; WHO, World Health Organization.

Updated analyses

Updated analyses were performed with a median FU time of 6.5 years at the data cutoff date and the analysis of OS was based on a total of 719 deaths (66%), with 494 events (68%) reported in the ADT arm and 225 events (62%) reported in the ADT + docetaxel arm.

In the M1 population, the estimated hazard ratio (HR) for OS in this updated analysis was 0.81 (95% CI: 0.69 to 0.95), characterizing a reduction of 19% in risk of death with ADT + docetaxel compared to ADT (p=0.009). Median overall survival (95% CI) in the docetaxel + ADT arm was 58.8 months, compared to 43.2 months in the ADT only arm, corresponding to a 16 months survival benefit for the patients treated with docetaxel.

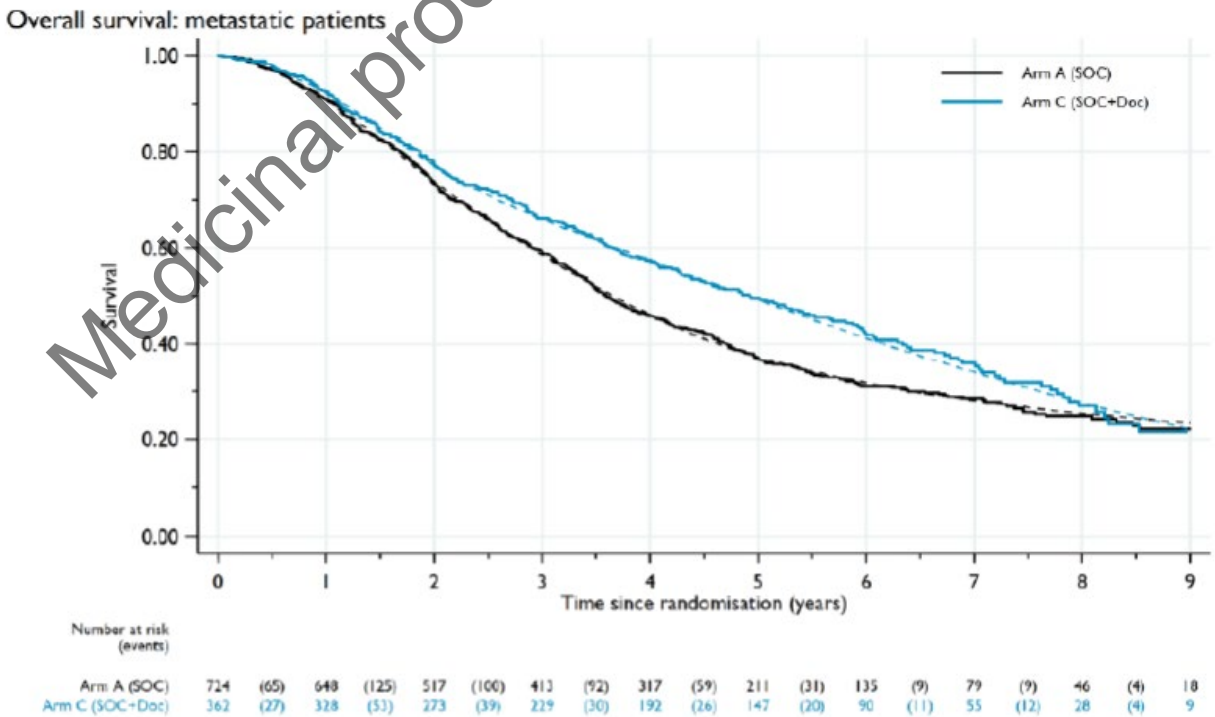
Table 1 - Stampede study, Primary OS analysis and Updated OS analysis

M1 patients	Primary analysis (3.5 years)	Updated analysis (6.5 years)
N° of deaths in ADT arm	350/724 (48%)	494/724 (68%)
Median OS, months	43	43.2*
N° of deaths in Doc + ADT arm	144/362 (39.8%)	225/362 (62%)
Median OS, months	62	58.8*
HR (95%CI),	0.76 (0.62-0.92)	0.81 (0.69 to 0.95)
p-value	p=0.005	p=0.009

Source: Stampede CSR Tables 109 and 110, Updated Stampede analysis Tables 22 and 25

*: medians (OS, FFS, SRE) in the updated analyses were provided in years in the STAMPEDE updated CSR and converted into months (year x12) throughout this response document for consistency with primary analysis.

Figure 1 - Overall survival: metastatic patients



Additional analyses based on metastasis burden

The STAMPEDE study was retrospectively analyzed by subgroups according to metastasis burden at randomization, using the definition that was used for the CHAARTED study.

Metastasis burden was assessable for 830/1086 (76%) patients, including 362/830 (43.6%) patients with low and 468/830 (56.4%) patients with high metastasis burden. These subgroups were representative of the full M1 cohort in terms of stratification factors.

In the subgroup of patients with a high metastasis burden, median OS was 39.6 in the docetaxel +ADT treatment group and 34.8 months in the ADT alone group; HR=0.81, 95% CI 0.64-1.02, p=0.064. In the subgroup of patients with a low metastasis burden, median OS was 93.6 in the docetaxel +ADT treatment group and 76.8 months in the ADT alone group; HR=0.76, 95% CI 0.54-1.07, p<0.107.

Test for interaction between treatment and disease volume was not significant, indicating absence of evidence for heterogeneity in the treatment effect in these 2 subgroups of patients.

Figures 2 and 3 provide the Kaplan Meier curves for the Updated analysis in the high and low metastasis burden M1 population, respectively.

Figure 2 - Overall survival: high-burden metastatic patients

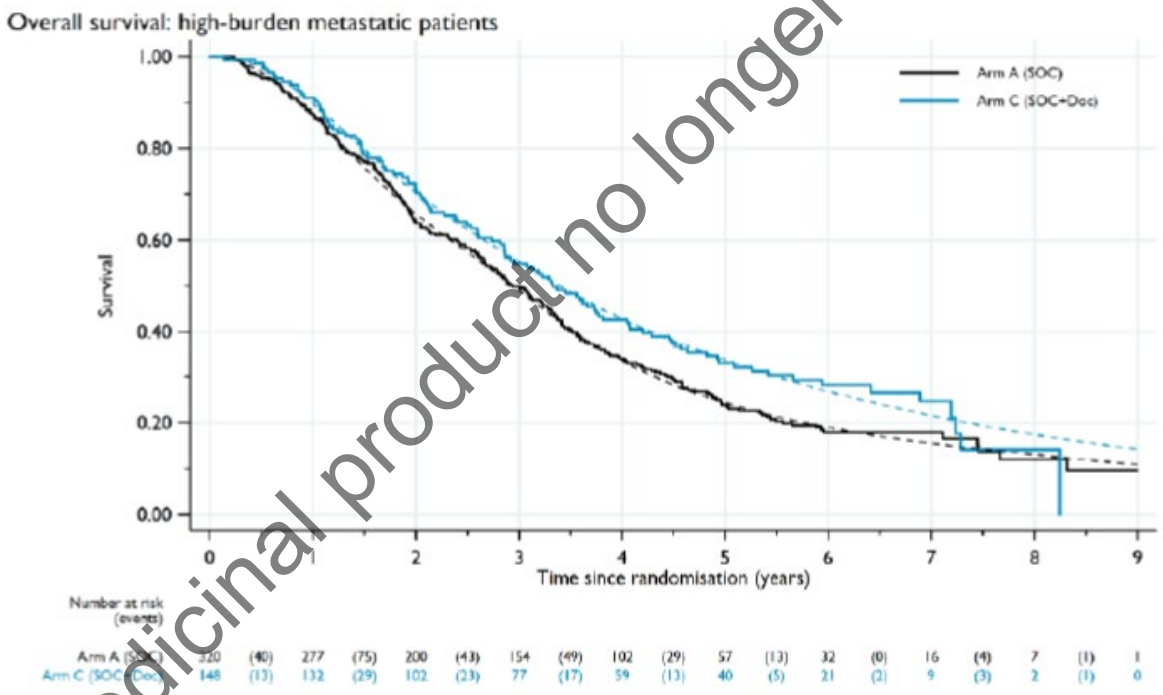
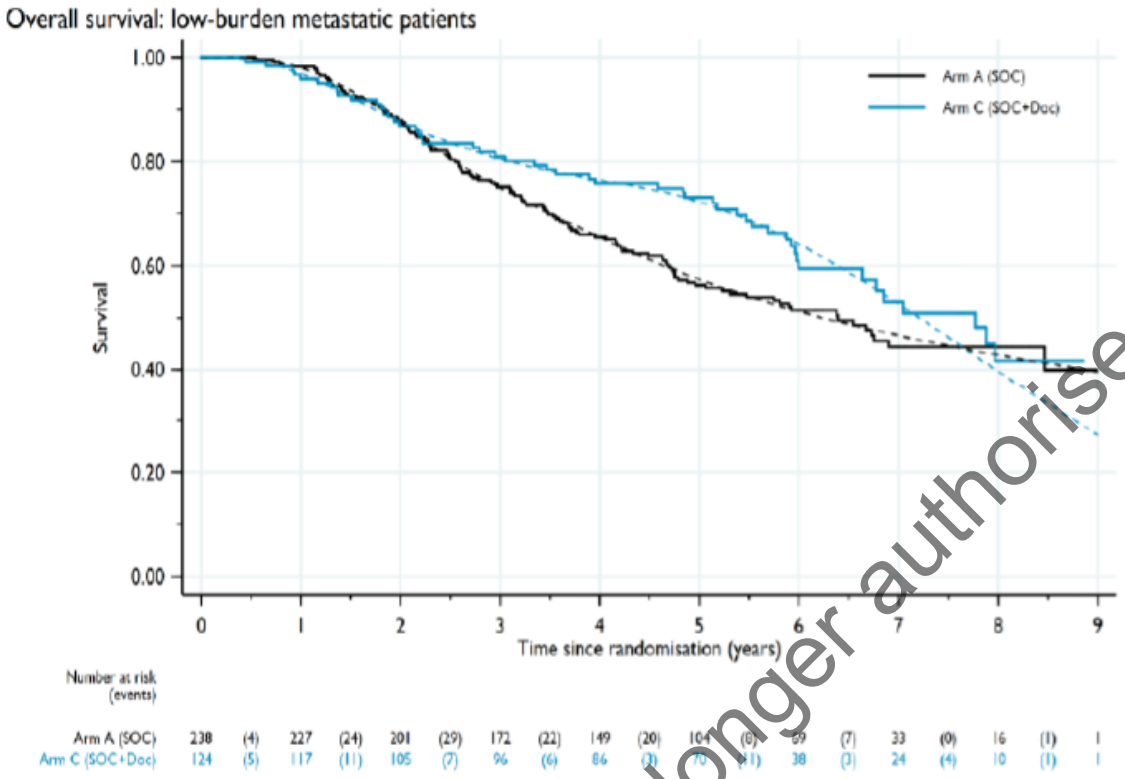


Figure 3 - Overal survival: low burden metastatic patients



Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 1. Summary of Efficacy for trial <trial>

Title: STAMPEDE		
Study identifier	MRC PR08	
Design	international, open-label, adaptive, multicenter, controlled, multi-arm-multi-stage (MAMS), randomized study with a seamless phase 2/3 design comparing the efficacy (OS as primary endpoint) and safety of adding new agents (either in monotherapy or in combination) to ADT versus ADT alone in patients with hormone-naïve high risk locally advanced or metastatic prostate cancer who were commencing first line long term hormone therapy	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	8 years not applicable not applicable
Hypothesis	Subgroup analysis restricted to metastatic patients supporting the present claim	
Treatments groups	ADT	ADT, 724
	ADT + Docetaxel	ADT + Docetaxel, 362

Endpoints and definitions	Primary endpoint	OS	Overall Survival
	Secondary	FFS	Failure-free Survival
Database lock	13-May-2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Subgroup analysis restricted to metastatic patients supporting the present claim		
Descriptive statistics and estimate variability	Treatment group	ADT	ADT+Docetaxel
	Number of subject	724	362
	OS (median)	43	62
	95% CI	40-48	51-73
	FFS (median)	12.0	20.4
	95% CI	9.6 – 12.0	16.8-25.2

Effect estimate per comparison	Primary endpoint	Comparison groups	ADT+Docetaxel vs ADT
		Adjusted hazard ratio	0.76
		95% CI	0.62 - 0.92
		P-value	0.005
	Secondary endpoint	Comparison groups	ADT+Docetaxel vs ADT
		Adjusted hazard ratio	0.66
		95% CI	0.57 0.76
		P-value	< 0.001

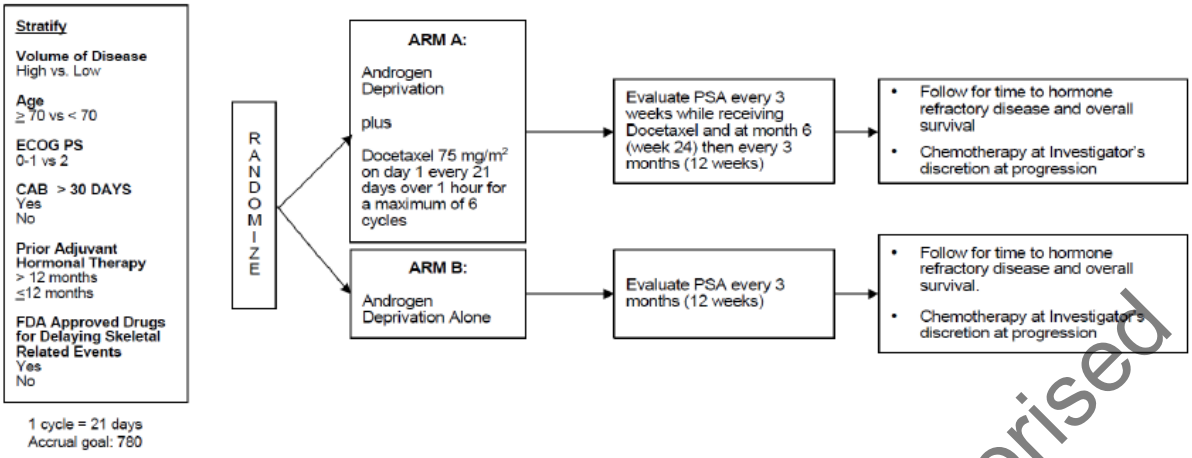
Supportive studies

CHAARTED study

Methods

The CHAARTED study was an open-label, multicenter, randomized Phase 3 study to compare the efficacy (OS as primary endpoint) and safety of adding docetaxel to ADT versus ADT alone, in patients with metastatic prostate cancer who were commencing first line long term hormone therapy. CHAARTED was conducted at 83 sites in the USA. Accrual took place between July 2006 and December 2012.

Figure 6: CHAARTED design



Abbreviations: CAB, complete androgen blockade; ECOG PS, Eastern Cooperative Oncology Group Performance Score; PSA, prostate-specific antigen.

Study participants

Eligible patients had a pathological diagnosis of prostate cancer, radiologic evidence of metastatic disease, and an ECOG performance-status score of ≤2. Prior adjuvant ADT was allowed if the duration of therapy was 24 months or less and progression had occurred more than 12 months after completion of therapy. Patients who were receiving ADT for metastatic disease were eligible if there was no evidence of progression, and treatment had commenced within 120 days before randomization. Patients with prior chemotherapy in the adjuvant or neoadjuvant setting were ineligible.

Main inclusion criteria:

1. Histologically or cytologically confirmed prostate cancer

- Metastatic disease
- On androgen-deprivation therapy for < 120 days

2. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-2 (PS 2 eligible only if decline in PS is due to metastatic prostate cancer)

3. Biology

- Absolute neutrophil count ≥ 1,500/mm^3
- Platelet count ≥ 100,000/mm^3
- Bilirubin ≤ upper limit of normal (ULN)
- Alanine aminotransferase (ALT) ≤ 2.5 times ULN
- Creatinine clearance ≥ 30 mL/min
- Prothrombin time (PT) and international normalized ratio (INR) ≤ 1.5 times ULN (unless on therapeutic anticoagulation)
- Partial thromboplastin time (PTT) ≤ 1.5 times ULN (unless on therapeutic anticoagulation)

4. At least 4 weeks since prior major surgery and recovered from all toxicity prior to randomization

5. Prior adjuvant or neoadjuvant hormonal therapy allowed provided the following are true:

- Therapy was discontinued ≥ 12 months ago AND there is no evidence of disease, as defined by 1 of the following:
    - PSA < 0.1 ng/dL after prostatectomy plus hormonal therapy
    - PSA < 0.5 ng/dL and has not doubled above nadir after radiotherapy plus hormonal therapy
- Therapy lasted no more than 24 months
    - Last depot injection must have expired by the 24-month mark

6. Prior palliative radiotherapy allowed if commenced within 30 days before starting androgen deprivation

7. Anti-androgen therapy allowed as single-agent therapy ≤ 7 days before medial castration to prevent flare

8. More than 30 days (or 6 half-lives) (whichever is longer) since prior participation in another clinical trial

9. Concurrent antiandrogen therapy (e.g., bicalutamide or flutamide) allowed, but not as sole hormonal therapy

Main exclusion criteria:

1. Prostate-specific antigen (PSA) level has risen and met criteria for progression from its lowest point between the start of androgen-deprivation therapy and randomization

2. Prior malignancy in the past 5 years except for basal cell or squamous cell carcinoma of the skin

- Other malignancies that are considered to have low potential to progress (e.g., grade 2, T1a transitional cell carcinoma) may be allowed if approved by study chair

3. Peripheral neuropathy > grade 1

4. History of severe hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80

5. Active cardiac disease, including the following:

- Active angina
- Symptomatic congestive heart failure
- Myocardial infarction within the past 6 months

6. Prior chemotherapy in adjuvant or neoadjuvant setting

7. Prior hormone therapy in the metastatic setting

8. Concurrent 5-alpha reductase inhibitors

Treatments

In the experimental arm, docetaxel was to be administered for a maximum duration of 6 treatment cycles at an intended dose of 75 mg/m² on Day 1 of a 3-week cycle. Dexamethasone was given pre-docetaxel infusion to suppress allergic/anaphylactic reactions.

Outcomes/Endpoint

The primary endpoint was overall survival.

The secondary objectives were aimed at assessing treatment failure (PFS), clinical progression (time from randomization to PSA progression or clinical progression, time to clinical progression and PFS) and biochemical progression (PSA Response).

The secondary efficacy endpoints were defined as follow:

- Time to CRPC: the time from randomization to PSA progression or clinical progression (increasing symptomatic bone metastases, progression per RECIST criteria, or clinical deterioration due to cancer per the Investigator's opinion), whichever occurred first.
- Time to clinical progression: the time from randomization to clinical progression (increasing symptomatic bone metastases, progression per RECIST criteria, or clinical deterioration due to cancer per the Investigator's opinion).
- PFS: the time from randomization to PSA progression, clinical progression, or death, whichever occurred first (for patients who progressed or died); or the time from randomization until the date last known progression-free (for patients who are alive without progression, or patients who died without documented progression and the death occurred more than 3 months after the date of last disease assessment).
- PSA response: a PSA level <0.2 ng/mL measured for two consecutive measurements at least 4 weeks apart; assessed at 6- and 12-month time points.
- Evaluation of the QoL: primarily assessed by the self-administered Functional Assessment of Cancer Therapy-Prostate (FACT-P) scoring tool as a measure of overall QoL. Additional assessments were made with the FACT-Taxane (FACT-T; to assess QoL associated with adverse effects of taxane treatment), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F; to assess fatigue), and the Brief Pain Inventory (BPI) Short Form. QoL was assessed at baseline and at 3, 6, 9, and 12 months.

Sample size

790 patients were included in the study.

The CHAARTED study underwent two major amendments. With each amendment, the sample size was adjusted so that the study would have 80% power to detect a 33.3% difference in median OS between the docetaxel + ADT and the ADT-alone arms, with the use of a stratified log-rank test at a one-sided α level of 2.5%.

At study inception, only patients with high-volume disease were to be enrolled, and the sample size was to be 568 patients. After 53 patients had been enrolled, an amendment was issued allowing the inclusion of patients with LVD and to initiate a prospective stratification of HVD versus LVD, and the sample size was increased to 600 patients. The final amendment was made after 579 patients had been enrolled, to reflect new data documenting an increase in median OS owing to the use of PSA in the detection and monitoring of disease activity and to address the September 2011 report of the data and safety monitoring committee, which noted that 70% of enrolled patients had HVD.

The final design required the enrolment of 780 patients (399 events), with projections of median overall survival with ADT alone of 33 months among patients with HVD and 67 months among patients with LVD. Interim analyses were to be performed before all semi-annual meetings of the data and safety monitoring committee starting when approximately 25% of the planned full information was obtained and continuing until either the criteria for early stopping were met or full information was obtained (after 399 deaths).

Extent of disease (HVD versus LVD) was included as an additional stratification factor in the CSR. Accrual of 12 patients per month for about 5.5 years (780 patients) followed by 1.5 years of follow-up was anticipated to achieve full information.

Demographic of study population

There were 397 randomized patients in the docetaxel + ADT group and 393 randomized patients in the ADT-only group. The median age was 64 years in the docetaxel + ADT group and 63 years in the ADT-only group. In both treatment arms, approximately 70% and 29% of patients had an ECOG performance-status

score of 0 and 1, respectively; approximately 65% of patients had HVD; and approximately 67% and 70% of patients had a Gleason score of 8 or higher in the docetaxel + ADT and ADT-only groups, respectively. In both groups, approximately 73% of the patients had received no prior local therapy for prostate cancer with curative intent.

Randomization

Kaplan-Meier estimates were used for event-time distributions. Cox proportional-hazard models (stratified on age, ECOG, use of complete androgen blockade and FDA approved drugs for delaying skeletal related events, time of prior adjuvant hormonal therapy, and extent of disease) were used to estimate hazard ratios for time-to-event end points. Stratified log-rank tests were used to compare event-time distributions between the two treatment groups, with a one-sided significance level of 2.5%. Response rates were compared with the use of Fisher's exact test. P-values are two-sided, and confidence intervals were at the 95% level.

The changes in QoL from baseline to follow-up were evaluated using the Wilcoxon signed rank test. A mixed effect model was used to evaluate the differences in FACT-P (Version 4) total scores and trial outcome index scores between the two arms over time.

Blinding

The study was open label.

Statistical methods

Descriptive statistics were used to characterize patients at study entry. Kaplan–Meier estimates were used for event-time distributions. Cox proportional- hazard models, stratified according to the factors described above, were used to estimate hazard ratios for time-to-event end points. Stratified log-rank tests were used to compare event-time distributions between the two groups. Response rates were compared with the use of Fisher's exact test. An intention-to-treat analysis was conducted that included all randomly assigned patients regardless of eligibility and treatment status. P values are two-sided, and confidence intervals are at the 95% level.

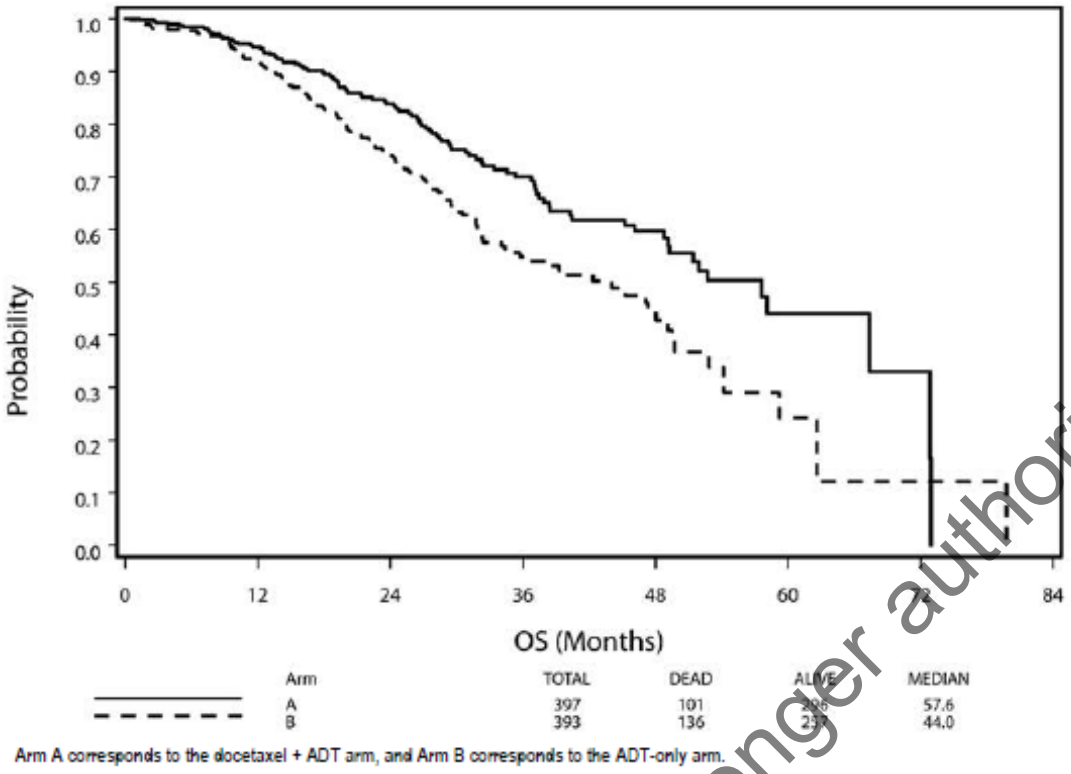
Results

- Primary efficacy endpoint: Overall Survival

Analysis of OS was based on a total of 237 deaths, with 101 events (25.4%) reported in the docetaxel + ADT arm and 136 events (34.6%) reported in the ADT-only arm. About 84% of the deaths were due to prostate cancer.

After a median follow-up of 28.9 months, the median overall survival with ADT plus docetaxel (combination therapy) was 57.6 months, compared to 44.0 months with ADT alone; the estimated HR was 0.61 (95% CI: 0.47-0.80; p = 0.0003).

Figure 7: Kaplan-Meier overall survival (all patients) - CHAARTED



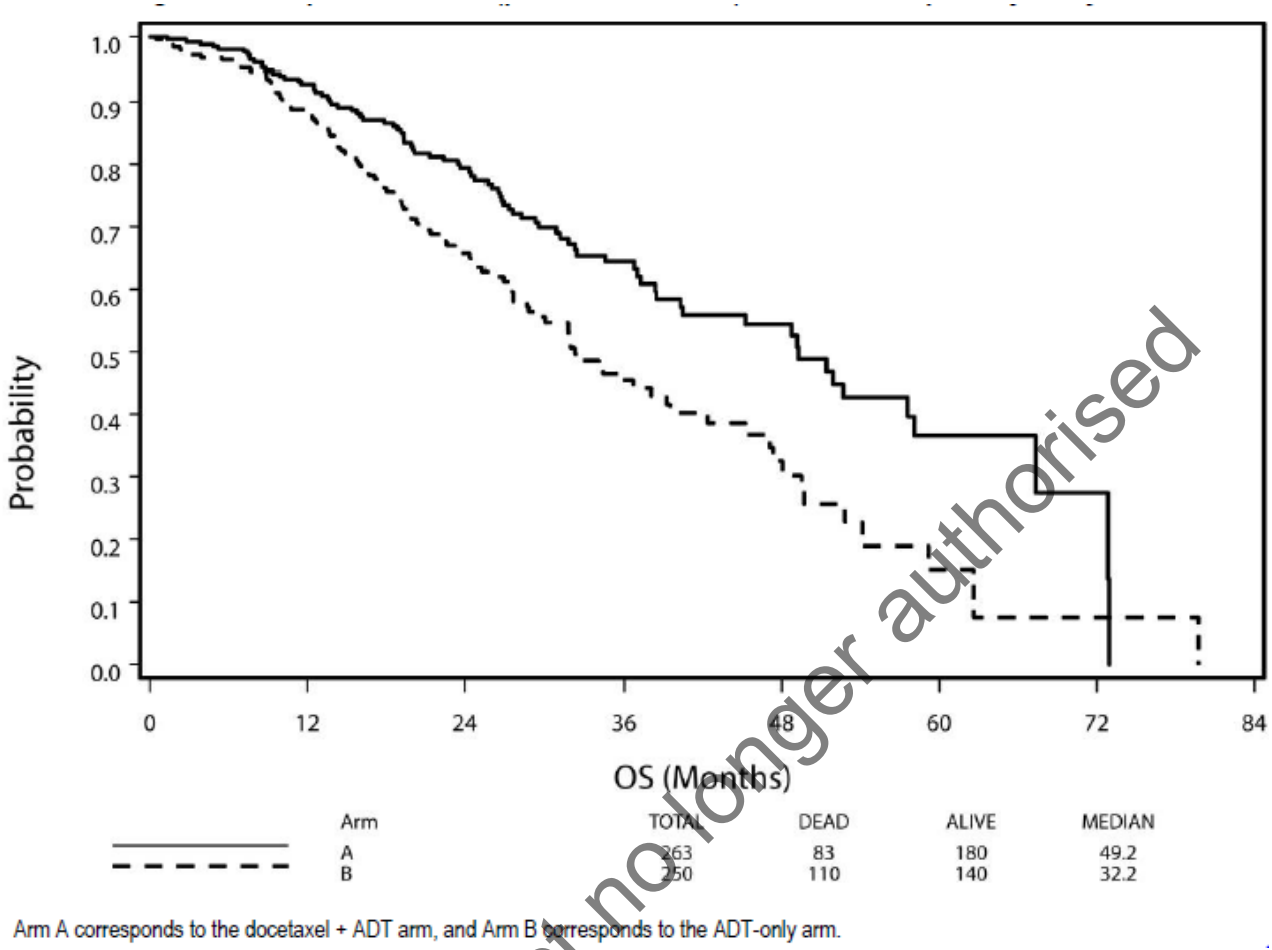
Arm A corresponds to the docetaxel + ADT arm, and Arm B corresponds to the ADT-only arm.

The median time to biochemical, symptomatic, or radiographic progression was 20.2 months in the combination group, as compared with 11.7 months in the ADT-alone group (hazard ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001). The rate of a prostate-specific antigen level of less than 0.2 ng per milliliter at 12 months was 27.7% in the combination group versus 16.8% in the ADT-alone group (P<0.001).

The OS was analyzed by disease volume: 66.2% and 63.5% of patients had HVD in the docetaxel + ADT and ADT-only arms, respectively, and 33.8% and 36.5% of patients had LVD in the docetaxel + ADT and ADT-only arms, respectively.

The median OS for the patients with HVD was 49.2 months versus 32.2 months for the docetaxel + ADT and ADT-only arms (HR 0.60, 95% CI: 0.45-0.81; p <0.001), respectively.

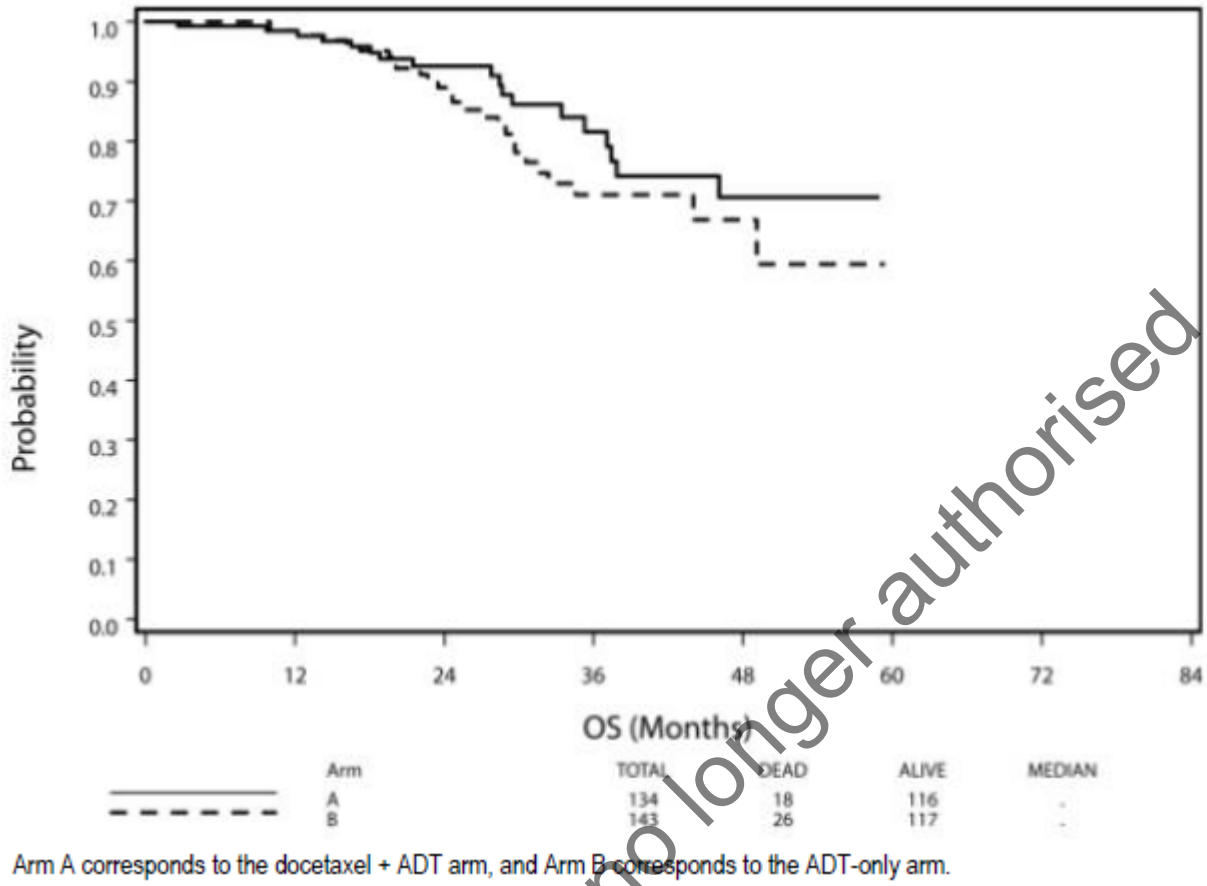
Figure 8:Kaplan-Meier OS (patients with HVD) - CHAARTED primary analysis



Arm A corresponds to the docetaxel + ADT arm, and Arm B corresponds to the ADT-only arm.

The median OS for the patients with LVD was not reached for either arms (HR 0.60, 95% CI: 0.32-1.13; p = 0.11) (Figure 10); however, the study was not powered to detect differences in the LVD subset as the data were not mature at the time of the primary analysis.

Figure 9: Kaplan-Meier OS (patients with LVD) - CHAARTED primary analysis



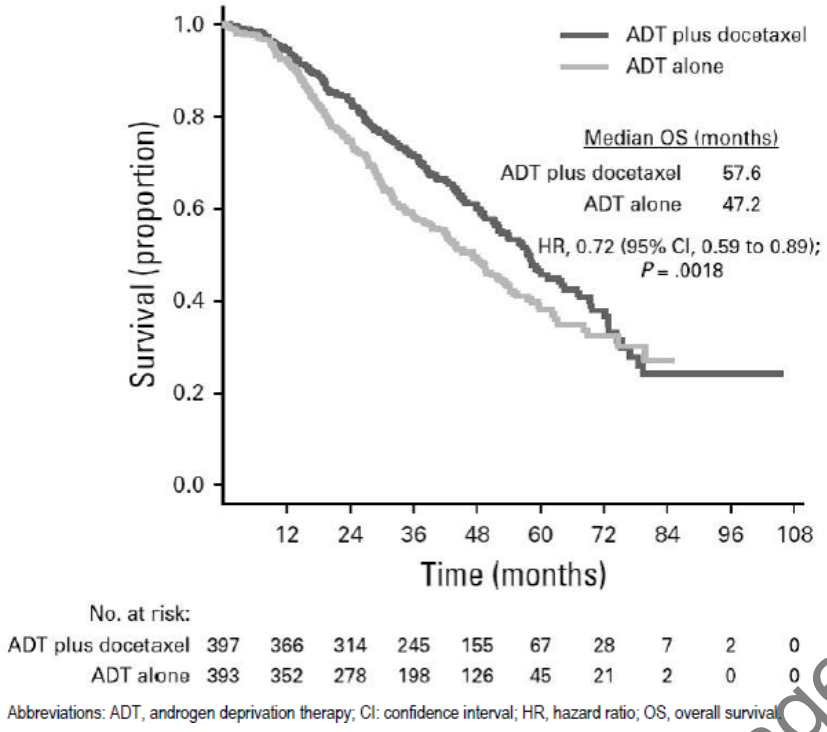
Arm A corresponds to the docetaxel + ADT arm, and Arm B corresponds to the ADT-only arm.

Updated analyses

Updated analyses were performed with a median FU time of 53.7 months at the data cutoff date and the analysis of OS was based on a total of 399 deaths (51%), with 211 events (54%) reported in the ADT arm and 188 events (47%) reported in the ADT + docetaxel arm.

In these updated analyses, the estimated HR for OS was 0.72 (95% CI: 0.59 to 0.89, p=0.0018). Median overall survival (95% CI) in the docetaxel + ADT arm was 57.6 months (52 to 63.9), compared to 47.2 months (41.8 to 52.8) in the ADT only arm.

Figure 10: Kaplan-Meier OS - all patients - CHAARTED long-term follow-up



Abbreviations: ADT, androgen deprivation therapy; CI: confidence interval; HR, hazard ratio; OS, overall survival

Among patients with HVD (median follow-up of 53.7 months), the median OS benefit with docetaxel + ADT treatment was 16.8 months (the median OS was 51.2 versus 34.4 months for the docetaxel + ADT arm and the ADT-only arm, respectively; HR 0.63 [95% CI: 0.50-0.79; p <0.001]). Among patients with LVD (median follow-up of 53.7 months), the median OS was 63.5 months and not reached for the docetaxel + ADT arm and the ADT-only arm, respectively; HR 1.04 [95% CI: 0.70-1.55; p = 0.86]).

- Secondary efficacy endpoints:

Secondary endpoints for the CHAARTED study included time to the development of CRPC, time to clinical progression, progression-free survival, and PSA complete response at 6 and 12 months.

Table 3: Summary of secondary efficacy endpoints

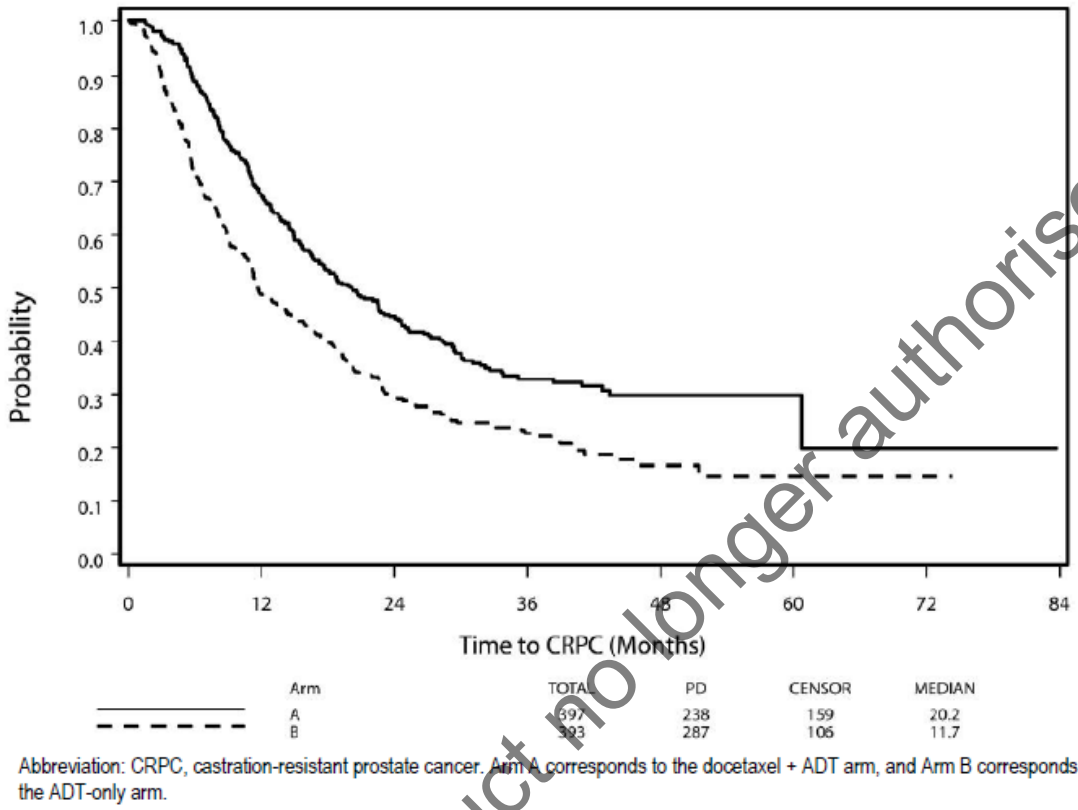
Endpoint	Treatment arm	Number of events	Outcome (95% CI)	HR (95% CI)
Time to CRPC (median)	ADT	287/393	11.7 months (10.8-14.7)	0.61 (0.51-0.72), p<0.0001
	Doc + ADT	238/397	20.2 months (17.2-23.6)	
Time to CP (median)	ADT	228/393	19.8 months (17.9-22.8)	0.61 (0.50-0.75), p<0.0001
	Doc + ADT	180/397	33.0 months (27.3-41.2)	
PFS (median)	ADT	294/393	11.6 months (10.8-14.3)	0.60 (0.51-0.72), p<0.0001
	Doc + ADT	243/397	19.8 months (16.7-22.8)	

Endpoint	Treatment arm	Number of events	Outcome (CR rate)	p-value
PSA Response (6 months)	ADT	77/393	19.6%	p<0.0001
	Doc + ADT	127/397	32.0%	
PSA Response (12 months)	ADT	66/393	16.8%	p<0.0001
	Doc + ADT	110/397	27.7%	

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; CP, clinical progression; CRPC, castration-resistant prostate cancer; Doc, docetaxel; HR, hazard ratio; PFS, progression-free survival; PSA prostate-specific antigen.

Regarding time to CRPC, there were 525 patients who experienced either PSA progression or clinical progression (238 in the docetaxel + ADT arm and 287 in the ADT arm). Median time to CRPC was 20.2 months (95% CI: 17.2-23.6) and 11.7 months (95% CI: 10.8-14.7) for patients in the docetaxel + ADT and ADT arms, respectively (HR 0.61, 95% CI: 0.51-0.72; p <0.0001).

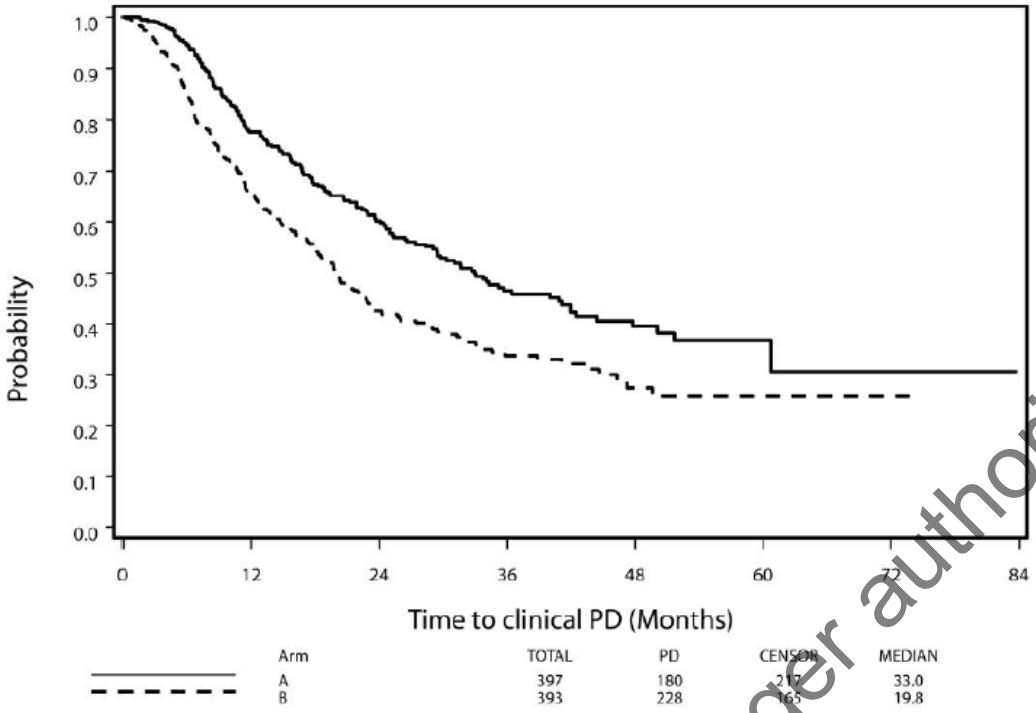
Figure 11: Time to CRPC - CHAARTED



Abbreviation: CRPC, castration-resistant prostate cancer. Arm A corresponds to the docetaxel + ADT arm, and Arm B corresponds to the ADT-only arm.

Regarding time to clinical progression, a total of 408 patients had experienced clinical progression at cut-off date (180 and 228 in the docetaxel + ADT and ADT-only treatment arms, respectively). The median time to clinical progression was 33.0 months (95% CI: 27.3-41.2) and 19.8 months (95% CI: 17.9-22.8) in the docetaxel + ADT and ADT-only treatment arms, respectively (HR 0.61, 95% CI: 0.50-0.75; p <0.0001).

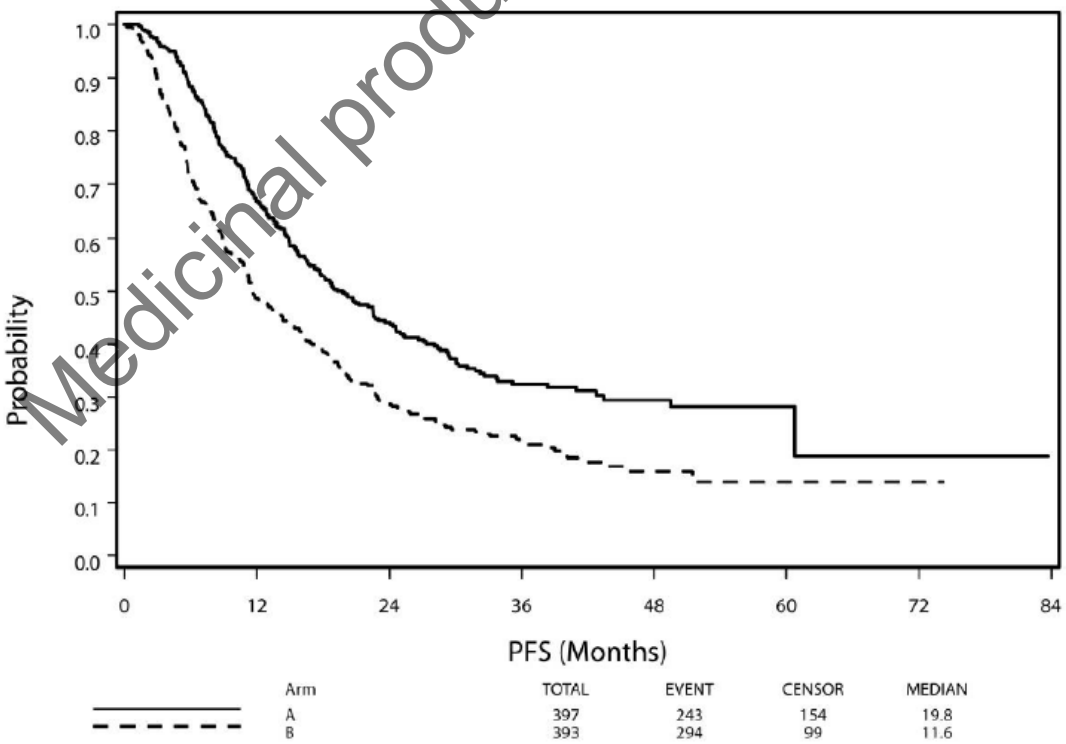
Figure 12: Time to clinical progression - CHAARTED



Abbreviation: PD, progressive disease. Arm A corresponds to the docetaxel + ADT arm, and Arm B corresponds to the ADT-only arm.

Regarding progression-free survival, at the time of data cut-off, there were 537 PFS failure events (243 and 294 events occurred in the docetaxel + ADT and ADT-only arms, respectively). Median PFS was 19.8 months (95% CI: 16.7-22.8) and 11.6 months (95% CI: 10.8-14.3) in the docetaxel + ADT and ADT-only treatment arms, respectively (HR 0.60, 95% CI: 0.51-0.72; p <0.0001).

Figure 13: Progression-free survival - CHAARTED



Abbreviations: PFS, progression free survival.
Arm A corresponds to the docetaxel + ADT arm, and Arm B corresponds to the ADT-only arm.

PSA response, the PSA response rates at 6 months were 32.0% and 19.6% and at 12 months were 27.7% and 16.8% in the docetaxel + ADT and ADT-only arms, respectively (p <0.0001).

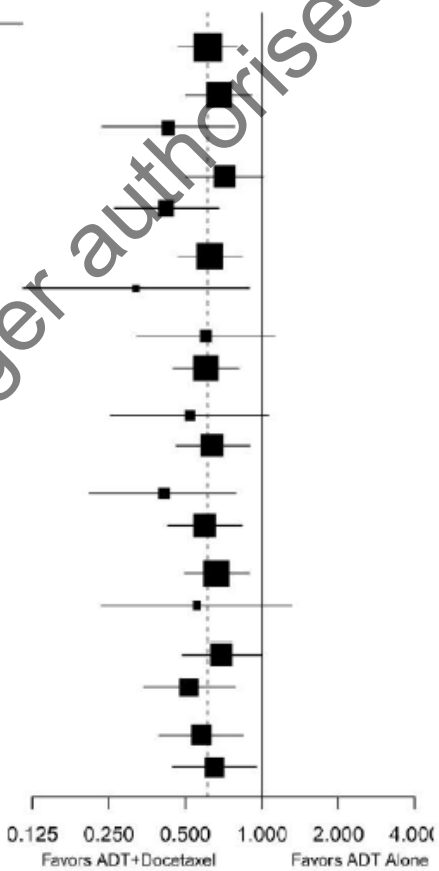
Long-term follow-up, the overall median follow-up was 53.7 months.

Overall, the median time to CRPC was 19.4 months and 11.7 months in the docetaxel + ADT and the ADT arms, respectively (HR 0.61, 95% CI: 0.52-0.73; p <0.001).

Similarly, the overall median time to clinical progression was 33.0 months and 19.8 months in the docetaxel + ADT and the ADT arms, respectively (HR 0.62, 95% CI: 0.51-0.75; p <0.001).

Ancillary analyses: subgroup analyses

Group	N	HR	95% CI
All Patients	790	0.61	(0.47, 0.80)
Age <70	612	0.68	(0.50, 0.91)
Age >=70	178	0.43	(0.23, 0.78)
ECOG PS 0	549	0.71	(0.50, 1.01)
ECOG PS 1-2	241	0.42	(0.26, 0.67)
Race - White	674	0.62	(0.47, 0.83)
Race - Other/Unknown	116	0.32	(0.11, 0.89)
Low Volume Disease	277	0.60	(0.32, 1.13)
High Volume Disease	513	0.60	(0.45, 0.81)
Visc +/- Bone Mets (BM)	123	0.52	(0.25, 1.07)
High Volume with BM alone	389	0.64	(0.46, 0.89)
Gleason Score <8	221	0.41	(0.21, 0.80)
Gleason Score >=8	484	0.60	(0.43, 0.83)
No Prior Local Therapy	575	0.66	(0.50, 0.89)
Prior Local Therapy	214	0.55	(0.23, 1.31)
CAB >30 Days - No	459	0.69	(0.49, 0.99)
CAB >30 Days - Yes	331	0.52	(0.34, 0.79)
SRE - No	448	0.58	(0.40, 0.84)
SRE - Yes	347	0.65	(0.45, 0.96)



The area of each box is proportional to the inverse of the variance of the log hazard ratio (small boxes correspond to large variances). The horizontal line through the box gives the 95% confidence interval on the ratio. The dashed vertical line shows the overall hazard ratio among all patients. The x axis of the forest plot is scaled according to the natural logarithm of the hazard ratio.

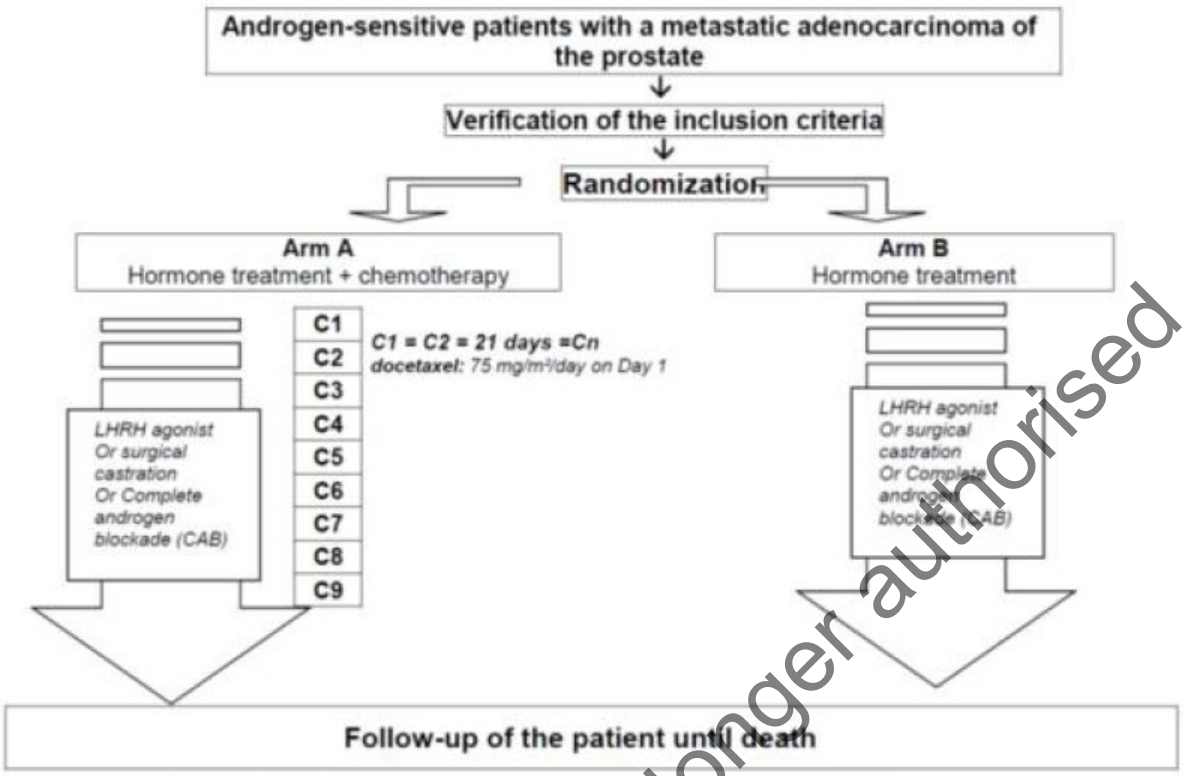
Abbreviations: BM, bone metastases; CAB, combined androgen blockade; CI: confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; SRE, skeletal related events.

GETUG-AFU15 study

Methods

The GETUG-AFU15 study was an open-label, multicenter, randomized Phase 3 study to compare the efficacy (OS rate at 36 months as primary endpoint) and safety of adding docetaxel to ADT versus ADT alone, in patients with metastatic prostate cancer who were commencing first line long term hormone therapy. GETUG-AFU15 was conducted at 29 sites in France and 1 site in Belgium. Accrual took place between October 2004 and December 2008.

Figure 14: GETUG-AFU15 design



Abbreviations: C, cycle; CAB, complete androgen blockade; LHRH, luteinizing hormone releasing hormone.

Study participants

Eligible patients had a life expectancy of at least 3 months, histologically confirmed adenocarcinoma of the prostate and radiologically proven metastatic disease, and an ECOG performance-status score of ≤2.

A lower proportion of men were metastatic at diagnosis of their prostate cancer in the docetaxel + ADT arm (67%) compared to the ADT-only arm (76%). The mean duration between diagnosis of the primary tumor and randomization was longer in docetaxel + ADT arm (12.55 months) compared to the ADT arm (11.35 months). The Gleason score was ≥7 in 91% of the study population: 90% and 93% in the docetaxel + ADT and ADT arms, respectively. The majority of patients (72%) had metastases at the diagnosis of prostate cancer with a majority of patients with metastases in the bone (81%) and lymph nodes (55%).

Main inclusion criteria:

1. Histologically proven prostatic adenocarcinoma
2. Measurable or assessable metastatic disease
3. Age ≥ 18 years
4. ECOG performance index ≤ 2
5. Life expectancy ≥ 3 months
6. Hematological function: white cells ≥ 2000/mm^3, polynuclear neutrophils ≥ 1000/mm^3, platelets ≥100,000/mm^3
7. Liver function satisfactory: bilirubin, transaminases ☐1.5 times the upper limit of normal (less than 2.5 x normal in cases of liver metastases)
8. Renal function satisfactory: serum creatinine ☐150 µmol/L

9. No previous chemotherapy for metastatic prostate cancer (1st line of treatment of metastatic cancer)

10. Chemotherapy in an adjuvant or neoadjuvant situation or for elevation of PSA is accepted if it has been completed more than a year beforehand, with proof of absence of changes in PSA and/or appearance of metastases for more than one year.

11. Adjuvant and/ or neoadjuvant Hormone therapy or Hormone therapy for elevation of PSA is accepted if it was completed more than a year beforehand, with evidence of absence of progression in PSA and/or appearance of metastases for more than a year.

12. Hormone therapy may have been started for the metastatic relapse but must not have been administered for over 2 months on inclusion in the study

13. Absence of radiotherapy on the metastatic sites for at least 4 weeks

Main exclusion criteria:

The patients included in this study should not meet any of the following non-inclusion criteria:

1. Presence of uncontrolled, symptomatic or asymptomatic cerebral metastases

2. Severe cardiovascular disease (symptomatic coronary disease, congenital heart failure, classes 3 and 4 of the NYHA classification)

3. Severe peripheral neuropathy

4. A history of cancer other than treated cutaneous baso-cellular cancer in the 5 years preceding inclusion in the study

5. Subjects who have been castrated surgically

6. Active infection or other serious underlying disease which may prevent the subject from receiving the treatment

7. A history of or ongoing psychiatric disease

8. Subject already included in another therapeutic study with an experimental compound,

9. People deprived of liberty or under guardianship,

10. Impossibility of undergoing medical follow-up in the study for geographical, social or psychological reasons

Treatments

In the experimental arm, docetaxel was to be administered for a maximum duration of 9 treatment cycles at an intended dose of 75 mg/m² on Day 1 of a 3-week cycle.

Outcomes/Endpoint

The primary efficacy endpoint was the 3-year OS.

The secondary efficacy endpoints were survival without clinical progression, survival without biological progression and the evaluation of the QoL.

The secondary efficacy endpoints were defined as follow:

- Survival without clinical progression (cPFS): the time from randomization to the date of the first investigation (bone scintigraphy, pelvic scan, or MRI) that showed clinical progression. For those

patients with bone lesions only, progression was defined as the appearance of one or more new bone lesions on bone scan.

- Survival without biological/laboratory progression (bPFS): the time from randomization until the date of biological/laboratory progression, or death of any cause. Biological/laboratory progression was defined by two Prostate Working Group (PWG) definitions 1 and 2 (1999 and 2007, respectively), based on PSA level cutpoints (detailed further in the CSR).
- Evaluation of the QoL: as assessed by the self-administered European Organisation for Research and Treatment of Cancer 30-item quality of life questionnaire (EORTC QLQ-C30), completed for the docetaxel + ADT arm on Day 1 of Cycle 4, Day 21 of Cycle 9 (or at the end of treatment), and then twice a year; and for the ADT-only arm at 3 months, and then every 6 months. A treatment side effects analysis was also conducted to supplement this endpoint, as described in Section 11.3.2 of the CSR.

Sample size

385 patients were included in the study.

At the time of study design of GETUG-AFU15, the data in the literature concerning the survival of patients treated for metastatic prostate cancer with hormone therapy was approximately 30 months. The median duration of response to initial hormone therapy was 24 months. To increase OS at 3 years from 50% to 65% in the docetaxel + ADT group, with a two-sided test, α=0.05 and a power of 80%, 172 subjects per arm (73 events) were needed (a total of 344 subjects). An increase of 10% was planned to compensate for patients lost to follow up, thus 189 randomized subjects per arm; a total of 378 subjects were therefore required for the study. This sample size was calculated assuming an enrolment period of approximately 4.5 years, and total study duration of approximately 8.5 years to observe the required 146 events.

Demographic of study population

The baseline characteristics were similarly comparable between the 2 arms of the GETUG-AFU15 trial, with 192 randomized patients in the docetaxel + ADT group and 193 randomized patients in the ADT-only group. The mean age was 62.7 years in the docetaxel + ADT group and 63.4 years in the ADT-only group. In both treatment arms, the mean Karnofsky index score was approximately 94, with a median score of 100 in both groups. The patients were divided by disease volume (48% and 47% of patients had HVD in the docetaxel + ADT arm and ADT-only arms, respectively) in a post-hoc analysis.

Randomization

Distributions of time-to-event variables and associated 95% confidence intervals were estimated with the use of the Kaplan-Meier product-limit method. The log-rank test was considered as the primary analysis for comparison of treatment groups. Adjusted treatment effects were estimated using the Cox proportional-hazards model. Qualitative variables were presented as percentages, and were compared using a $\chi 2$ test or a Fisher test; quantitative variables were presented as means and standard deviations (SD) or medians and extremes, and were compared using a Student t or Mann-Whitney test.

Blinding

The study was open label.

Statistical methods

The estimated distributions of time-to-event variables and associated 95% CIs were with the Kaplan-Meier product-limit method. The log-rank test was the primary analysis for comparison of treatment groups. The estimated adjusted and unadjusted treatment effects were with the Cox proportional hazards model. Safety

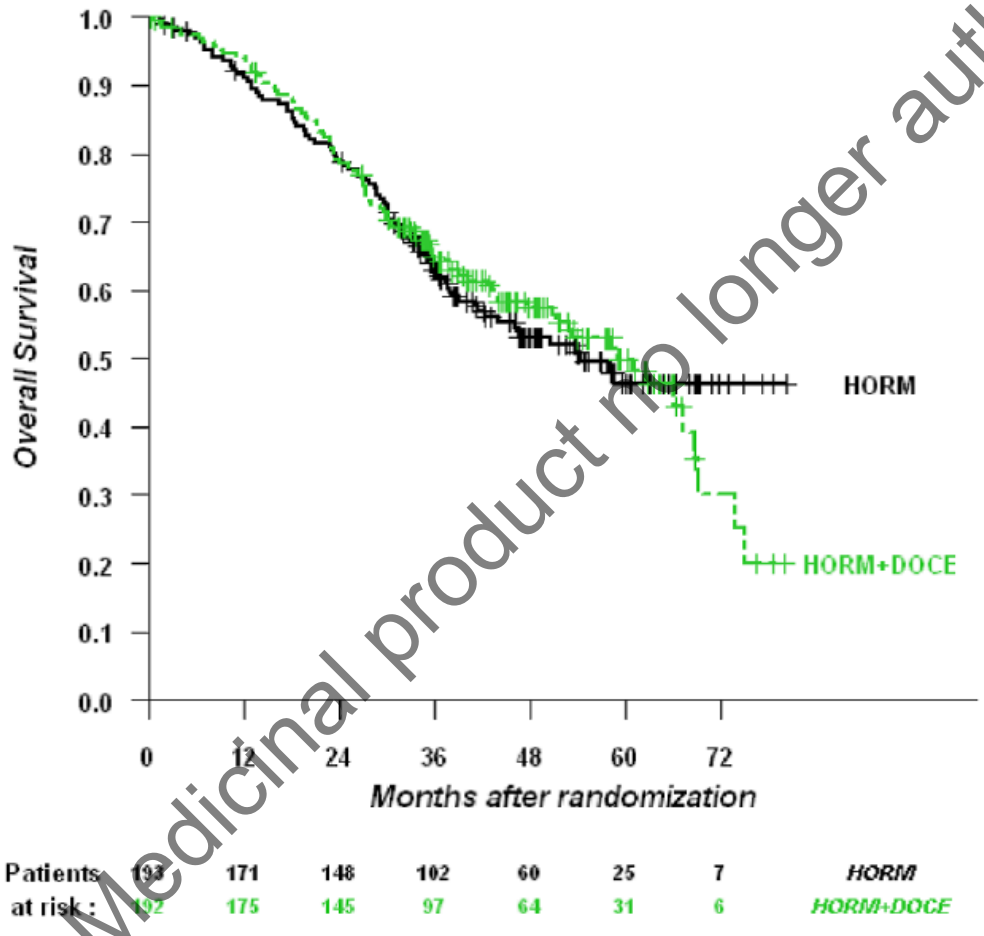
analyses were based on the population exposed to the assigned treatment. Post-hoc subgroup analyses were assessed whether specific baseline characteristics affected overall survival and PFS.

Results

Primary efficacy endpoint (ITT):

At the cut-off date, 176 patients had died, with 88 events (45.8%) reported in the docetaxel + ADT arm and 88 events (45.6%) reported in the ADT-only arm. The 3-year OS (the primary efficacy endpoint) was 64.2% (95% CI: 57.5-71.6) and 62.9% (95% CI: 56.3-70.2) in the docetaxel + ADT and ADT arms, respectively, and the observed median OS was 58.9 months (95% CI: 50.8-69.1) and 54.2 months (95% CI: 42.2-NR) in the docetaxel + ADT and ADT-only arms, respectively, with an estimated HR of 1.01 (95% CI: 0.75-1.36; p = 0.955). Of note, 62% of patients in the GETUG-AFU15 ADT-only treatment arm received docetaxel upon disease progression in the primary analysis.

Figure 15: Overall survival (all patients) - GETUG-AFU15



Abbreviations: HORM, ADT treatment arm; HORM + DOCE, docetaxel + ADT treatment arm.

Long-term follow-up:

A post-hoc analysis of the GETUG trial was performed with an extended follow-up period. This analysis also stratified OS based on volume of disease (patients with HVD and LVD). The updated analysis was performed after a median follow-up of 83.9 months (95% CI: 82.9-84.7), at which point 242 patients had died (115 and 127 patients were in the docetaxel + ADT and ADT arms, respectively; 147 and 95 patients were in HVD and LVD subgroups, respectively). This corresponds to a 63% maturity level. The majority of deaths were due to disease progression (82% of patients), while other (9.5%) and unknown (8.2%) causes were reported.

In the overall population, the median OS in the long-term follow-up was 62.1 months (95% CI: 49.5-73.7) and 48.6 months (95% CI: 40.9-60.6) in the docetaxel + ADT and ADT arms, respectively (HR 0.88, 95% CI: 0.68-1.14; p = 0.3). By the time of the follow-up analysis, 85% of patients in the GETUG-AFU15 ADT-only treatment arm received docetaxel upon disease progression.

In patients with HVD, the median OS was 39.8 months (95% CI: 28.0-53.4) and 35.1 months (95% CI: 29.9-43.6) in the docetaxel + ADT and ADT-only arms, respectively; HR: 0.78, 95% CI: 0.56-1.09; p = 0.14.

In patients with LVD, the median OS was not reached (NR; 95% CI: 69.5-NR) and 83.4 months (95% CI: 61.8-NR) in the docetaxel + ADT and ADT-only arms, respectively, HR: 1.02, 95% CI: 0.67-1.55; p = 0.9.

Secondary efficacy endpoint:

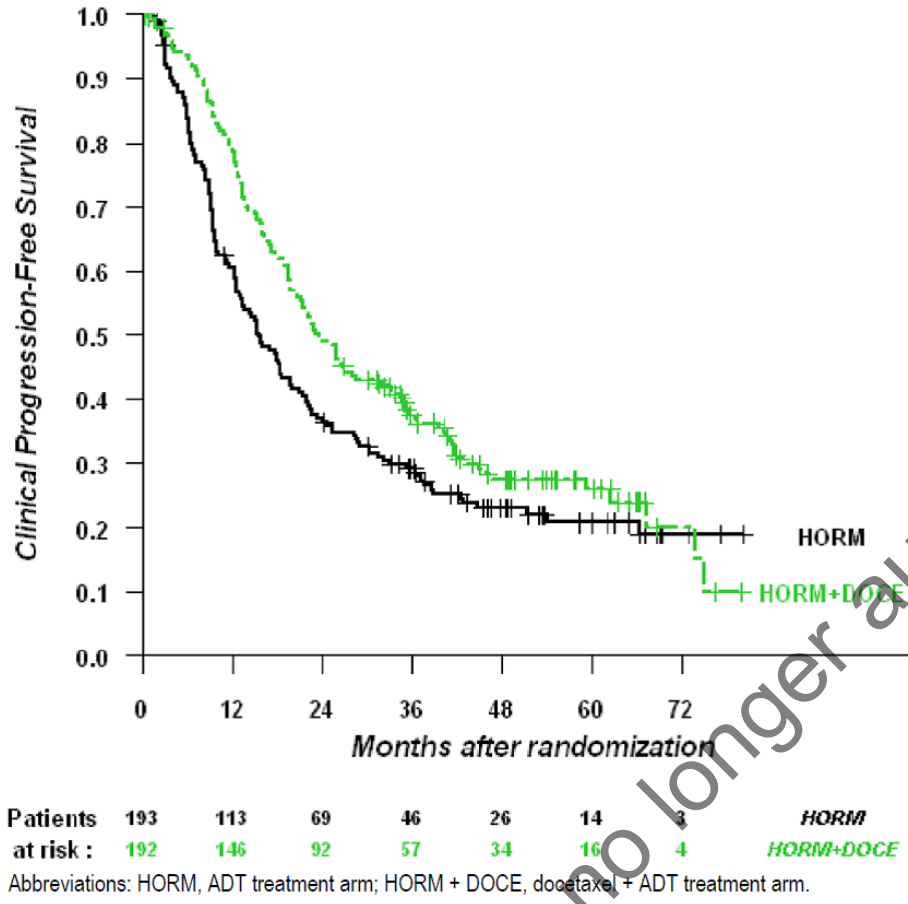
For clinical PFS, at the time of data cut-off, there were 279 cPFS failure events (134 and 145 events occurred in the docetaxel + ADT and ADT-only arms, respectively). The median cPFS was 23.46 months (95% CI: 20.47-31.87) and 15.44 months (95% CI: 12.45-19.78) in the docetaxel + ADT and ADT-only treatment arms, respectively, HR 0.75, 95% CI: 0.59-0.94; p = 0.0147.

Table 4: cPFS analysis

Study arm	N	cPFS events	Median cPFS, months (95% CI)	3-year cPFS, months (95% CI)	5-year cPFS, months (95% CI)	HR (95% CI)	Test	Unadjusted p-value
ADT	193	145	15.44 (12.45-19.78)	29.19 (23.34-36.51)	20.7 (15.17-28.23)	1	Log rank	0.0147
ADT + Doc	192	134	23.46 (20.47-31.87)	37.58 (31.15-45.33)	25.95 (19.72-34.14)	0.75 (0.59-0.94)		

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; Doc, docetaxel; cPFS, clinical progression-free survival; HR, hazard ratio.

Figure 16: cPFS (all patients) - GETUG-AFU15



Abbreviations: HORM, ADT treatment arm; HORM + DOCE, docetaxel + ADT treatment arm.

A sensitivity analysis was also conducted, in which an average HR was determined for cPFS due to non-proportional hazard over time (ie, there was decreasing beneficial effect of chemotherapy over time); the estimated treatment effect was HR 0.69 (95% CI: 0.54-0.89).

For Biological PFS, the median biological/laboratory progression-free survival (bPFS) was reported according to two different PWG definitions 1 and 2 (1999 and 2007, respectively).

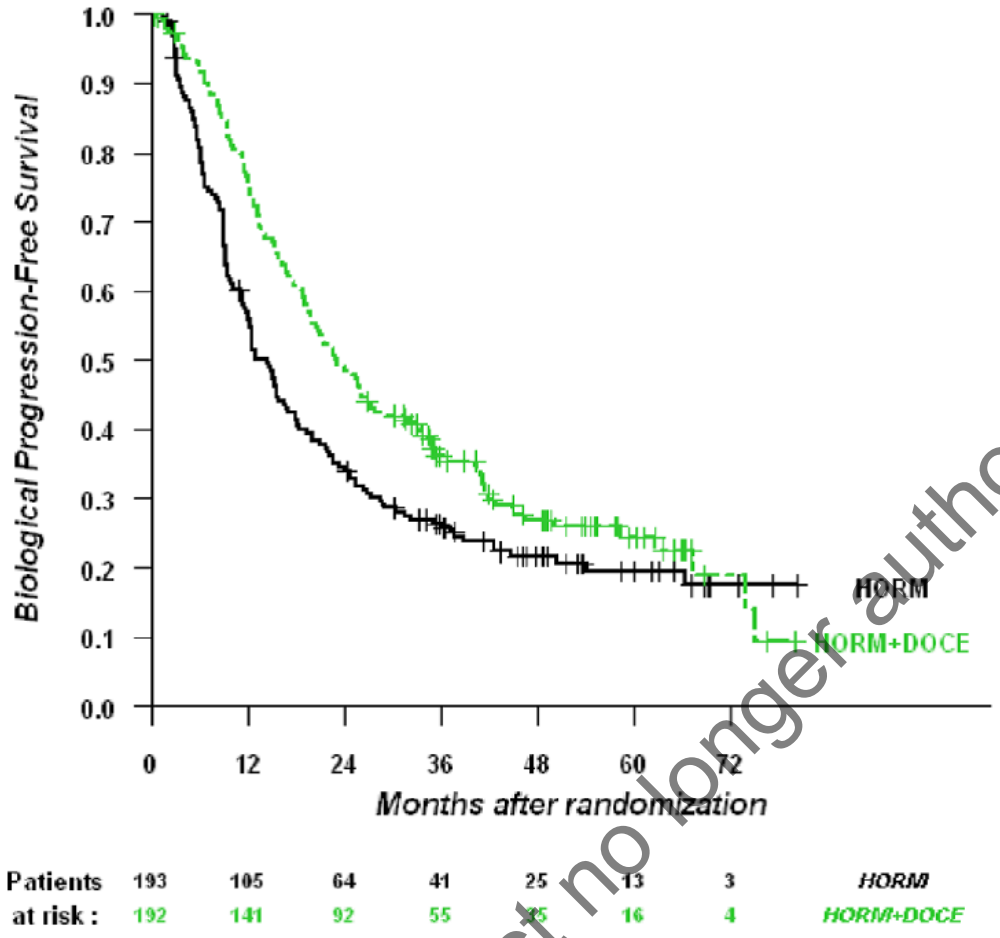
bPFS, PWG1 (1999) definition

At the time of data cut-off, there were 287 bPFS failure events (138 and 149 events occurred in the docetaxel + ADT and ADT-only arms, respectively) assessed under the PWG 1 (1999) definition. The median bPFS was 22.93 months (95% CI: 19.6-28.4) and 12.91 months (95% CI: 11.93-17.71) in the docetaxel + ADT and ADT-only treatment arms, respectively, HR 0.72, 95% CI: 0.57-0.91; p = 0.0052.

Table 5: bPFS assessed under PWG 1 (1999) definition

Study arm	N	bPFS events	Median bPFS, months (95% CI)	3-year bPFS, months (95% CI)	5-year bPFS, months (95% CI)	HR (95% CI)	Test	Unadjusted p-value
ADT	193	149	12.91 (11.93-17.71)	25.76 (20.18-32.88)	19.35 (14.02-26.7)	1	Log rank	0.0052
ADT + Doc	192	138	22.93 (19.6-28.4)	36.1 (29.77-43.77)	24.48 (18.42-32.53)	0.72 (0.57-0.91)		

Abbreviations: ADT, androgen deprivation therapy; bPFS, biological/laboratory progression-free survival; CI, confidence interval; Doc, docetaxel; HR, hazard ratio; PWG, Prostate Working Group.



Abbreviations: HORM, ADT treatment arm; HORM + DOCE, docetaxel + ADT treatment arm; PWG, Prostate Working Group.

As for cPFS, a sensitivity analysis was also conducted for bPFS based on the PWG 1 (1999) definition in which an average HR was determined for bPFS due to non-proportional hazard over time (there was decreasing beneficial effect of chemotherapy over time); the estimated treatment effect was HR 0.66 (95% CI: 0.52-0.84), similar to that seen for cPFS.

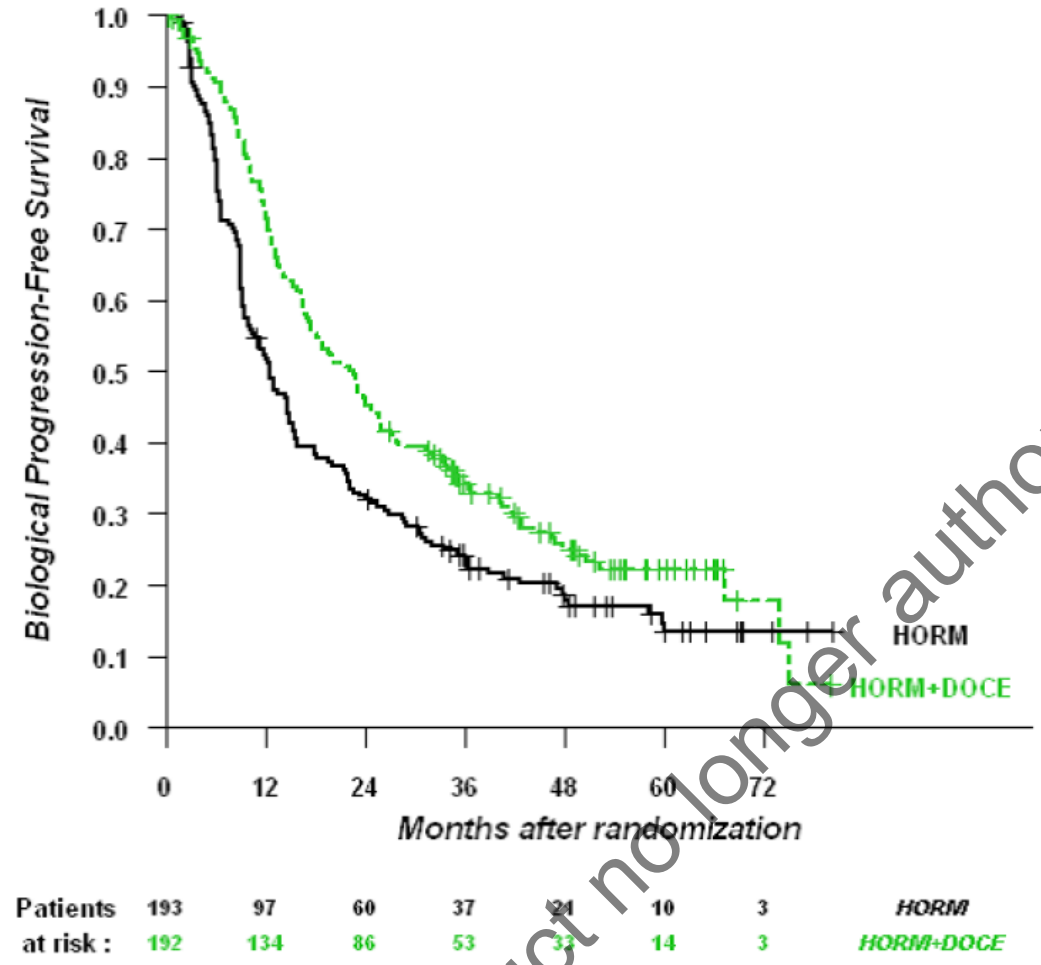
bPFS, PWG2 (2007) definition

At the time of data cut-off, there were 298 bPFS failure events (142 and 156 events occurred in the docetaxel + ADT and ADT-only arms, respectively) assessed under the PWG 2 (2007) definition. The median bPFS was 22.37 months (95% CI: 17.38-25.89) and 12.42 months (95% CI: 9.89-15.11) in the docetaxel + ADT and ADT-only treatment arms, respectively, HR 0.70, 95% CI: 0.56-0.88; p = 0.002.

Study arm	N	bPFS events	Median bPFS, months (95% CI)	3-year bPFS, months (95% CI)	5-year bPFS, months (95% CI)	HR (95% CI)	Test	Unadjusted p-value
ADT	193	156	12.42 (9.89-15.11)	23.59 (18.2-30.57)	13.38 (8.68-20.64)	1	Log rank	0.002
ADT + Doc	192	142	22.37 (17.38-25.89)	34.17 (29.97-41.75)	22.24 (16.55-29.88)	0.70 (0.56-0.88)		

Abbreviations: ADT, androgen deprivation therapy; bPFS, biological/laboratory progression-free survival; CI, confidence interval; Doc, docetaxel; HR, hazard ratio; PWG, Prostate Working Group.

Figure: Kaplan-Meier for bPFS, PWG2 definition



Abbreviations: HORM, ADT treatment arm; HORM + DOCE, docetaxel + ADT treatment arm; PWG, Prostate Working Group.

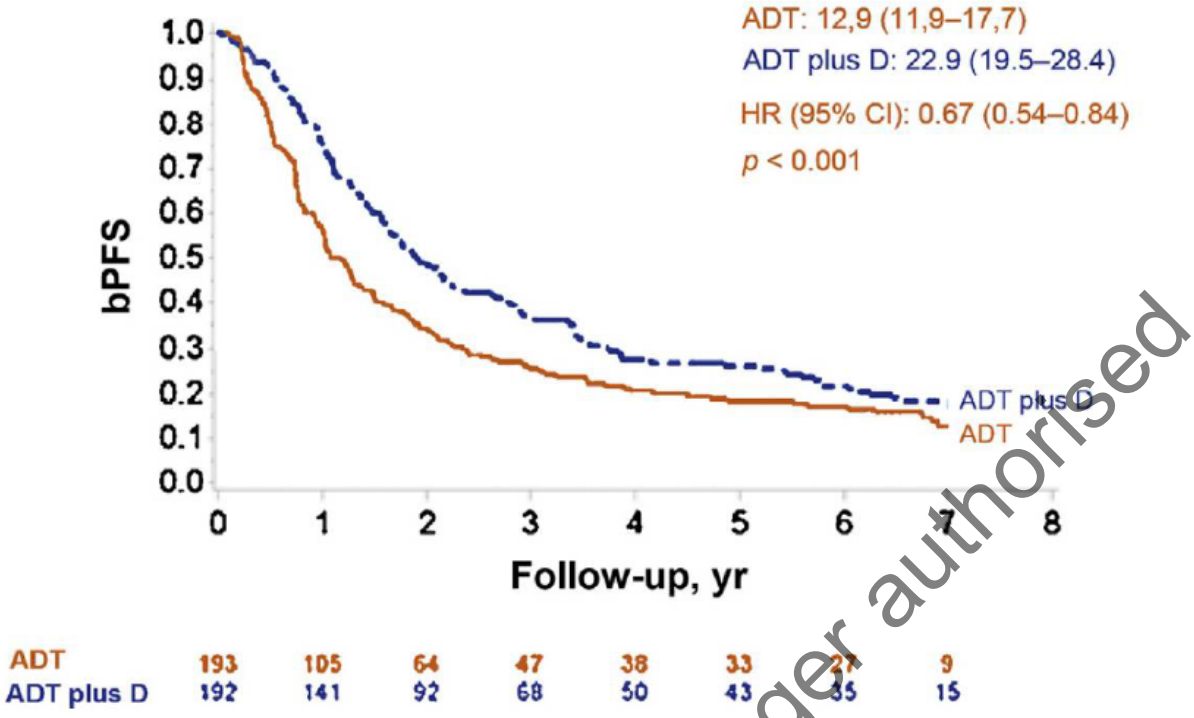
For QoL, scores were comparable at baseline (participation rate: 90.1%; scores for each arm were not reported). Mean QoL scores (± SD) were lower at 3 months in the docetaxel + ADT treatment arm compared to the ADT-only treatment arm (63.95 ± 18.5 versus 70.96 ± 20.7, respectively, p = 0.005). Similarly at 6 months the mean QoL score was lower in the docetaxel + ADT treatment arm versus the ADT-only treatment arm (61.84 ± 20.2 versus 70.92 ± 16.8, respectively, p = 0.001). However, no differences in mean global and functional scores were recorded between the docetaxel + ADT and ADT-only arms at 12 months (67.62 ± 18.4 versus 66.36 ± 20.2, respectively, p = 0.696), although appetite loss (2.31 ± 8.5 versus 9.96 ± 22.8, p = 0.005), and constipation (10.95 ± 21.0 versus 21.69 ± 31.0, p = 0.012) were more frequent (corresponding to lower toxicity single-item QoL scores) in the docetaxel + ADT arm than the ADT-only arm at 12 months.

Long term follow-up analysis:

A long-term follow-up analysis was performed with median follow-up of 83.9 months.

The median bPFS was 22.9 months (95% CI: 19.5-28.4) and 12.9 months (95% CI: 11.9-17.7) in the docetaxel + ADT and ADT-only treatment arms, respectively (HR 0.67, 95% CI: 0.54-0.84; p <0.001).

Figure: bPFS- long-term analysis (Kaplan-Meier)



Abbreviations: ADT, androgen deprivation therapy; ADT plus D, androgen deprivation therapy + docetaxel; bPFS, biological/laboratory progression-free survival; HR, hazard ratio.

A similar trend was observed in radiographic progression-free survival (rPFS). The median rPFS was 22.9 months (95% CI: 20.5-31.4) and 15.3 months (95% CI:12.4-19.8) in the docetaxel + ADT and ADT-only treatment arms, respectively (HR 0.69, 95% CI: 0.55-0.87; p = 0.002).

Analysis performed across trials

STAMPEDE, CHAARTED, and GETUG-AFU15 were the three studies included in this meta-analysis.

Demographic of studies populations

STAMPEDE and CHAARTED studies were suggestive of worse prognoses, and as such the patients in those studies were perhaps more likely to gain benefit from chemotherapy compared to patients in the GETUG-AFU15 study. The most noticeable differences in demographics were as follow:

- Patient Gleason scores: in the GETUG-AFU15 study, there were lower percentages of patients with scores of 8-10 compared to the other two studies.
- Disease volume: 66% and 64% of patients had HVD in the CHAARTED docetaxel + ADT and ADT-only arms, respectively, versus 48% and 47%, respectively, in the GETUG-AFU15 study.
- Median PSA values: the patients in the GETUG-AFU15 study had the lowest values (values were approximately 64, 51, and 26 ng/mL in the STAMPEDE, CHAARTED, and GETUG-AFU15 studies, respectively).
- Performance status: approximately 30% versus 2% of patients in the CHAARTED and GETUG-AFU15 studies, respectively, reported ECOG PS of 1-2 (whereas STAMPEDE reported WHO PS for patients, approximately 21% of whom reported WHO PS 1-2).

In addition, the STAMPEDE study included patients with non-metastatic (230 patients [39%] and 460 patients [39%] in the docetaxel + ADT and ADT groups, respectively), while patients with non-metastatic disease were not included in the other two studies.

Table 6: Patients demographic by study

	STAMPEDE		CHAARTED		GETUG-AFU15	
	ADT (N=1184)	Doc + ADT (N=592)	ADT (N=393)	Doc + ADT (N=397)	ADT (N=193)	Doc + ADT (N=192)
Age (years)						
Median (range)	65 (41-82)	65 (40-81)	63 (39-91)	64 (36-88)	64 (43-84)	63 (46-79)
Mean (SD)	NR	NR	NR	NR	63.4 (8.1)	62.7 (7.5)
PS (N, %)	WHO		ECOG		ECOG[a]	
0	922 (77.9)	461 (77.9)	272 (69.4)[b]	277 (69.8)	176 (96)	181 (99)
1	250 (21.1)	127 (21.5)	115 (29.3)	114 (28.7)	7 (4)	2 (1)
2	12 (1.0)	4 (0.7)	5 (1.3)	6 (1.5)		
Karnofsky Index						
Mean (SD)	NR	NR	NR	NR	92.27 (9.86)	94.86 (7.69)
Median (range)	NR	NR	NR	NR	100 (60-100)	100 (70-100)
Gleason score (N, %)						
8-10	805 (68.0)	433 (73.1)	243 (70.0)	241 (67.3)	NR (59)	NR (55)
7	249 (21.0)	97 (16.4)	83 (23.9)	95 (26.8)	NR (33)	NR (35)
4-6	29 (2.4)	13 (2.2)	21 (6.1)	21 (5.9)	NR	NR
2-6	31 (2.6)	14 (2.4)	NR	NR	NR (8)	NR (10)
Median PSA (ng/mL)						
Median (range)	64 (0-15747)	63 (0-9999)	52.1 (0.1-8056.0)	50.9 (0.2-8540.1)	25.85 (0.1-11900)	26.7 (0.05-2170)
Metastatic status (%)						
At diagnosis	51%	50%	NR	NR	76%	67%
At baseline	61%	61%	100%	100%	100%	100%
Prognostic Group (%)						
Good	NR	NR	NR	NR	50%	49%
Intermediate	NR	NR	NR	NR	30%	28%
Poor	NR	NR	NR	NR	21%	22%
Disease volume (N, %)[c]						
HVD	NA	NA	249 (63.5)	263 (66.2)	91 (47)	92 (48)
LVD	NA	NA	143 (36.5)	134 (33.8)	102 (53)	100 (52)
Prior treatment (N, %)						
Radiotherapy	NR	NR	33 (8.4)	27 (6.8)	17%	19%
Prostatectomy	NR	NR	73 (18.6)	81 (20.4)	13%	17%
ADT	1110 (93.8)[d]	558 (94.3)[d]	NR	NR	8%	10%
Chemotherapy	NR	NR	NR	NR	0%	1%
No local treatment	NR	NR	286 (73.0)	289 (72.8)	NR	NR

	STAMPEDE		CHAARTED		GETUG-AFU15	
	ADT (N=1184)	Doc + ADT (N=592)	ADT (N=393)	Doc + ADT (N=397)	ADT (N=193)	Doc + ADT (N=192)
Time from ADT to randomization						
Median (range)	41 days (77-105)	43 days (45-108)	1.3 months (0.03-3.9)	1.2 months (0.03-3.9)	NR	NR
Time from diagnosis to randomization						
Median (range)	75 days (0-4070)	76 days (3-5033)	NR	NR	2.07 months (0.23-149.55)	2.5 months (0.16-118.14)

Abbreviations: ADT, androgen deprivation therapy; Doc, docetaxel; ECOG, Eastern Cooperative Oncology Group; HVD, high volume of disease; LVD, low volume of disease; NA, not available; NR, not reported; PS, performance score; SD, standard deviation; WHO, World Health Organization.

Sources: data from initial data cut-off: STAMPEDE, CHAARTED, and GETUG-AFU15 CSRs (5.3.5.1).

a ECOG PS data were reported for GETUG-AFU15 in (9).

b As reported in Table 6 of the CHAARTED CSR.

c A post-hoc analysis was conducted based on disease volume for GETUG-AFU15 (9).

d This is the reported rate of "HT started before randomization" as per Table 14 of the STAMPEDE CSR; however it likely includes ongoing ADT, as the CRF does not distinguish between prior and ongoing hormone therapy.

Disposition of patients

A total of 2951 patients were randomized in the 3 RCTs to receive either docetaxel + ADT or ADT-only treatment, of whom 1181 were randomized to docetaxel + ADT treatment and 1770 were randomized to ADT treatment. Among the 2951 patients, 60 patients were randomized but did not receive their assigned treatment. However, all patients were included in their respective ITT population for the efficacy analyses.

Table 7: Summary of patients disposition by study

	STAMPEDE		CHAARTED		GETUG-AFU15	
	ADT (N=1184) n (%)	Doc + ADT (N=592) n (%)	ADT (N=393) n (%)	Doc + ADT (N=397) n (%)	ADT (N=193) n (%)	Doc + ADT (N=192) n (%)
Randomized	1184 (100.0)	592 (100.0)	393 (100.0)	397 (100.0)	193 (100.0)	192 (100.0)
Efficacy population (ITT)	1184 (100.0)	592 (100.0)	393 (100.0)	397 (100.0)	193 (100.0)	192 (100.0)
Did not receive assigned treatment	0 (0.0)	46 (8)	0 (0.0)	7 (1.8)	3 (1.6)[c]	4 (2.1)[d]
Alive at initial data cut-off	769 (64.9)[a]	417 (70.4)[b]	257 (65.4)	296 (74.6)	105 (54.4)	104 (54.2)
Died at initial data cut-off	415 (35.1)	175 (29.6)	136 (34.6)	101 (25.4)	88 (45.6)	88 (45.8)
Died at long-term data cut-off	NA	NA	211 (53.7)	188 (47.4)	127 (65.8)	115 (59.9)

Abbreviations: ADT, androgen deprivation therapy; Doc, docetaxel; ITT, intention to treat; NA, not applicable.

Sources: data from initial data cut-off: STAMPEDE, CHAARTED, and GETUG-AFU15 CSRs (5.3.5.1); data from long-term analyses: reference (7), CHAARTED; and reference (9), GETUG-AFU15.

a 75 patients (6.3%) were alive at the initial data cut-off, but no data were available for these patients in the year preceding data cutoff.

b 40 patients (6.8%) were alive at the initial data cut-off, but no data were available for these patients in the year preceding data cutoff.

c In addition, 1 patient (0.5%) received docetaxel.

d 2 of these patients (1.0%) also did not receive ADT because consent was withdrawn.

Completion status data were reported for each study's intervention arms (docetaxel + ADT). Of the 1181 patients who were randomized to receive docetaxel + ADT, 878 patients completed treatment per protocol (ie, 6 cycles for the STAMPEDE and CHAARTED studies, and 9 cycles for the GETUG-AFU15 study), 57 patients did not receive docetaxel, and 246 patients discontinued early. Among the 1181 randomized to

receive docetaxel + ADT, 77% and 84% of patients who received docetaxel in the STAMPEDE and CHAARTED studies completed the full 6 cycles of treatment, respectively, whereas about 46% of patients completed the full 9 cycles of treatment in the GETUG-AFU15 study.

Table 8: Summary of patient treatment completion and discontinuation status by study

	STAMPEDE Doc + ADT (N=592) n (%)	CHAARTED Doc + ADT (N=397) n (%)	GETUG-AFU15 Doc + ADT (N=192) n (%)
Treatment completion[a]	454 (76.7)	335[c] (84.4)	89[d] (46.4)
Did not receive docetaxel	46 (7.8)[b]	7 (1.8)	4 (2.1)
Discontinuations	92 (15.6)	55 (13.9)	99 (51.6)
Toxicity/AEs	72 (12.2)	30 (7.6)	39 (20.3)
Treatment refusal[e]	6 (1.0)	5 (1.3)	43 (22.4)
Disease progression	5 (0.8)	12 (3.0)	6 (3.1)
Death	2 (0.3)	2 (0.5)	4 (2.1)
Concurrent illness[f]	5 (0.8)	1 (0.3)	2 (1.0)
Other[g]	2 (0.3)	5 (1.3)	5 (2.6)

Abbreviations: ADT, androgen deprivation therapy; Doc, docetaxel.

Sources: CSRs (5.3.5.1) for STAMPEDE (Tables 41 and 42), CHAARTED (Table 8), and GETUG-AFU15 (Table 19).

a Treatment completion for STAMPEDE and CHAARTED consisted of completion of 6 cycles, whereas for GETUG-AFU15 it consisted of 9 cycles.

b In STAMPEDE, 42 patients never started docetaxel treatment, and 4 had not reported starting treatment when the database was frozen in May 2015 (see also Table 29 of the CSR [5.3.5.1]).

c Of the 335 patients who completed treatment, 315 clearly completed 6 cycles per protocol. As detailed in the CHAARTED CSR, an old version of the chemotherapy summary form was used for an additional 20 patients; of these, 17 appear to have received 6 cycles of treatment (16 with full dose and 1 with dose reduction) based on the cumulative dose of docetaxel, 1 patient did not provide cumulative dose information (so the number of cycles could not be estimated), and the remaining 2 patients had reported dose modifications and may have received 6 cycles.

d The GETUG-AFU15 CSR does not specifically state how many patients completed 9 cycles; it is noted however that 99 patients received <9 cycles, and 4 patients did not receive docetaxel. The remaining 89 patients are listed in this table as having completed 9 cycles of treatment.

e Treatment refusal includes patient refusal; patient, clinician, or investigator decision; and patient withdrawal.

f Concurrent illness includes incurrent illness, incurrent disease, and other complicating disease.

g See study CSRs for other reasons for discontinuation.

Subsequent therapies upon disease progression

In the primary analysis, 62% of patients in the ADT-only treatment arm received docetaxel at disease progression, and in the long-term follow-up analysis, 127 out of 149 patients (85%) with disease progression in the ADT-only treatment arm received docetaxel. In comparison, 48% and 41% of patients with disease progression in the CHAARTED and STAMPEDE ADT-only treatment arms received docetaxel in the primary analysis, respectively. No major difference in other subsequent therapies was observed with the exception of a slightly higher use of cabazitaxel and abiraterone or enzalutamide at progression in the docetaxel + ADT arm of CHAARTED.

Table 9: Subsequent therapies upon disease progression by study

	STAMPEDE (primary analysis)		CHAARTED (primary analysis)		GETUG-AFU15 (primary analysis)		GETUG-AFU15 (long-term analysis)	
	ADT (N=1184) n (%)	Doc + ADT (N=592) n (%)	ADT (N=393) n (%)	Doc + ADT (N=397) n (%)	ADT (N=193) n (%)	Doc + ADT (N=192) n (%)	ADT (N=193) n (%)	Doc + ADT (N=192) n (%)
Patients with disease progression	761	315	287	238	NR	NR	149	NR
Life-extending therapies								
Docetaxel	313 (41)	44 (14)	137 (48)	54 (22.7)	NR (62)	NR (28)	127 (85)	54 (NA)
Cabazitaxel	26 (3)	22 (7)	37 (13)	57 (24)	NR	NR	15 (10)	16 (NA)
Abiraterone/ enzalutamide	243 (32)	114 (36)	104 (36)	105 (44)	NR	NR	48 (32)	48 (NA)
Radium 223	6 (1)	6 (2)	0 (0)	0 (0)	NR	NR	0 (0)	0 (0)
Sipuleucel-T	NR	NR	19 (7)	22 (9)	NR	NR	NR	NR
Other therapies								
Other chemotherapy[a]	26 (3)	21 (7)	27 (9.4)	29 (12.1)	NR	NR	NR	NR
Zoledronic acid	128 (17)	35 (11)	NR	NR	NR	NR	NR	NR
Antiandrogens[b]	512 (67)	181 (57)	91 (32)	80 (34)	NR	NR	NR	NR
Stilboestrol	84 (11)	38 (12)	NR	NR	NR	NR	NR	NR
Dexa-methasone	104 (14)	39 (12)	NR	NR	NR	NR	NR	NR
Prednisolone	72 (9)	28 (9)	NR	NR	NR	NR	NR	NR

Abbreviations: ADT, androgen-deprivation therapy; Doc, docetaxel; NA, not available; NR, not reported.

Source: adapted from Table 3 of reference (15); STAMPEDE data were reported in the CSR, Table 167 (5.3.5.1), CHAARTED data were reported from the primary analysis (2), and GETUG-AFU15 primary analysis data were from the CSR (5.3.5.1); long-term follow-up analysis data were available for GETUG-AFU15 (9).

a In the STAMPEDE study: other chemotherapy besides docetaxel or cabazitaxel; in the CHAARTED study: mitoxantrone and/or platinum.

b For CHAARTED, this category was antiandrogen and/or ketoconazole.

Comparative results

Primary efficacy endpoint, OS:

Across the studies, the median duration of follow-up for the primary OS analyses was 43 months, 28.9 months, and 50 months for the STAMPEDE, CHAARTED, and GETUG-AFU15 studies, respectively. In the long-term follow-up OS analyses for CHAARTED and GETUG-AFU15, the median duration of follow-up was 53.7 months and 83.9 months, respectively.

Table 10: Summary of primary endpoints by study

	STAMPEDE		CHAARTED		GETUG-AFU15	
	ADT (N=1184)	Doc + ADT (N=592)	ADT (N=393)	Doc + ADT (N=397)	ADT (N=193)	Doc + ADT (N=192)
Primary analysis[a]						
Median follow-up						
Months (range)	43 (IQR: 31-61)	43 (IQR: 30-60)	28.9 (NR)	28.9 (NR)	50 (39-63)	50 (39-63)
Median OS, months (range)						
Overall	68 (95% CI: 60-91)	77 (95% CI: 70-NR)	44.0 (34.4-49.1)	57.6 (49.1-72.8)	54.2 (42.2-NR)	58.9 (50.8-69.1)
Median OS, HR (95% CI)						
Overall	0.78 (0.66-0.93; p=0.006)		0.61 (0.47-0.80; p=0.0003)		1.01 (0.75-1.36; p=0.955)	
3-year OS (%), (95% CI)						
3-year OS[b]	NA	NA	NA	NA	62.9 (56.3-70.3)	64.2 (57.5-71.6)
Long-term follow-up analyses[c]						
Median follow-up						
Months (95% CI)	NA	NA	53.7 (NR)	53.7 (NR)	83.9 (82.9-84.7)	83.9 (82.9-84.7)
Median OS, months (range)						
Overall	NA	NA	47.2 (41.8-52.8)	57.6 (52.0-63.9)	48.6 (40.9-60.6)	62.1 (49.5-73.7)
Median OS, HR (95% CI)						
Overall	NA		0.72 (0.59-0.89; p=0.0018)		0.88 (0.68-1.14; p=0.3)	

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; Doc, docetaxel; IQR, interquartile range; NA, not applicable; NR, not reported; OS, overall survival

Sources: data from initial data cut-off: STAMPEDE (Tables 7 and 113), CHAARTED, and GETUG-AFU15 CSRs; data from long-term analyses: CHAARTED, reference (7), and GETUG-AFU15, reference (9).

a Primary analysis: as reported in the CSRs (see 5.3.5.1).

b No HR was reported for 3-year OS in the GETUG-AFU15 study.

c Long-term analysis: for CHAARTED, reference (7); for GETUG-AFU15, reference (9).

Secondary efficacy endpoints - primary analysis:

The secondary endpoints varied throughout the three studies.

Secondary endpoints in the primary analysis period across the studies included FFS (components of which included biochemical progression, PFS, and death from prostate cancer) and SRE (STAMPEDE); PFS, time to CRPC, time to clinical progression (CP), PSA response, and QoL (CHAARTED); and cPFS, bPFS, and QoL (GETUG-AFU15).

Table 11: Secondary endpoints by study (primary analysis)

	STAMPEDE		CHAARTED		GETUG-AFU15	
	ADT (N=1184)	Doc + ADT (N=592)	ADT (N=393)[b]	Doc + ADT (N=397)[c]	ADT (N=193)[d]	Doc + ADT (N=192)[e]
Primary analysis[a]						
Median follow-up						
Months (range)	43 (IQR: 31-61)	43 (IQR: 30-60)	NR[f]	NR[f]	50 (39-63)	50 (39-63)
Treatment failure, months; median (95% CI)						
FFS	20 (NR)	37 (NR)	NA	NA	NA	NA
SRE	106 (NR)	NR	NA	NA	NA	NA
PSA failure	24 (NR)	43 (NR)	NA	NA	NA	NA
PFS	46 (NR)	67 (NR)	NA	NA	NA	NA
PCa-death	91 (NR)	102 (NR)	NA	NA	NA	NA
PFS	NA	NA	11.6 (10.8-14.3)	19.8 (16.7-22.8)	NA	NA
Treatment failure HRs (95% CI)						
FFS	0.61 (0.53-0.70; p<0.0001)		NA		NA	
SRE	0.60 (0.48-0.74;p=0.127x10^{-5})		NA		NA	
PSA failure	0.59 (0.52-0.68; p=0.34x10^{-13})		NA		NA	
PFS	0.70 (0.60-0.81; p=0.25x10^{-5})		NA		NA	
PCa-death	0.79 (0.65-0.96; p=0.019)		NA		NA	
PFS	NA		0.60 (0.51-0.72; p<0.0001)		NA	
Clinical progression, months; median (95% CI)						
Time to CP	NA	NA	19.8 (17.9-22.8)	33.0 (27.3-41.2)		
Time to CRPC	NA	NA	11.7 (10.8-14.7)	20.2 (17.2-23.6)	NA	NA
cPFS	NA	NA	NA	NA	15.4 (12.5-19.8)	23.5 (20.5-31.9)
Clinical progression HRs (95% CI)						
Time to CP	NA		0.61 (0.50-0.75; p<0.0001)		NA	
Time to CRPC	NA		0.61 (0.51-0.72; p<0.0001)		NA	
cPFS	NA		NA		0.75 (0.59-0.94; p=0.0147)	
Biochemical progression, months; median (95% CI)[g]						
bPFS PWG 1 (1999)	NA	NA	NA	NA	12.9 (11.9-17.7)	22.9 (19.6-28.4)
bPFS PWG 2 (2007)	NA	NA	NA	NA	12.4 (9.89-15.1)	22.4 (17.4-25.9)
PSA Response – 6 mo	NA	NA	19.6%	32.0%	NA	NA
PSA Response – 12 mo	NA	NA	16.8%	27.7%	NA	NA

	STAMPEDE		CHAARTED		GETUG-AFU15	
	ADT (N=1184)	Doc + ADT (N=592)	ADT (N=393)[b]	Doc + ADT (N=397)[c]	ADT (N=193)[d]	Doc + ADT (N=192)[e]
Biochemical progression: statistical comparisons (95% CI)						
bPFS PWG 1 (1999)	NA		NA		HR 0.72 (0.57-0.91; p=0.0052)	
bPFS PWG 2 (2007)	NA		NA		HR 0.70 (0.56-0.88; p=0.002)	
PSA Response – 6 mo	NA		p<0.0001[h]		NA	
PSA Response – 12 mo	NA		p<0.0001[h]		NA	
Quality of life scores; mean[i]						
Baseline	NA	NA	118.7 (SE 1.2)	119.4 (SE 1.1)	NR	NR
QoL - 3 mo	NA	NA	118.3 (SE 1.2)	116.6 (SE 1.1)	70.96 (SD 20.7)	63.95 (SD 18.5)
QoL – 6 mo	NA	NA	116.7 (SE 1.3)	118.4 (SE 1.1)	70.92 (SD 16.8)	61.84 (SD 20.2)
QoL – 9 mo	NA	NA	117.5 (SE 1.3)	118.4 (SE 1.2)	NA	NA
QoL – 12 mo	NA	NA	116.4 (SE 1.3)	119.2 (SE 1.3)	66.36 (SD 20.2)	67.62 (SD 18.4)

Abbreviations: ADT, androgen deprivation therapy; bPFS, biological progression-free survival; CI, confidence interval; CP, clinical progression; cPFS, clinical progression-free survival; CR, complete response; Doc, docetaxel; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer 30-item quality of life questionnaire ; FACT-P, Functional Assessment of Cancer Therapy-Prostate; FFS, failure-free survival; HR, hazard ratio; HVD, high volume of disease; LVD, low volume of disease; NA, not applicable; NR, not reported; PFS, progression-free survival; PWG, Prostate Working Group; QoL, quality of life; SD, standard deviation; SE, standard error; SRE, skeletal-related events.

Source: data from initial data cut-off: STAMPEDE, CHAARTED, and GETUG-AFU15 CSRs (5.3.5.1).

a Primary analysis: as reported in the CSRs (see 5.3.5.1).

b For the CHAARTED ADT arm, there were 249 patients with HVD and 143 with LVD.

c For the CHAARTED Doc + ADT arm, there were 263 patients with HVD and 134 with LVD.

d For the GETUG-AFU15 ADT arm disease burden post-hoc analysis, there were 91 patients with HVD and 102 with LVD.

e For the GETUG-AFU15 Doc + ADT arm disease burden post-hoc analysis, there were 92 patients with HVD and 100 with LVD.

f The data cut-off for secondary endpoints in CHAARTED was 23 December 2014, however a median follow-up period was not reported at that point.

g PSA Response data were reported in percent of patients experiencing CR in the given timeframe.

h No HRs were calculated for PSA Response.

i In CHAARTED, QoL was assessed using the FACT-P scoring tool (as an overall QoL measure), whereas in GETUG-AFU15 QoL was assessed using the EORTC QLQ-C30 tool. Means were reported with standard errors (CHAARTED) and standard deviations (GETUG-AFU15) and are presented in this table. There was no 9-month QoL assessment made in the GETUG-AFU15 study. A QoL assessment using the EORTC QLQ-C30 with the prostate-specific module QLQ PR25 was planned for the STAMPEDE study, however at the time of this filing it was not available from the Sponsor.

Secondary efficacy endpoints - long-term follow-up analysis:

Secondary endpoints in the long-term analysis periods included time to CRPC and time to CP (CHAARTED), and rPFS and bPFS (GETUG-AFU15).

Table 12: Secondary endpoints by study (long-term follow-up analysis)

	STAMPEDE		CHAARTED		GETUG-AFU15	
	ADT (N=1184)	Doc + ADT (N=592)	ADT (N=393)[b]	Doc + ADT (N=397)[c]	ADT (N=193)[d]	Doc + ADT (N=192)[e]
Long-term follow-up analyses[a]						
Median follow-up						
Months	NA	NA	53.7	53.7	83.9	83.9
Clinical progression, months; median (95% CI)						
Time to CRPC	NA	NA	11.7 (10.8-14.4)	19.4 (16.8-22.6)	NA	NA
Time to CP	NA	NA	19.8 (17.8-22.5)	33.0 (29.1-40.9)	NA	NA
rPFS	NA	NA	NA	NA	15.3 (12.4-19.8)	22.9 (20.5-31.4)
Clinical progression HRs (95% CI)						
Time to CRPC	NA		0.61 (0.52-0.73; p<0.001)		NA	
Time to CP	NA		0.62 (0.51-0.75; p<0.001)		NA	
rPFS	NA		NA		0.69 (0.55-0.87; p=0.002)	
Biochemical progression, months; median (95% CI)						
bPFS	NA	NA	NA	NA	12.9 (11.9-17.7)	22.9 (19.5-28.4)
Biochemical progress HRs (95% CI)						
bPFS	NA		NA		0.67 (0.54-0.84; p<0.001)	

Abbreviations: ADT, androgen deprivation therapy; bPFS, biological progression-free survival; CI, confidence interval; CP, clinical progression; cPFS, clinical progression-free survival; CRPC, castration-resistant prostate cancer; Doc, docetaxel; FFS, failure-free survival; HR, hazard ratio; HVD, high volume of disease; LVD, low volume of disease; NA, not applicable; NR, not reported; PFS, progression-free survival; PWG, Prostate Working Group; rPFS, radiographic progression-free survival.
Source: references (7, CHAARTED) and (9, GETUG-AFU15).

a Long-term analysis: for CHAARTED, reference (7); for GETUG-AFU15, reference (9).
b For the CHAARTED ADT arm, there were 249 patients with HVD and 143 with LVD.
c For the CHAARTED Doc + ADT arm, there were 263 patients with HVD and 134 with LVD.
d For the GETUG-AFU15 ADT arm disease burden post-hoc analysis, there were 91 patients with HVD and 102 with LVD.
e For the GETUG-AFU15 Doc + ADT arm disease burden post-hoc analysis, there were 92 patients with HVD and 100 with LVD.

Results in subpopulations:

Table 13: Summary of OS subgroup analyses by study

	STAMPEDE		CHAARTED		GETUG-AFU15	
	ADT (N=1184)[a]	Doc + ADT (N=592)[b]	ADT (N=393)[c]	Doc + ADT (N=397)[d]	ADT (N=193)[e]	Doc + ADT (N=192)[f]
Primary analysis[g]						
Median follow-up						
Months (range)	43 (IQR: 31-61)	43 (IQR: 30-60)	28.9 (NR)	28.9 (NR)	50 (39-63)	50 (39-63)
Median OS, months (95% CI)						
M1 patients[h]	43 (40-48)	62 (51-73)	NA	NA	NA	NA
M0 patients[h]	Not reached	Not reached (83-not reached)	NA	NA	NA	NA
HVD	NA	NA	32.2 (NR)	49.2 (NR)	NA[i]	NA[i]
LVD	NA	NA	NR	NR	NA[i]	NA[i]
Median OS, HR (95% CI)						
M1 patients[h]	0.76 (0.62-0.92; p=0.005)		NA		NA	
M0 patients[h]	0.95 (0.62-1.47; p=0.828)		NA		NA	
HVD	NA		0.60 (0.45-0.81; p<0.001)		NA[i]	
LVD	NA		0.60 (0.32-1.13; p=0.11)		NA[i]	
Long-term follow-up analyses[j]						
Median follow-up						
Months (95% CI)	NA	NA	53.7 (NR)[j]	53.7 (NR)[j]	83.9 (82.9-84.7)	83.9 (82.9-84.7)
Median OS, months (95% CI)						
HVD	NA	NA	34.4 (30.1-42.1)	51.2 (45.2-58.1)	35.1 (29.9-43.6)	39.8 (28.0-53.4)
LVD	NA	NA	NR (59.9-NR)	63.5 (58.3-78.5)	83.4 (61.8-NR)	NR (69.5-NR)
Median OS, HR (95% CI)						
HVD	NA		0.63 (0.50-0.79; p<0.001)		0.78 (0.56-1.09; p=0.14)	
LVD	NA		1.04 (0.70-1.55; p=0.86)		1.02 (0.67-1.55; p=0.9)	

Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; Doc, docetaxel; HVD, high volume of disease; IQR, interquartile range; LVD, low volume of disease; IQR, interquartile range; NA, not applicable; NR, not reported; M1, metastatic disease; OS, overall survival

Sources: data from initial data cut-off: STAMPEDE, CHAARTED, and GETUG-AFU15 CSRs; data from long-term analyses: reference (7, CHAARTED) and reference (9, GETUG-AFU15).

a For the STAMPEDE ADT arm, there were 724 patients with M1 disease and 460 patients with M0 disease.

b For the STAMPEDE Doc + ADT arm, there were 362 patients with M1 disease and 230 patients with M0 disease.

c For the CHAARTED ADT arm, there were 249 patients with HVD and 143 with LVD.

d For the CHAARTED Doc + ADT arm, there were 263 patients with HVD and 134 with LVD.

e For the GETUG-AFU15 ADT arm disease burden post-hoc analysis, there were 91 patients with HVD and 102 with LVD.

f For the GETUG-AFU15 Doc + ADT arm disease burden post-hoc analysis, there were 92 patients with HVD and 100 with LVD.

g Primary analysis: as reported in the CSRs (see 5.3.5.1).

h A metastatic subgroup analysis was conducted for STAMPEDE because the study also included non-metastatic patients (39% of patients had M0 disease, and 61% had M1 disease). No subgroup analyses in M1 patients were performed for CHAARTED or GETUG-AFU15 because these studies only included patients with M1 disease; for OS results in these patients, see Table 19. Similarly, only results for a M0 subgroup are presented for STAMPEDE because no patients with M0 disease were included in CHAARTED and GETUG-AFU15.

i A HVD/LVD subgroup analysis was not initially planned, but was performed retrospectively in the long-term follow-up analysis based on the CHAARTED definition of HVD and LVD (9).

j Long-term analysis: for CHAARTED, reference (7); for GETUG-AFU15, reference (9).

k In the long-term follow-up of CHAARTED, the reported median follow-up overall was 53.7 months; for patients with HVD it was 53.7 months, but for patients with LVD it was 53.8 months.

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The MAH provided three randomized open studies and one meta-analysis of these three studies to support the hypothesis that docetaxel brings a survival benefit to patients suffering from a metastatic prostate cancer when given on top of ADT; i.e., earlier than the currently approved indication, when hormone sensitivity is lost.

These studies were not conducted under the responsibility of the MAH. They all compare docetaxel added to a backbone of ADT (with or without steroids) to the backbone alone.

In the largest study (STAMPEDE), only one comparison in one sub-population is of relevance for the sought indication: docetaxel was not the only drug tested and the study enrolled as well patients without metastases. The relevant analysis is thus a subgroup analysis on metastatic patients prospectively designed (since metastatic disease was a stratification factor). There is no description of alpha-protection measures. The early analysis provided is in accordance with the statistical plan and is fully powered (at least in the whole population).

The CHAARTED study included only metastatic patients.

The smallest study, GETUG-AFU15 used the 3-year OS as a primary endpoint and presents the specificity that taxanes were extensively used at progression in the control group.

Efficacy data and additional analyses

An overall survival benefit was associated with docetaxel + ADT treatment compared with ADT only in the primary analysis in the STAMPEDE study for all patients (corresponding to a 9-month benefit in median OS and HR 0.78, 95% CI: 0.66-0.93; p = 0.006), and in the CHAARTED study (corresponding to a 13.6-month benefit in median OS and HR 0.61, 95% CI: 0.47-0.80; p = 0.0003). However, no benefit was shown in the smaller GETUG-AFU15 trial (corresponding to a statistically non-significant 4.7-month improvement in median OS and HR 1.01, 95% CI: 0.75-1.36; p = 0.955).

The median time to SRE in STAMPEDE was 106 months in the ADT-only group, but was not reached in the docetaxel + ADT group. A significant SRE benefit was associated with docetaxel + ADT compared to ADT-only treatment (HR 0.60, 95% CI: 0.48-0.74; p = 0.127 x10-5), and the 5-year SRE-free rate was 75% and 66% in the docetaxel + ADT and ADT-only groups, respectively. When the analysis was restricted to the first 84 months of the trial, a 6.5-month benefit in mean time to SRE was associated with docetaxel + ADT compared to ADT-only treatment.

The median time to PSA failure, PFS, and prostate-cancer related deaths were also improved with docetaxel + ADT treatment in the STAMPEDE study. Median time to PSA failure was improved by 19 months with docetaxel + ADT compared to ADT-only treatment, corresponding to a significant PSA failure benefit (HR 0.59, 95% CI: 0.52-0.68; p = 0.34 x10-13). There was a 21-month benefit in median PFS for docetaxel + ADT compared to ADT-only treatment, corresponding to a significant PFS benefit (HR 0.70, 95% CI: 0.60-0.81; p = 0.25 x10-5). The 5-year PFS was 53% and 49% in the docetaxel + ADT and ADT-only groups, respectively. There was an 11-month benefit in median time to death due to prostate cancer for docetaxel + ADT compared to ADT-only treatment, respectively, corresponding to a survival advantage (subHR 0.79, 95% CI: 0.65-0.96; p = 0.019).

In CHAARTED, median PFS was improved by 8.2 months with docetaxel + ADT compared to ADT-only treatment, representing a reduction in risk of disease progression by 40% (HR 0.60, 95% CI: 0.51-0.72; p <0.0001). Median times to CP and CRPC were both improved by 13.2 months and 8.5 months with docetaxel treatment, respectively, corresponding to HR 0.61 (95% CI: 0.50-0.75; p <0.0001) and 0.61 (95% CI:

0.51-0.72; p <0.0001), respectively. Finally, the PSA response rates were improved with docetaxel treatment at both 6-month and 12-month timepoints.

Despite no OS benefit in the docetaxel + ADT treatment group in the GETUG-AFU15 study, the study did show benefit in cPFS and bPFS docetaxel + ADT compared to ADT-only treatment; cPFS was improved by 8.1 months, representing a reduction in risk of clinical progression by 25% (HR 0.75, 95% CI: 0.59-0.94; p = 0.0147), and bPFS as assessed by both PWG 1 and 2 definitions (1999 and 2007, respectively) showed a benefit of 10 months by each definition (corresponding to HR 0.72 [95% CI: 0.57-0.91; p = 0.0052] and HR 0.70 [95% CI: 0.56-0.88; p = 0.002], respectively).

Although the QoL scores for patients in the docetaxel + ADT treatment group were lower than the ADT-only treatment group early in the CHAARTED and GETUG-AFU15 studies, by 12 months there was no substantial difference between the two treatment groups.

Updated analyses of the STAMPEDE study:

The provided updated analyses were performed with a median FU time of **6.5 years** (vs 3.5 years for the primary analyses) at the data cutoff date and the analysis of OS was based on a total of **719 deaths (66%)** (vs *494 deaths (45%)* for the primary analyses), with **494 events (68%)** (vs *350 events (48%)* for the primary analyses) reported in the ADT arm and **225 events (62%)** (vs *144 events (40%)* for the primary analyses)reported in the ADT + docetaxel arm.

Updated estimated hazard ratio (HR) for OS was 0.81 (95% CI: 0.69 to 0.95), characterizing a **statistically significant and clinically meaningful reduction of 19% in risk of death with ADT + docetaxel** compared to ADT (p=0.009).

Median overall survival (95% CI) in the docetaxel + ADT arm was 58.8 months, compared to 43.2 months in the ADT only arm, corresponding to a **16 months survival benefit for the patients treated with docetaxel**.

Updated analyses of the CHAARTED study

Updated analyses were performed with a median FU time of 53.7 months at the data cutoff date and the analysis of OS was based on a total of 399 deaths (51%) (vs *237 deaths (30%)* for the primary analyses), with 211 events (54%) (vs *136 events (35%)* for the primary analyses) reported in the ADT arm and 188 events (47%) (vs *101 events (25%)* for the primary analyses) reported in the ADT + docetaxel arm.

In these updated analyses, the estimated HR for OS was 0.72 (95% CI: 0.59 to 0.89), characterizing a **statistically significant and clinically meaningful reduction of 28% in risk of death** with ADT + docetaxel compared to ADT (p=0.0018).

Median overall survival (95% CI) in the docetaxel + ADT arm was 57.6 months (52 to 63.9), compared to 47.2 months (41.8 to 52.8) in the ADT only arm, corresponding to a **10.4 months survival benefit for the patients treated with docetaxel**.

Updated analyses of STAMPEDE and CHAARTED studies

Overall, updated analyses of these 2 studies, with more mature data, c**onfirmed the primary analyses** and, **demonstrated a statistically significant survival benefit** for patients treated with docetaxel and ADT by comparison to ADT alone.

The STAMPEDE study was retrospectively **analyzed by subgroups according to metastasis burden** at randomization, using the definition that was used for the CHAARTED study.

The estimated HR in these 2 subgroups were, numerically, of similar magnitude and **test for interaction between treatment and disease volume was not significant**, supporting the **absence of evidence**

for heterogeneity in the treatment effect in these 2 subgroups of patients, in contrast to what was reported in the CHAARTED study.

Of note, the **ESMO** guidelines and **EAU guidelines** recommended to offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.

The **new analysis** of the STAMPEDE study, with the largest subgroup of patients with a low metastatic burden, showed a **consistent treatment effect irrespective of metastasis burden**, providing additional important information to support the use of upfront docetaxel in all M1 patients who are fit enough for chemotherapy.

- The updated results provided by the MAH for STAMPEDE and CHAARTED studies are **enough mature** to support the claimed indication.
- The **benefit** of anticipating the treatment of prostate cancer with docetaxel at the hormone sensitive stage is **demonstrated** by a **statistically significant** survival benefit for patients treated with docetaxel and ADT by comparison to ADT alone.
- The new analysis of the STAMPEDE study, with the largest subgroup of patients with a low metastatic burden, showed a **consistent treatment effect irrespective of metastasis burden**.
- In the light of this **data**, the claimed indication is supported.

In the GETUG-AFU15 study, there is no apparent benefit related to docetaxel with a HR close to 1, and K-M curves are quite superimposable. The extensive use of taxanes at progression in the control arm (85% of patients with disease progression in the ADT-only treatment arm received docetaxel as subsequent therapy) could explain this neutral effect.

Secondary endpoints in the long-term analysis periods included time to CRPC and time to CP (CHAARTED), and rPFS and bPFS (GETUG-AFU15). Similarly to the primary analyses, the secondary endpoint results for the long-term analyses showed benefit of treatment with docetaxel + ADT when assessed for all patients. Consistent with the primary analysis, the median times to CP and CRPC in the CHAARTED long-term analysis were improved with docetaxel + ADT treatment by 13.2 months and 7.7 months in all patients, respectively, corresponding to HRs of 0.62 (95% CI: 0.51-0.75; p <0.001) and 0.61 (95% CI: 0.52-0.73; p <0.001), respectively. In the GETUG-AFU15 study, the same trend was observed. The median rPFS was improved by 7.6 months with docetaxel + ADT treatment in all patients, corresponding to a reduction in risk of radiographic disease progression by 31% (HR 0.69 [95% CI: 0.55-0.87; p = 0.002]). Similarly, the median bPFS for this study was improved by 10 months with docetaxel + ADT treatment in all patients (HR 0.67 [95% CI: 0.54-0.84; p <0.001]).

2.4.3. Conclusions on the clinical efficacy

Docetaxel has demonstrated activity in all submitted studies, supported by secondary endpoints. The updated results provided for STAMPEDE and CHAARTED studies are mature enough to support the claimed indication. A consistent treatment effect was shown irrespective of metastasis burden. The benefit of anticipating the treatment of prostate cancer with docetaxel at the hormone sensitive stage is demonstrated by a statistically significant survival benefit for patients treated with docetaxel and ADT by comparison to ADT alone. The claimed indication is supported.

2.5. Clinical safety

Introduction

Docetaxel is a member of the taxane anti-cancer group of drugs that promote tubulin assembly in vitro and stabilizes microtubules against cold induced depolymerization. Other compounds in this group include cabazitaxel (Jevtana®), paclitaxel (Taxol®), and paclitaxel albumin (Abraxane®).

The safety profile of docetaxel is close in nature to that of other taxanes. Treatment with microtubule-stabilizing drugs is associated with adverse events that include anemia, neutropenia, thrombocytopenia, febrile neutropenia, infection, pyrexia, peripheral sensory neuropathy, motor neuropathy, myalgia, arthralgia, asthenia, fatigue, nausea, vomiting, anorexia, stomatitis/mucositis, dehydration, diarrhea, dyspnea, arrhythmia, fluid retention/edema, skin reaction, injection site reaction, bilirubin increase, aspartate aminotransferase/serum glutamicoxaloacetic transaminase (AST/SGOT) increase, alanine aminotransferase/serum glutamicpyruvic transaminase (ALT/SGPT) increase, and hypersensitivity reaction.

Severe neutropenia and febrile neutropenia are the most prominent risks for docetaxel and may need, for certain categories of patients, secondary and even primary prevention with growth factors. The incidence of severe hypersensitivity can be reduced with adequate premedication with corticosteroids.

The current filing is to align labeling information of docetaxel with these guidelines, using the same background information consisting of these three randomized controlled trials. The safety data from the STAMPEDE study will form the main source of the safety information to be included in the Labeling.

Patient exposure

Safety parameters collected across the three studies included adverse events (AEs) and clinical laboratory tests. However, safety data collection and safety data reporting differed across the three studies, resulting in limitations for the safety analysis.

For the CHAARTED trial, conducted under the sponsorship of ECOG, only severe AEs were collected. Furthermore, in the control arm, AEs were not routinely documented although major AEs were to be recorded. Seriousness in the CHAARTED study was assessed according to the National Cancer Institute's (NCI) Adverse Event Expedited Reporting System (AdEERs) for commercial products.

Safety evaluation timepoints:

Safety evaluations were performed at specific timepoints during the course of the studies.

- After randomization in the STAMPEDE study, patients were followed-up every 6 weeks for 6 months, then every 3 months to 2 years, then every 6 months to 5 years, and then annually. Safety evaluations were discontinued upon disease progression.

In addition, patients in the docetaxel arm were seen every 3 weeks for docetaxel administration; a complete blood count (CBC) with differential and platelets was required at baseline and on day 1 of each treatment cycle, as were serum bilirubin and renal function, up to discontinuation of docetaxel.

- After randomization in the CHAARTED study, patients were followed up every 3 months to 2 years, then every 6 months to 5 years, and then annually. Safety evaluations were discontinued upon disease progression.

In addition, patients in the docetaxel arm were seen every 3 weeks for docetaxel administration; a CBC with differential and platelets was required at baseline and on Day 1 of each treatment cycle, as were liver function tests, up to discontinuation of docetaxel.

- After randomization in the GETUG-AFU15 study, patients were followed up every 3 months to 3.5 years, then every 6 months. Safety evaluations were discontinued upon disease progression.

In both treatment arms, a CBC with differential and platelets, biochemistry, glycemia, albumin, renal function, and liver function tests were required at each follow up visit up to the month 42 evaluation.

In addition, patients in the docetaxel arm were seen every 3 weeks for docetaxel administration; a CBC with differential, platelets, biochemistry, glycemia, albumin, renal function, and liver function tests were required at baseline and on day 1 of each treatment cycle.

Regarding the STAMPEDE study, in both treatment arms, AEs (including laboratory AEs), were recorded on the Toxicity form of the CRF, at each study visit, including severity assessment. The toxicity form of the CRF consisted of a list of pre-printed AEs. Whenever an event was serious, a SAEs form was to be filled in. Overall, the relationship to study treatment was not recorded for non-serious adverse events.

Regarding the CHAARTED study, in the docetaxel arm, AEs (including laboratory AEs) were evaluated at the end of each treatment cycle, before re-administration of docetaxel, and recorded on the toxicity form of the CRF, at once, at the end of the chemotherapy. Event collection was limited to Grade ≥4 for blood/bone marrow and metabolic events, and to Grade ≥3 for other non-hematologic event. After discontinuation of the chemotherapy, AEs were collected at each study visit, until disease progression. For the patients randomized to the control arm, AEs were not routinely documented in the CRF, and only major events were recorded at each study visit, until disease progression.

Regarding the GETUG-AFU15 study, for the patients assigned to the docetaxel arm, AEs (including laboratory AEs) were recorded at each cycle of chemotherapy and at the end of chemotherapy, 30 days following the last administration of docetaxel. For the patients assigned to the control arm, AEs (including laboratory AEs) were recorded on the toxicity form of the CRF at the 3, 6, and 9 months visit following randomization. Severity was graded according to NCI CTCAE v 3.0. Overall, the relationship to study treatment was not recorded for non-serious adverse events.

Safety evaluation definitions

In the STAMPEDE study, AEs were defined as any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

In the CHAARTED and GETUG-AFU15 protocols, AEs were not specifically defined.

In STAMPEDE and GETUG-AFU15, SAEs were defined as any AE that:

- Resulted in death
- Was life-threatening
- Required hospitalization or prolongation of existing hospitalization
- Resulted in persistent or significant disability or incapacity (in GETUG-AFU15, this was "serious temporary incapacity")
- Consisted of a congenital anomaly or birth defect (in GETUG-AFU15, this was phrased as an event that "results in a congenital abnormality, birth defect or abortion")
- Other important medically significant condition

Seriousness and subsequent reporting in the CHAARTED study were assessed and performed according to the NCI's AdEERs for commercial products. In this system, unexpected Grade 4 AE with possible/probable or definite relationship and Grade 5 AE, irrespective of relationship or expectedness, were subject to expedited reporting. In addition, in line with international rules and as per ECOG rules, any event that resulted in

persistent or significant disabilities/incapacities, congenital anomalies, or birth defects was subject to expedited reporting.

Data analysis considerations

All analyses were performed by the sponsors of the studies, and all study reports were prepared by the respective sponsors of the 3 studies. Sanofi has no access to the databases of the 3 studies and hence could not perform additional analyses.

The reasons for treatment discontinuation in the studies were as follow:

- STAMPEDE: disease progression while on therapy, unacceptable toxicity, intercurrent illness which prevent further treatment, withdrawal of consent for treatment, any alteration in the patient's condition which justifies the discontinuation of treatment in the clinician's opinion, or intention to commence a new anti-cancer treatment due to evidence of relapse.
- CHAARTED: disease progression, extraordinary medical circumstance, patient withdraws consent, or unacceptable toxicity.
- GETUG-AFU15: toxicity, disease progression, withdrawal of consent, loss to follow-up, or a major breach of the protocol

The main available demographic, baseline and disease characteristics data in the three studies are summarized in the two table below:

Disposition of patients

A total of 2951 male patients with HSPC were randomized in the three RCTs to receive either ADT alone or docetaxel + ADT, of whom 2909 were included in the safety analyses.

Table 14: Summary of study patient populations

	STAMPEDE		**CHAARTED**		**GETUG-AFU15**	
n	**ADT**	**Doc+ADT**	**ADT**	**Doc+ADT**	**ADT**	**Doc+ADT**
Randomized	1184	592	393	397	193	192
Did not receive assigned treatment	0	46	0	6*d*	4*f*	4*h*
Received alternate treatment	46	0	0	0	0	1*i*
Further exclusions from safety analysis	23[a]	1*b*	1*c*	1*e*	3*g*	0
Safety population for analyses	1207	545	392	390	186	189

STAMPEDE n	**ADT**	**Doc+ADT**	**CHAARTED**		**GETUG-AFU15**	
≥65 years	673	296	**ADT**	**Doc+ADT**	**ADT**	**Doc+ADT**
≥75 years			NA	NA	NA	NA
	128	48	NA	NA	NA	NA

a Twenty three (23) patients with no AE assessment were excluded from the safety analysis.
b One (1) patient with no AE assessment was excluded from the safety analysis.
c One (1) patient with no follow-up information available was excluded from the safety analysis.
d Six (6) patients did not start treatment.
e One (1) patient with treatment status unknown was excluded from the safety analysis.
f Three (3) patients withdrew consent prior to treatment initiation, and1 patient received docetaxel + ADT.

g Three (3) patients did not have a safety assessment (two due to early deaths; one for an unknown reason).
h Four (4) patients did not receive docetaxel because their consent was withdrawn.
i This patient was randomized to receive ADT, but received docetaxel + ADT.

Overall, 1124 patients were treated with docetaxel + ADT and were included in the safety analyses. Among these 1124 patients, 935 (83.2%) were to be treated with 6 cycles of docetaxel (from the STAMPEDE and form the CHAARTED studies), while 189 (16.8%, from GETUGAFU15) were to be treated with 9 cycles of docetaxel.

A total of 878 of the 1124 patients (78.1%) in the safety population assigned to the docetaxel + ADT treatment arms completed the intended treatment across the studies; in STAMPEDE and CHAARTED, 454 patients (83.3%) and 335 patients (85.9%) completed 6 cycles of treatment per protocol, respectively, whereas 89 patients (47.1%) completed 9 cycles of treatment in the GETUG-AFU15 study.

A total of 246 patients assigned to the docetaxel + ADT treatment arms discontinued treatment early across the studies; in STAMPEDE and CHAARTED, 92 patients (16.9%) and 55 patients (14.1%) completed less than 6 cycles of treatment, respectively, while 99 patients (52.4%) completed less than 9 cycles of treatment in GETUG-AFU15. Of those patients who discontinued treatment, 72 patients (13.2%), 30 patients (7.7%), and 39 patients (20.6%) discontinued due to toxicities in the STAMPEDE, CHAARTED, and GETUG-AFU15 studies, respectively.

Table 15: Summary of patient treatment completion status by study

n (%)	STAMPEDE Doc + ADT (N = 545)	CHAARTED Doc + ADT (N = 390)	GETUG-AFU15 Doc + ADT (N = 189)
Treatment completion	454 (83.3)	335[a] (85.9)	89[b] (47.1)
Discontinuations	92 (16.9)	55 (14.1)	99 (52.4)
Toxicity/AEs	72 (13.2)	30 (7.7)	39 (20.6)

a Of the 335 patients who completed treatment, 315 clearly completed 6 cycles per protocol. As detailed in the CHAARTED CSR Table 8, an old version of the chemotherapy summary form was used for an additional 20 patients; of these, 17 appear to have received 6 cycles of treatment (16 with full dose and 1 with dose reduction) based on the cumulative dose of docetaxel, 1 patient did not provide cumulative dose information (so the number of cycles could not be estimated), and the remaining 2 patients had reported dose modifications and may have received 6 cycles.

b The GETUG-AFU15 CSR does not specifically state how many patients completed 9 cycles; it is noted however that 99 patients received <9 cycles, and 4 patients did not receive docetaxel. The remaining 89 patients are listed in this table as having completed 9 cycles of treatment.

Demography:

While patient ages were similar across the studies, the percentage of patients in GETUG-AFU15 with ECOG PS 1-2 was significantly lower than in the CHAARTED study (the STAMPEDE study used WHO PS).

Table 16: Patient demographics

	STAMPEDE		CHAARTED		GETUG-AFU15	
ITT population	**ADT Doc + ADT (N = 1184)**	**(N = 592)**	**ADT Doc + ADT (N = 393)**	**(N = 397)**	**ADT Doc + ADT (N = 193)**	**(N = 192)**
Age (years)						
Median age	65	65	63	64	NR	NR
Range	41-82	40-81	39-91	36-88	NR	NR
Mean age (SD)	NR	NR	NR	NR	63.4 (8.1)	62.7 (7.5)
PS (N, %)		**WHO**		**ECOG**	**ECOG**	
0	922 (78)	461 (78)	272 (69.4)	277 (69.8)	176 (96) (99)	181
1	250 (21)	127 (21)	115 (29.3)	114 (28.7)	7 (4)	2 (1)
2	12 (1)	4 (1)	5 (1.3)	6 (1.5)		
Unknown	0	0	1	0	NR	NR
Karnofsky index						
Mean (SD)	NA	NA	NA	NA	92.27 (9.86) (7.69)	94.86

Disease characteristics were well balanced within each of the three studies. In each study, the majority of the patients had a Gleason score of at least 8. While all patients were metastatic at baseline in the CHAARTED and GETUG-AFU15 studies, the STAMPEDE study accepted patients with less advanced disease and 39% of the patients had non-metastatic disease.

Across the studies, differences in disease characteristics included a lower percentage of patients in the GETUG-AFU15 study with Gleason scores of 8-10 compared to the other two studies, and a lower median baseline PSA value in GETUG-AFU15 compared to the other studies (approximately 26 ng/mL, versus approximately 64 ng/mL and 51 ng/mL in STAMPEDE and CHAARTED, respectively).

Table 17: Disease characteristics at baseline (ITT population)

STAMPEDE		**CHAARTED**		**GETUG-AFU15**	
ADT		**Doc + ADT (N = 592)**	**ADT (N = 393)**	**Doc + ADT (N = 397)**	**ADT (N = 193)**	**Doc + ADT (N = 192)**
ITT population (N = 1184)						
Initial Gleason score (%)						
≤7	24	19	26.5	29.5	41	45
≥8	68	73	61.8	60.7	59	55
Unknown	8	8	11.7	9.8	NA	NA
Metastatic status at baseline (%)						
M0	39	39	NA	NA	NA	NA
M1	61	61	100	100	100	100
Metastatic (%)						
Post initial treatment	3	3	15.8	15.8	24	33
At diagnosis	58	59	69.5	69.8	76	67
Unknown	NA	NA	14.8	14.4	NA	NA
Organs involved (%)						
Bone	54	52	NR	NR	82	81
Nodes	19	17	NR	NR	57	53
Lung	3	2	NR	NR	12	12
Liver	1	1	NR	NR	2	5
Other	4	4	NR	NR	NA	NA
PSA (ng/mL) at start of ADT/baseline						
Median (range)	64 (0-15747)	63 (0-9999)	52.1 (0.1-8056)	50.9 (0.2-8540.1)	25.85 (0.1-11900)	26.7 (0.05-2170)

Adverse events

The CSRs for the STAMPEDE, CHAARTED, and GETUG-AFU15 studies were completed on 24 January 2019, 25 November 2015, and 06 February 2017, respectively; no new analyses were performed.

The STAMPEDE and CHAARTED studies assessed docetaxel + ADT therapy over 6 cycles, whereas the GETUG-AFU15 study assessed the therapy over 9 cycles. Due to the variations in analyses across studies, AEs are presented for the following periods:

- STAMPEDE: over the entire duration of the study and up to 6 months on study (the time corresponding to the period of chemotherapy)
- CHAARTED: over the entire time on study treatment
- GETUG-AFU15: up to 6 months on treatment in the control arm and up to the discontinuation of chemotherapy in the experimental arm.

Regarding STAMPEDE:

Over the entire duration of the study, almost all treated patients experienced at least one AE. More patients with Grade ≥3 AEs were observed in the docetaxel arm (283 patients, 52%) than in the ADT arm (384 patients, 32%). SAEs were also more frequently reported in the docetaxel arm compared to the ADT-only arm (31% versus 10%, respectively).

The same pattern was observed when considering the period of time corresponding to the duration of the chemotherapy (up to 6 months).

Table 18: Overview of patients with at least one AE

N (%)	ADT	Docetaxel + ADT
	1205	544
	1135 (94)	540 (99)
Safety Overview up to 6 months		
Patients with any AE		
Patients with any Grade ≥3 AEs	*196 (16)*	*196 (36)*
Patients with Grade≥3 AEs, excluding laboratory AEs	*189 (16)*	*191 (35)*
Patients with any serious AEs	*54 (4)*	*150 (28)*
Patients with any serious AEs Grade ≥3	42 (3)	119 (22)
Safety Overview over the entire time on study	1207	545
Patients with any AE	1192 (99)	544 (100)
Patients with any Grade ≥3 AEs	*384 (32)*	*283 (52)*
Patients with Grade≥3 AEs, excluding laboratory AEs	*369 (31)*	*274 (50)*
Patients with any serious AEs	*124 (10)*	*170 (31)*
Patients with any serious AEs Grade ≥3	*92 (8)*	*136 (25)*

Overall, 100% and 99% of the patients in the docetaxel + ADT and in the ADT treatment arms, respectively, reported at least one AE.

AEs reported in the following body systems were more commonly reported (≥10 percentage point difference, all grades) in the docetaxel + ADT versus ADT-only group, respectively:

- Gastrointestinal (81% versus 53%)
- General disorders (82% versus 59%)
- Musculoskeletal disorders (80% versus 71%)
- Skin toxicities (69% versus 25%)
- Nervous system toxicities (55% versus 28%)
- Respiratory toxicities (50% versus 31%)
- Blood and lymphatic (46% versus 28%)
- Peripheral edema toxicities (28% versus 14%)
- Blood and bone marrow toxicities (23% versus 6%)
- Ocular toxicities (23% versus 10%)

By decreasing order of frequency, the most frequent AEs (all grades, reported in at least 10% of the patients in the docetaxel + ADT arm) were hot flashes, lethargy, urinary frequency, impotence, nail changes, diarrhea, anemia, constipation, arthralgia, bone pain, generalized pain, insomnia, nausea, stomatitis, fluid retention, dyspepsia, myalgia, dyspnea, neutropenia, abdominal pain, coughing, asthenia, headache, flatulence, flu-like symptoms, febrile neutropenia, dizziness, upper respiratory tract infection, anorexia, rash, increased ALT, vomiting, hypersensitivity, and fever.

AEs (all grades) reported in excess of at least 10% in the docetaxel + ADT arm compared to the ADT-only arm were nail changes (difference: +42%), stomatitis (+25%), diarrhea (+24%), lethargy (+23%), constipation (+18%), nausea (+17%), neutropenia (+17%), febrile neutropenia (+14%), fluid retention (+13%), dyspepsia (+12%), and anemia (+12%).

For Grade ≥3 AEs, toxicities in the following body systems were more commonly in the docetaxel + ADT arm compared to the ADT-only arm, respectively:

- Blood and lymphatic toxicities (15% versus 2%)
- Blood and bone marrow toxicities (13% versus 0%)
- Gastrointestinal disorders (8% versus 3%)
- General disorders (6% versus 4%)
- Respiratory toxicities (5% versus 2%)

By decreasing order of frequency, the most frequent Grade ≥3 AEs (reported by more than 2% of the patients in the docetaxel + ADT arm) were febrile neutropenia, neutropenia, impotence, and diarrhea.

Grade ≥3 AEs reported in excess of at least 2% in the docetaxel + ADT arm compared to the ADT arm were febrile neutropenia (difference: +14%), neutropenia (+12%), and diarrhea (+3%).

AEs reported in the following body systems were more commonly reported (≥10 percentage point difference, all grades) in the docetaxel + ADT versus ADT-only group, respectively:

- General disorders (77% versus 40%)
- Gastrointestinal (74% versus 31%)
- Skin toxicities (63% versus 16%)
- Nervous system toxicities (41% versus 16%)
- Respiratory toxicities (39% versus 16%)
- Blood and lymphatic (38% versus 13%)
- Blood and bone marrow toxicities (21% versus 4%)
- Peripheral edema toxicities (18% versus 7%)
- Ocular toxicities (17% versus 5%)

In the endocrine disorders body system, AEs were less commonly reported (≥10 percentage point difference, all grades) in the docetaxel + ADT versus ADT-only group, respectively.

- Endocrine disorders (65% versus 78%)

By decreasing order of frequency, the most frequent AEs (all grades, reported in at least 10% of the patient in the docetaxel +ADT arm) were lethargy, hot flashes, nail changes, diarrhea, impotence, anemia, stomatitis, urinary frequency, constipation, nausea, insomnia, dyspepsia, neutropenia, bone pain, fluid retention, generalized pain, dyspnea, febrile neutropenia, abdominal pain, arthralgia, myalgia, flu like symptoms, headache, coughing, upper respiratory tract infection, asthenia, flatulence and hypersensitivity.

AEs, all grades, reported in excess of at least 10% in the docetaxel + ADT arm compared to the ADT arm were nail changes (difference: +38%), lethargy (+35%), stomatitis (+27%), diarrhea (+26%), nausea (+18%), dyspepsia (+17%), neutropenia (+17%), anemia (+17%), constipation (+16%), febrile neutropenia (+15%) and fluid retention (+11%).

Overall, over the first 6 months on treatment, there was no difference between treatment arms with regard to the proportion of patients reporting at least one severe (Grade ≥3) AEs (16% in each treatment arms).

For Grade ≥3 AEs, toxicities in the following body systems were more common in the docetaxel + ADT arm compared to the ADT-only arm, respectively:

- Blood and lymphatic toxicities (15% versus 1%)
- Blood and bone marrow toxicities (13% versus 0%)
- Gastrointestinal disorders (5% versus 1%)
- Respiratory toxicities (4% versus 1%)
- General disorders (5% versus 2%)

In the endocrine disorders body system, Grade ≥3 AEs were less common in the docetaxel + ADT versus ADT-only group, respectively.

- Endocrine disorders (4% versus 7%)

By decreasing order of frequency, the most frequent Grade ≥3 AEs, reported by more than 2% of the patients in the docetaxel + ADT arm were febrile neutropenia, neutropenia, impotence and diarrhea.

Grade ≥3 AEs, reported in excess of at least 2% in the docetaxel + ADT arm compared to the ADT arm were febrile neutropenia (difference: +15%), neutropenia (+12%), and diarrhea (+3%).

Grade ≥3 impotence was more frequent in the ADT-only arm (6% versus 3%).

Regarding the CHAARTED study:

In accordance with ECOG/protocol rules, systematic safety data collection in the CHAARTED study was performed in the docetaxel + ADT arm, only, and was focused on Grade ≥3 AEs. Safety data were not systematically documented in the control arm; only "major" events were to be reported, precluding safety comparison between treatment arms.

In the docetaxel + ADT arm, the most frequently occurring treatment-related Grade ≥3 AEs were neutropenia (12.1%, including 9% Grade 4 events), febrile neutropenia (6.1%), and fatigue (4.1%). Grade ≥3 allergic reactions were reported in 2.1% of the patients. Related Grade ≥3 diarrhea, vomiting, stomatitis, peripheral neuropathy, sensory neuropathy, and thromboembolic events occurred at rate of ≤1%.

Regarding the GETUG-AFU15 study:

No safety overview analysis was performed for the GETUG-AFU15 study.

AEs were more frequent in the docetaxel + ADT arm, with an overall safety profile consistent with the known safety profile of docetaxel.

As expected, the most frequent all-grade toxicities occurring in the docetaxel + ADT arm were hematological toxicities (primarily anemia and neutropenia, in 72% and 50% of the patients, respectively) and gastrointestinal toxicities (primarily diarrhea [31%], nausea [29%], constipation [22%], and mucositis [21%]). All-grade sensory neuropathy and edema were each reported in 29% of the patients treated with docetaxel. All-grade fatigue was reported in 74% of the patients treated with docetaxel.

Low grade increased ALT and AST were more reported in 23% and 20% of the patients treated with docetaxel.

AEs (all grades) reported in excess of at least 10% in the docetaxel + ADT arm compared to the ADT-only arm were fatigue (+54%), alopecia (+53%), anemia (+50%), neutropenia (+47%), nail change (+39%), diarrhea (+29%), nausea (+27%), sensory neuropathy (+25%), edema (+24%), mucositis (+21%), constipation (+17%), dyspnea (+16%), cough (+13%), rash/desquamation (+13%), skin reaction (+13%), infection without neutropenia (11%), ALT and AST increases (+11%), and fever (+10%).

AEs related to hormone therapy were reported at similar incidences in the two treatment arms, with the notable exception of all grade hot flashes which were more frequent in the ADT-only arm (63%) compared to the docetaxel + ADT arm (37%).

Few Grade ≥3 AEs were reported in the ADT-only arm. Grade ≥3 AEs reported with a higher incidence in ≥ 5% in the docetaxel + ADT arm by comparison to the ADT-only arm were neutropenia (32% versus 0%), febrile neutropenia (7% versus 0%), and fatigue (7% versus 1%).

Other frequently (≥5% of the patients) reported Grade ≥3 AEs were decreased libido and erectile dysfunction, which were reported at similar rates in both treatment arms.

Analysis of adverse events by main organ system across study

In this section are presented, side by side, the safety results of the STAMPEDE and GETUGAFU15 studies. Results of the CHARTEED study were not included because the systematic collection of AEs was limited to the related Grade ≥3 events for the experimental arm.

For the STAMPEDE study, the results are from the analysis up to 6 months on study.

- **Hematology**

Anemia was the most frequently reported hematologic toxicity. All grade events were more frequent in the docetaxel + ADT treatment arms than in the ADT arms. Barely any severe events (Grade ≥3) were reported.

In the two studies, neutropenia (Grade ≥3) was reported very commonly (≥10%). Febrile neutropenia was reported at rates ranging from 8% to 15%, higher than what was reported in the hormone resistant patient setting (3% of the patients in the TAX 327 study [10]).

Neither of the studies required prevention of severe neutropenic complications with growth factor.

In the GETUG-AFU15 study, the Independent Data Monitoring Committee recommended G-CSF (5 µg/kg/day subcutaneously once daily) from day 5 to day 10 after each docetaxel administration, after two deaths were reported related to febrile neutropenia and neutropenic infection among the first 108 patients randomized to the docetaxel arm.

Table 19: Summary of hematological toxicities

% of patients	***STAMPEDE***		***GETUG-AFU15***	
	ADT (N = 1207)	***Doc + ADT (N = 545)***	***ADT (N = 186)***	***Doc + ADT (N = 189)***
All grades:				
Anemia	*13%*	*30%*	*22%*	*72%*
Neutropenia	*2%*	*19%*	*3%*	*50%*
Febrile neutropenia	*0%*	*15%*	*0%*	*8%*
Thrombocytopenia	*2%*	*3%*	*5%*	*11%*
Grade ≥3:				
Anemia	*0%*	*0%*	*1%*	*2%*
Neutropenia	*0%*	*12%*	*0%*	*32%*
Febrile neutropenia	*0%*	*15%*	*0%*	*7%*
Thrombocytopenia	*0%*	*0%*	*0%*	*1%*

- Gastrointestinal disorders

As expected with docetaxel, GI toxicities were very commonly reported. By contrast, severe events (Grade ≥3) were reported, in general, in less than 1% of the patients. The most frequent severe events were diarrhea, reported in 3% of the patients, in the STAMPEDE study.

Table 20: Summary of gastrointestinal toxicities

% of patients	STAMPEDE		GETUG-AFU15	
	ADT (N = 1207)	Doc + ADT (N = 545)	ADT (N = 186)	Doc + ADT (N = 189)
All grades:				
Diarrhea	9%	35%	2%	31%
Stomatitis/pharyngitis	1%	28%	0%	8%
Constipation	11%	27%	5%	22%
Nausea	6%	24%	2%	29%
Dyspepsia	5%	22%	NR	NR
Abdominal pain	7%	14%	NR	NR
Flatulence	7%	10%	NR	NR
Vomiting	3%	9%	0%	8%
GI hemorrhage	2%	2%	NR	NR
Mucositis	NR	NR	0	21
Grade ≥3:				
Diarrhea	0%	3%	0	1%
Stomatitis/pharyngitis	0%	0%	0%	1%
Constipation	0%	0%	0%	0%
Nausea	0%	0%	0%	0%
Dyspepsia	0%	0%	NR	NR
Abdominal pain	0%	0%	NR	NR
Flatulence	0%	0%	NR	NR
Vomiting	0%	1%	0%	0%
GI hemorrhage	0%	0%	NR	NR
Mucositis	NR	NR	0%	1%

- Respiratory disorders

Dyspnea and coughing events were more frequent in the patients treated in the docetaxelcontaining arms of the two studies compared to those treated with ADT-only. In the STAMPEDE study, upper respiratory tract infections were also more frequent in the patients treated with docetaxel + ADT.

Severe events (Grade ≥3) were reported in 2% or less of the patients. The most frequent severe event was dyspnea, reported in 2% of the patients in the docetaxel +ADT arm of the GETUG-AFU15 study.

Table 21: Summary of espiratory disorders

% of patients	***STAMPEDE***		***GETUG-AFU15***	
	ADT (N = 1207)	***Doc + ADT (N = 545)***	***ADT (N = 186)***	***Doc + ADT (N = 189)***
All grades:				
Dyspnea	*7%*	*16%*	*3%*	*19%*
Coughing	*4%*	*11%*	*1%*	*14%*
Upper respiratory tract infection	*3%*	*10%*	*NR*	*NR*
***Grade ≥3**:*				
Dyspnea	*0%*	*1%*	*0%*	*2%*
Coughing	*0%*	*0%*	*0%*	*0%*
Upper respiratory tract infection	*0%*	*1%*	*NR*	*NR*

- Endocrine disorders

As expected with ADT, endocrine disorders were commonly reported in both studies. Hot flashes were less frequent in the docetaxel + ADT arms of the two studies than in the ADT-only arms, with a more pronounced difference in the GETUG-AFU15 study. Severe events (Grade ≥3) were reported in less than 10% of the patients. Of note, when considering the entire duration of treatment, no differences were noted between treatment arms in the STAMPEDE study.

Table 22: Summary of endocrine disorders

% of patients	STAMPEDE		GETUG-AFU15	
	ADT (N = 1207)	Doc + ADT (N = 545)	ADT (N = 186)	Doc + ADT (N = 189)
All grades:				
Hot flashes	73%	61%	63%	37%
Impotence/erectile dysfunction[a]	41%	31%	12%	11%
Decreased libido	NR	NR	15%	11%
Breast enlargement	2%	0%	5%	4%
Breast pain	2%	0%	NR	NR
Diabetes	1%	4%	NR	NR
Grade ≥3:				
Hot flashes	2%	1%	2%	4%
Impotence/erectile dysfunction[a]	6%	3%	8%	8%
Decreased libido	NR	NR	5	6
Breast enlargement	0%	0%	1%	0%
Breast pain	0%	0%	NR	NR
Diabetes	0%	1%	NR	NR

- Liver function disorders

In the GETUG-AFU15 study, AEs of low grade increased LFTs were more commonly reported in the docetaxel-containing arm; this is consistent with the known safety profile of docetaxel, which is frequently associated with mild serum elevations of aminotransferases. No such difference was observed in the STAMPEDE study; however no conclusion should be drawn from this observation, as no analysis of systematic laboratory test results has been performed.

Table 23: Summary of hepatic disorders

% of patients	STAMPEDE		GETUG-AFU15	
	ADT (N = 1207)	Doc + ADT (N = 545)	ADT (N = 186)	Doc + ADT (N = 189)
All grades:				
Abnormal hepatic function	3%	4%	NR	NR
Increased ALT	6%	7%	12%	23%
Increased AST	2%	1%	9%	20%
Bilirubin increase	0%	0%	3%	3%
Increased ALP	NR	NR	22%	28%
Grade ≥3:				
Abnormal hepatic function	0%	0%	NR	NR
Increased ALT	0%	0%	1%	2%
Increased AST	0%	0%	1%	2%
Bilirubin increase	0%	0%	0%	0%
Increased ALP	NR	NR	2%	4%

Serious adverse event/deaths/other significant events

Deaths

Most deaths in these studies involving advanced cancer patients were due to progressive disease.

In STAMPEDE, there were a total of 590 patient deaths; 175 and 415 in the docetaxel + ADT and ADT-only arms, respectively. Overall, 143 (82%) and 347 (84%) were due to prostate cancer, whereas 7 (4%) and 11 (3%) were due to AEs which occurred at any time from the beginning of the trial in the docetaxel + ADT and ADT-only treatment arms, respectively. In the docetaxel + ADT arm, two patients died within 30 days following the last administration of docetaxel.

Of the 7 patients who died in relation to AEs in the docetaxel + ADT treatment arm:

- Two patients experienced a SAE and death within 30 days of their last docetaxel treatment (one patient [patient 3067] was found dead at home, with a postmortem examination showing a cerebral infarction; the other experienced neutropenic sepsis, which resulted in death and was considered a SAR.
- One patient [patient 16004] experienced a SAE within 30 days of docetaxel treatment, but died over 30 days after his last docetaxel treatment (the primary cause of death was bronchopneumonia).

- The remaining 4 patients experienced a SAE and death over 30 days after their last docetaxel treatment (the cause of death for each patient was gastric cancer [second malignancy], an acute respiratory event, pancreatic cancer, and myocardial infarction respectively).

Of the 11 patients in the ADT-only arm, 7 experienced death within 30 days of receiving their last dose of ADT.

Table 24: Summary of deaths - STAMPEDE

N (%)	**ADT (N = 1184)**	**Doc + ADT (N = 592)**
Any death during the study	415	175
Prostate cancer	347 (84)	143 (82)
Adverse event[a]	11 (3)	7 (4)
Death within 60 days from randomization	4 (1)	3 (2)
Other	60 (14)	26 (16)
Deaths within 30 days from last reported docetaxel dose	NA	3
Prostate cancer	NA	2
Adverse event	NA	2*b*
Others	NA	0
Death more than 30 days from last reported docetaxel dose	NA	172
Prostate cancer	NA	141
Adverse event	NA	5
Others	NA	26

a At the time of the primary analysis database freeze, outcomes for all fatal AEs were not coded. A total of 4 and 3 patients in the ADT-only and docetaxel + ADT arms, respectively, experienced Grade 5 AEs, while the others experienced Grade 2-4 AEs that eventually resulted in death.

b One AE death was also reviewed as a death due to prostate cancer.

In CHAARTED, there were 237 patient deaths at the cut-off date (101 deaths in the docetaxel + ADT arm, and 136 in the ADT-only arm). There was 1 death of unknown cause during the course of docetaxel therapy (the patient was found dead at home), which was considered to be possibly related to docetaxel.

In GETUG-AFU15, death data were not analyzed and no listings were produced. At the cut-off date, 176 patients had died (88 in each treatment arm). It was noted that there were 4 deaths due to the following toxicities in the docetaxel + ADT treatment arm:

- Septic shock with pneumopathy and febrile neutropenia (related to docetaxel)
- General health deterioration (related to docetaxel)
- Neutropenic sepsis (possibly related to docetaxel and ADT [bicalutamide and goserelin acetate])

- Suspected embolism (possibly related to docetaxel and ADT [goserelin acetate])

Other serious adverse events

No summary of SAEs was performed for the STAMPEDE study.

No summary of AdEERs was performed for the CHAARTED study.

No summary of serious adverse events was performed for the GETUG-AFU15 study.

Narratives for the following two patients from the **STAMPEDE** study (experiencing fatal events related to docetaxel as per investigator judgement) were written based on information from the Sanofi pharmacovigilance database:

- Sanofi PV Case ID: [redacted]

Pt: [redacted], docetaxel + ADT treatment arm

A 68 year-old patient initiated treatment with docetaxel (142 mg) and goserelin on 12 December 2006 for metastatic prostate cancer. No relevant medical history or concomitant medication was reported.

On 19 December 2006 he was diagnosed with neutropenic sepsis (grade 4), and on the next day he was admitted to the critical care unit. He was treated with antibiotics (NOS) iv, G-CSF, and oxygen therapy with "respiratory support". The patient died on [redacted]. The primary cause of death has been reported as bronchopneumonia fatal with secondary cause of neutropenic sepsis. No autopsy was performed.

The investigator considered the fatal event was definitely related to docetaxel. Underlying prostate cancer was considered to be a contributing factor.

- Sanofi PV Case ID: [redacted]

Pt: [redacted], docetaxel + ADT treatment arm

A 75 year-old patient initiated docetaxel (140 mg) + ADT (goserelin was started 08 August 2012) on 17 September 2012. He last received cycle 3 of docetaxel on 05 November 2012 (no information for goserelin). No relevant medical history was reported. Concomitant medication included amlodipine, irbesartan, moxonidine, nifedipine, omeprazole, prednisolone, propranolol, and simvastatin.

On 14 November 2012, the patient was hospitalized due to febrile neutropenia. The white blood cell count was 1.7 x 109/L (normal range: 4-11 x 109/L), the neutrophil count was 0.20 x 109/L (normal range: 2.0-7.5 x109/L), and the hemoglobin level was 9.9 g/dL (normal range: 13.5-17 g/dL). Antibiotics (NOS) and intravenous fluid therapy were started. On an unknown date he was admitted to ICU with hypoxia, and on 23 November 2012, he was diagnosed with Pneumocystis carinii (Pneumocystis jirovecii). Despite treatment with antibiotics (NOS) and mechanical ventilation, his condition continued to deteriorate, and on 09 December 2012 dialysis was started. The patient died on [redacted]. The cause of death was reported as myocardial infarction. An autopsy was performed (the result was not reported).

The investigator considered the fatal event of myocardial infarction and febrile neutropenia were related to docetaxel and not to goserelin.

No narratives were written as part of the **CHAARTED** CSR. The narrative for the following patient who reported fatal event related to docetaxel + ADT was prepared based on information from the Sanofi pharmacovigilance database (case reported via AdEERs):

- Sanofi PV Case ID: [redacted] (original), [redacted] (11), [redacted] (2)

Pt: [redacted], docetaxel + ADT treatment arm

A 69 year-old male patient was diagnosed with prostate cancer in 2005, and received surgical treatment on March 2005 followed by hormonal therapy from March 2005 to January 2007. His preexisting conditions included hypertension, diabetes mellitus, cigarette smoker, coronary artery disease, hyperlipidemia, and Barrett's esophagus.

Concomitant medications included acetylsalicylic acid, hydrochlorothiazide/lisinopril, loperamide, omeprazole, bicalutamide, prochlorperazine edisylate, gabapentin, metformin hydrochloride, and metoprolol.

The patient was randomized to receive docetaxel + ADT (arm A). He received 4 cycles of docetaxel and goserelin from 21 July 2010 to 22 September 2010.

On [redacted], he was found dead at home. No laboratory data are available. No autopsy was performed.

The investigator considered that the event of "death" was possibly related to docetaxel.

Narratives for patients in the **GETUG-AFU15** study who experienced fatal SAEs possibly related to docetaxel were provided by Unicancer in the CSR, as follow:

- Patient [redacted]: Septic shock with pneumopathy and febrile neutropenia (Grade 4)

(FR-UNICANCER-[redacted])

A 58-year old man was included in the study on the 12 September 2005 and randomized to docetaxel + ADT. The patient received 1 cycle of docetaxel (75 mg/m2) and goserelin acetate (10.8 mg) on the 12 September 2005. He developed symptoms, including fever (40°C) and abdominal pain, related to a pneumopathy during the evening of 17 September 2005. Treatment with amoxicillin was initiated on the 17-Sep-2005. The patient was hospitalized on the 18 September 2005 with acute respiratory distress. A pneumopathy was diagnosed and the patient was treated with mechanical ventilation, vascular filling, and antibiotherapy. The patient died on the [redacted]. The investigator and the sponsor both considered the event related to the docetaxel but not reasonable related to the goserelin acetate.

- Patient [redacted]: General health deterioration (FR-UNICANCER-[redacted])

A 76-year old man was included in the study on the 14 April 2006 and randomized to docetaxel + ADT. Relevant medical history included hypertension and arrhythmia. The patient received 4 cycle of docetaxel (cumulative dose of 480 mg) with the last administration (120 mg) on the 10 July 2006. The patient was hospitalized for a vagal reaction with associated lumbar pain without neurological symptoms on the 26 May 2006, the patient recovered on the 27 May 2006. On the 12 June 2006 the patient was hospitalized with bowel obstruction with neutropenia (Grade 4), the patient was treated with growth factor and antibiotherapy. On the 13 July 2006, the patient was urgently hospitalized due to general health deterioration (Grade 4). The patient died on the [redacted]. The investigator and the sponsor both considered the event related to the docetaxel.

- Patient [redacted]: Neutropenic sepsis (FR-UNICANCER-[redacted])

A 73-year old man was included in the study on the 10 November 2006 and randomized to docetaxel + ADT. The patient received 2 cycle of docetaxel on the 20 November 2006 and on the 11 December 2006 (75 mg/m2). The patient was also administered oral daily bicalutamide (50 mg) from the 10 November 2006 till the 19 December 2006, and goserelin acetate on the 10 November 2006 (10.8 mg). On the 19 December 2006 the patient was hospitalized with febrile aplasia, tachycardia, and hypotension, and was treated with antibiotherapy. During the evening of the [redacted] December 2006 the patient had a cardiorespiratory failure and could not be resuscitated. The patient died on the [redacted]. The investigator and the sponsor both considered the event possibly related to docetaxel, bicalutamide, and goserelin acetate.

- Patient [redacted]: Embolism (FR-UNICANCER-[redacted])

A 75-year old man was included in the study on the 11 December 2006 and randomized to docetaxel + ADT. The patient received 2 cycle of docetaxel on the 20 December 2006 and on the 10 January 2007 (75 mg/m2). The patient was also administered goserelin acetate in December 2006. On the [redacted] the patient was hospitalized with a suspicion of embolism and died. The investigator and the sponsor both considered the event possibly related to docetaxel and goserelin acetate.

Laboratory findings

No analyses of laboratory data were performed for the three studies included in this submission.

No analyses of vital signs or physical findings were performed for the three studies included in this submission.

Safety in special populations

Safety analyses by special groups of patients were not performed for the CHAARTED and GETUG-AFU15 studies. The analyses for the STAMPEDE study were performed over the entire duration of the study treatment.

- Age

No major differences were reported between age categories. More patients aged ≥65 years in the docetaxel arm reported hypersensitivity reaction, neutropenia, anemia, fluid retention, dyspnea, and nail changes when compared to the patients aged less than 65 years. None of these increases in frequency reached the threshold of 10% difference.

Events of renal impairment and urinary frequency were slightly more frequent in patients aged ≥65 years, irrespective of treatment arms.

No such differences were observed for Grade ≥3 AEs, with the exception of neutropenia; neutropenia was reported in 14% of the patients treated with docetaxel and aged ≥65 years, and in 10% of the patients treated with docetaxel and aged less 65 years.

A tendency for more frequent febrile neutropenia in the elderly population was noted (17% versus 13% among patients aged ≥65 years and <65 years, respectively).

Table 25: Summary of AEs by age - STAMPEDE

Body system	**Age <65 years**		**Age ≥65 years**	
Event, % of patients	**ADT (N = 534)**	**Doc + ADT (N = 249)**	**ADT (N = 673)**	**Doc + ADT (N = 296)**
Any class	99%	100%	99%	100%
Hypersensitivity	4%	8%	3%	13%
Neutropenia	5%	17%	3%	24%
Anemia	26%	36%	29%	42%
Fluid retention	12%	22%	14%	29%

Renal Impairment	5%	5%	11%	10%

Body system	**Age <65 years**		**Age ≥65 years**	
Event, % of patients	**ADT (N = 534)**	**Doc + ADT (N = 249)**	**ADT (N = 673)**	**Doc + ADT (N = 296)**
Urinary frequency	50%	50%	53%	55%
Dyspnea	13%	19%	15%	25%
Nail changes	5%	43%	6%	50%

Table 26: Summary of AEs by age- Grade ≥3 - STAMPEDE

Body system	**Age <65 years**		**Age ≥65 years**	
Event, % of patients	**ADT (N = 534)**	**Doc + ADT (N = 249)**	**ADT (N = 673)**	**Doc + ADT (N = 296)**
Any class	31%	50%	33%	54%
Hypersensitivity	0%	1%	0%	1%
Neutropenia	0%	10%	1%	14%
Anemia	1%	0%	1%	0%
Fluid retention	0%	0%	0%	0%
Renal Impairment	0%	0%	1%	0%
Urinary frequency	2%	2%	3%	2%
Dyspnea	1%	0%	0%	2%
Nail changes	0%	1%	0%	1%

A similar analysis was performed for the patients aged ≥75 years.

Only 48 and 128 patients treated with docetaxel + ADT and ADT, respectively, were aged ≥75 years.

There was a general tendency for more frequent AEs in the patients treated with docetaxel aged ≥ 75 years compared to those aged <75 years. By a threshold of at least 10%, more patients aged ≥75 years in the docetaxel-containing arm reported neutropenia, anemia, diarrhea, dyspnea, and upper respiratory tract infection. An increased incidence of anemia in patients aged ≥75 years in the ADT-only arm was also observed.

Severe (Grade ≥3) neutropenia was reported more frequently in patients aged ≥75 years in docetaxel-containing arm compared to the ADT-only arm.

Table 27: Summary of AEs by age - STAMPEDE

Body system	**Age <75 years**	**Age ≥75 years**

Event, % of patients	ADT (N = 1079)	Doc + ADT (N = 497)	ADT (N = 128)	Doc + ADT (N = 48)
Any class	99%	100%	98%	98%
Neutropenia	4%	20%	3%	30%
Thrombocytopenia	3%	4%	4%	11%
Anemia	26%	38%	38%	51%
Myocardial infarction	1%	1%	0%	6%
Constipation	18%	36%	24%	45%
Diarrhea	22%	44%	16%	55%
Hypokalemia	2%	3%	1%	9%
Anorexia	7%	12%	11%	19%
Fluid retention	12%	25%	17%	30%
Renal Impairment	8%	7%	14%	13%
Urinary frequency	52%	52%	52%	57%
Coughing	10%	17%	13%	23%
Dyspnea	14%	21%	18%	36%
Upper respiratory tract infection	8%	14%	8%	28%
Nail changes	5%	46%	4%	53%
Rash	9%	12%	11%	17%

Table 28: Summary of AEs by age - Grade ≥3 - STAMPEDE

Body system	Age <75 years		Age ≥75 years	
Event, % of patients	ADT (N = 1079)	Doc + ADT (N = 497)	ADT (N = 128)	Doc + ADT (N = 48)
Any class	31%	51%	38%	60%
Neutropenia	1%	12%	0%	17%
Thrombocytopenia	0%	0%	0%	2%
Anemia	1%	0%	2%	0%

Myocardial infarction	1%	1%	0%	4%
Constipation	0%	1%	0%	2%
Diarrhea	1%	4%	2%	2%
Hypokalemia	0%	0%	0%	0%
Anorexia	0%	0%	0%	0%
Fluid retention	0%	0%	0%	0%
Renal Impairment	1%	0%	2%	0%
Urinary frequency	3%	2%	3%	2%
Coughing	0%	1%	0%	0%
Dyspnea	1%	1%	0%	0%
Upper respiratory tract infection	0%	1%	0%	2%
Nail changes	0%	1%	0%	2%
Rash	0%	0%	0%	0%

- Metastatic disease versus non-metastatic disease

Evaluation of the safety according to the baseline metastatic status was limited to the STAMPEDE study only.

There was a general tendency for the M0 patients to experience more frequent AEs compared to the M1 patients, irrespective of the treatment received. However, these differences were often more pronounced for the patients treated with docetaxel, with the exception of diarrhea and lethargy.

With a threshold of ≥10% difference, dyspepsia and arthralgia were reported more frequently in the M0 patients treated with docetaxel compared to the M1 patients treated with docetaxel, while incidences of these events were comparable between M0 and M1 patients treated with ADT alone.

Neutropenia, although not reaching the 10% threshold, was more frequently reported in the M0 patients treated with docetaxel than in the M1 patients (26% versus 17%).

As expected, bone pain was reported more frequently in the M1 patients than in the M0 patients, irrespective of the treatment received. There was no difference in incidence of bone pain between treatment arms for the M1 patients.

Table 29: Summary of AEs by baseline disease status - STAMPEDE

Body system	**M0**		**M1**	
Event, % of patients	**ADT (N = 472)**	**Doc + ADT (N = 212)**	**ADT (N = 735)**	**Doc + ADT (N = 333)**
Any	99%	100%	98%	100%

Urinary frequency	67%	63%	42%	46%
Flatulence	20%	25%	10%	10%
Diarrhea	37%	54%	11%	40%
Abdominal pain	17%	28%	10%	15%
Dyspepsia	14%	33%	12%	20%
Arthralgia	29%	42%	24%	31%
Neutrophils	4%	26%	4%	17%
GI Hemorrhage	14%	14%	3%	4%
Hot flashes	88%	84%	78%	76%
Fever	4%	15%	2%	7%
Flu-like symptoms	9%	21%	7%	13%
Myalgia	17%	28%	15%	20%
Insomnia	29%	37%	22%	30%
Anemia	28%	43%	27%	37%
Asthenia	9%	20%	9%	14%
Lethargy	60%	78%	47%	73%
Bone pain	21%	19%	46%	43%
Rash	9%	9%	9%	15%

Regarding the Grade ≥3 events, no clinically meaningful differences were noted between M0 and M1 patients treated with docetaxel. Severe neutropenia were slightly more frequent in the M0 patients when compared to the M1 patients (15% versus 11%). Severe bone pain was only reported in the M1 patients.

There was no difference in the incidence of febrile neutropenia between M0 and M1 patients treated with docetaxel; febrile neutropenia was reported in 15% of the M0 patients treated with docetaxel, and in 16% of the M1 patients treated with docetaxel.

Table 30: Summary of AEs by baseline disease status - Grade ≥3 - STAMPEDE

Body system	**M0**		**M1**	
Event, % of patients	**ADT (N = 472)**	**Doc + ADT (N = 212)**	**ADT (N = 735)**	**Doc + ADT (N = 333)**
Any	31%	52%	32%	52%
Urinary frequency	4%	3%	2%	2%

Flatulence	0%	0%	0%	0%
Diarrhea	1%	5%	1%	3%
Abdominal pain	1%	1%	0%	0%
Dyspepsia	0%	0%	0%	0%
Arthralgia	1%	0%	1%	0%
Neutrophils	0%	15%	1%	11%
GI Hemorrhage	1%	1%	0%	0%
Hot flashes	3%	3%	3%	2%
Fever	0%	0%	0%	1%
Flu-like symptoms	0%	0%	0%	0%
Myalgia	0%	0%	0%	0%
Insomnia	1%	2%	1%	0%
Anemia	1%	0%	1%	0%
Asthenia	0%	0%	1%	0%
Lethargy	2%	4%	2%	2%
Bone pain	0%	0%	5%	2%
Rash	0%	0%	0%	0%

Safety related to drug-drug interactions and other interactions

No drug interaction study was performed for the purpose of this application.

Discontinuation due to adverse events

A total of 141 patients discontinued treatment due to AEs; in STAMPEDE, 72 patients (13.2%) discontinued treatment, while 30 patients (7.7%) and 39 patients (20.6%) in the CHAARTED and GETUG-AFU15 studies, respectively, discontinued treatment due to AEs ("toxicity" in GETUGAFU15). No further information is available for these patients.

Post marketing experience

Because docetaxel has been indicated for hormone refractory prostate cancer, and the majority of pharmacovigilance data is from unsolicited reports (and therefore information is limited), pharmacovigilance data cannot be produced specifically for the HSPC indication.

In order to provide a more complete safety profile of docetaxel, a cumulative search from Taxotere® launch to 30 November 2018 was performed in the Sanofi global pharmacovigilance database to identify all adverse events/reactions reported with docetaxel from spontaneous reports, non-interventional post marketing

studies, and other solicited sources (for all indications, including unapproved indications). The report includes only those events where either the 'reporter causality' or the 'Company causality' is related to the selected product in the "Non-Interventional Post-Marketing Study and Reports from Other Solicited Sources".

Docetaxel has been on market more than 20 years (international birth date [IBD] of 30 November 1994). Safety evaluation reports are periodically submitted; the most recent PBRER was submitted with DLP of 30 November 2017, and accompanies this submission in 5.3.6 Reports of Postmarketing Experience.

Sales figures for the interval period were received for the period from 01 October 2016 through 30 September 2017. Exposure from the cumulative experience is available from 01 October 2001 through 30 September 2018 (17 years). Based on an estimate that the average body surface area is equal to 1.7 m2, the recommended dose of 100 mg/m2 represents 170 mg per patient per cycle. The total number of milligrams sold divided by 170 mg per patient per cycle is equal to the total number of cycles. On average, it is estimated that patients receive 5 cycles of docetaxel; therefore, the total number of cycles divided by 5 is equal to the approximate number of patients exposed to docetaxel. Since on the market, the estimated number of patients who received docetaxel commercially worldwide was therefore more than 2.8 million patients, cumulative, from 01 October 2001 through 30 September 2018.

Additionally, a cumulative search of the Sanofi global pharmacovigilance database was performed as a supplemental postmarketing experiences safety review. Cases were reported up to 30 November 2018. A total of 69,457 cases were retrieved with 217,427 events, of which the majority were reported under the SOCs skin and subcutaneous tissue disorders (N = 35,077), general disorders and administration site conditions (N = 29,720), and investigations (N = 24,882).

The thorough safety analysis of docetaxel, as performed and evaluated in these documents and in regular pharmacovigilance activities, showed that the safety profile of docetaxel has been consistent with reference safety information.

Safety data from published literature

Docetaxel has been reported in literature to increase the risk of severe neutropenia and complicated neutropenia in mHSPC patients.

After accrual of 215 patients in the GETUG-AFU15 study, 4 treatment-related deaths were reported, including one due to febrile neutropenia and one other due to neutropenia with infection. Following these events, the protocol was amended for systematic primary prevention with G-CSF after each administration of docetaxel. After this amendment was implemented, the proportion of patients with Grade 3-4 neutropenia fell from 41% to 15%, the proportion of patients with febrile neutropenia fell from 8% to 6%, and no subsequent toxic deaths were reported. For the overall study, the incidence of Grade 3-4 febrile neutropenia was 7%, and the incidence of Grade 3-4 infections with neutropenia was 2%.

High incidences of febrile neutropenia were reported in the CHAARTED and STAMPEDE studies (6.2% and 15% rates of febrile neutropenia, respectively), as well.

Similar results were reported earlier, from 2005 to 2008, in small-size studies in mHSPC patients. In these studies, using a dose of docetaxel ranging from 70 to 75 mg/m2 every 3 weeks, severe neutropenia was reported in 58%, 62%, and 61% of study patients, respectively.

Collectively, these observations contrasted with the results from the TAX 327 study in first line metastatic disease in metastatic castration-resistant prostate cancer (mCRPC) patients who had disease progression during hormonal therapy. In TAX 327, with docetaxel administered 75 mg/m2 every 3 weeks, Grade 3-4 neutropenia was reported in 32% of the patients, and febrile neutropenia in 3% of the patients.

This contrast in occurrence of severe neutropenia and neutropenic complications between mCRPC and mHSPC patients triggered evaluation of potential differences in the systemic clearance of docetaxel in these two different populations of patients. This study included 20 castrated and 10 non-castrated patients. Compared with mHSPC patients, the clearance of docetaxel in the mCRPC patients was increased by approximatively 100% and was associated with an approximatively two-fold reduction in area under the curve (AUC). The erythromycin breath test indicated that the hepatic activity of CYP3A4 was not altered in the castrated patients, and therefore that the increased clearance in castrated men was not the result of an increased CYP34A-mediated metabolism of docetaxel in the liver. The authors showed that the AUC of docetaxel in the liver was significantly higher in castrated rats when compared with intact animals, supporting the hypothesis of a greater uptake of docetaxel in the liver in castrated animals. The authors ultimately showed that in castrated animals, this increased uptake by the liver was associated with an increased expression of rOat2, a transporter that in part regulates the transfer of docetaxel from systemic circulation to hepatocytes.

Considering those results, a pharmacokinetic evaluation was conducted of 74 patients treated with docetaxel in the context of a registry trial in the Netherlands. Out of these 74 patients, all men with non-prostate cancer tumors served as controls (n = 36) for the 38 patients with metastatic hormone resistant prostate cancer patients. Dosage of docetaxel ranged from 30 mg/m2 to 100 mg/m2, given in different schedules. In the mCRPC patients, there was an increased docetaxel clearance compared to uncastrated men (48.4 L/h versus 42.1 L/h, respectively). In addition, both absolute neutrophil count nadir and white blood cell count nadir were higher in castrated patients (4.1 versus 1.7 ×109/L, 5.3 versus 3.1×109/L, respectively). This study provided further evidence of a more pronounced hematological toxicity in mHSPC patients compared to mCRPC men treated with docetaxel.

In 2016, the results of a meta-analysis of 7 phase 2-3 trials comparing docetaxel to non-docetaxel control arms (ie, the best supportive care including non-cytotoxic therapy or mitoxantrone) for prostate cancer were published, including a total of 5088 patients. In most studies, the use of G-CSF was at the discretion of the investigators. The global incidence of febrile neutropenia in patients treated with docetaxel was 10.7%. The relative risk (RR) of febrile neutropenia was higher in patients who received docetaxel compared to patients who did not (RR 16.8, 95% CI: 10.7-26.4; $p<0.0001$). Among the patients treated with docetaxel, there was a numerically higher incidence of febrile neutropenia in the mHSPC population when compared to the mCRPC population (12.4% versus 6.6%, respectively). Of note, this difference in incidences was not statistically significant ($p = 0.7$).

Following the publication of the STAMPEDE results in 2016, several authors published retrospective safety analyses of real life cohort of hormone sensitive prostate cancer patients, with either nodal or high risk locally advanced or metastatic disease. These cohorts of patients were in general of modest size, ranging from 39 to 63 patients, corresponding to the cumulative clinical experience at single institutions; consistently, high rates of febrile neutropenia or neutropenic sepsis were reported by these reports (ie, 13% febrile neutropenia; 30% febrile neutropenia; 20% neutropenic sepsis). In a single-institution retrospective analysis, 39 patients with mCRPC were compared to 22 patients with mHSPC; the incidences of neutropenic fever were 5% and 9% in the mCRPC and in the mHSPC patients, respectively.

In conclusion, there is a body of accumulating evidence for numerically higher incidences of severe neutropenia, febrile neutropenia, and neutropenic sepsis in patients with mHSPC when compared to mCRPC patients. Although in the largest analyzed data set the difference in incidences of febrile neutropenia between mCRPC and mHSPC patients did not reach statistical significance, consideration should be given to primary prophylaxis with growth factors, in particular for patients presenting other risk factors for febrile neutropenia; eg, age ≥65 years, previous radiotherapy, preexisting neutropenia, altered organ functions, and multiple comorbid conditions.

2.5.1. Discussion on clinical safety

The safety profile of docetaxel is close in nature to that of other taxanes. Treatment with microtubule-stabilizing drugs was described to be generally associated with adverse events that include anemia, neutropenia, thrombocytopenia, febrile neutropenia, infection, pyrexia, peripheral sensory neuropathy, motor neuropathy, myalgia, arthralgia, asthenia, fatigue, nausea, vomiting, anorexia, stomatitis/mucositis, dehydration, diarrhea, dyspnea, arrhythmia, fluid retention/edema, skin reaction, injection site reaction, bilirubin increase, aspartate aminotransferase/serum glutamicoxaloacetic transaminase (AST/SGOT) increase, alanine aminotransferase/serum glutamicpyruvic transaminase (ALT/SGPT) increase, and hypersensitivity reaction.

Based on the established safety profile of docetaxel in other indications, severe neutropenia and febrile neutropenia are the most prominent risks for docetaxel and may need, for certain categories of patients, secondary and even primary prevention with colony stimulating factors. The incidence of severe hypersensitivity can be reduced with adequate premedication with corticosteroids. The necessity of pre-medication with G-CSF or corticoids in certain cases is already adequately covered in the current PI.

Safety data to support the indication "for the treatment of patients with metastatic hormone sensitive prostate cancer in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone" are based primarily upon 3 randomized clinical trials (RCTs):

- STAMPEDE: Systemic Therapy in Advancing or Metastatic Prostate cancer: Evaluation of Drug Efficacy
- CHAARTED-E3805: Chemo-Hormonal therapy versus Androgen Ablation Randomized Trial for Extensive Disease in prostate cancer
- GETUG-AFU15: Hormone Therapy and Docetaxel or Hormone Therapy Alone in Treating Patients with Metastatic Prostate Cancer

The Applicant has chosen the STAMPEDE study to be the main study for safety reporting as for this study, safety data were reported most comprehensively. Also, the posology was in line with what is now proposed to be stated in the amended PI. This was acceptable.

Safety results for the CHAARTED and GETUG-AFU15 study were reported separately, limited safety data gained from these studies is only briefly discussed.

In the STAMPEDE study, no causality assessment was performed for the AEs and frequency of non-serious ADRs cannot be assessed based on the submitted data. In consequence, the table proposed for section 4.8 states that adverse events are listed "regardless of causal relationship". However, it seems that higher grade AEs (3-5) have been assessed for causality.

Substantially more adverse events in the class "Neutrophil toxicity" (=Neutropenia) have been reported for treatment arm C (SOC+Doc). This is true for AEs < grade 3 (approximately twice as much) and even more for ⩾ grade 3. No Grade 5 toxicities have been reported in the category "blood/bone marrow toxicity".Neutropenia is listed in the frequency category "very common", with the frequency 12% for G3-5 events, in the newly added table in section 4.8 of the amended SmPC. The risk of developing Neutropenia is already covered in the SmPC, e.g. in section 4.4 "Haematology". Adverse events of "Febrile neutropenia" have also been more frequently reported for treatment arm C (SOC+Doc). Results of the STAMPEDE trial regarding blood/bone marrow toxicity/ blood and lymphatic toxicity have been adequately covered in the proposed PI including its amendments.

GI haemorrhage is not stated as AE/ADR in the PI, this AE was, however, also not more frequently reported in treatment arm C (SOC+Doc) and this is therefore acceptable.

Adverse events in the class "general disorder toxicity" have been significantly more frequently reported in treatment arm C (SOC+Doc). Grade 4 or 5 toxicities did not occur, except one case of grade 4 asthenia in treatment arm A (SOC) and one case of grade 4 lethargy (maximal grade) in each of the treatment arms). Lethargy, flu-like syndromes and asthenia are listed as very common adverse events in the newly added table in section 4.8 of the amended SmPC, fever and oral candidiasis are listed in the frequency category "common". Results of the STAMPEDE trial regarding general disorder toxicity have been adequately covered in the proposed PI including its amendments.

Limited safety data available from the CHAARTED study indicate a safety profile generally in line with what was seen in the STAMPEDE trial. Peripheral neuropathy, sensory neuropathy and thromboembolic occurred at rate of ⩽1%. events are not listed as AEs/ADRs in the SmPC, as this reports only the safety results for the STAMPEDE trial.

Assessment of the safety data provided for the GETUG-AFU 15 study indicate a safety profile generally in line with what was seen in the STAMPEDE trial. However, alopecia (54% grade 1- 5), sensory neuropathy (29% grade 1-5) and haemoglobin (72% grade 1- 5) are not listed as AEs/ADRs in the SmPC, as this reports only the safety results for the STAMPEDE trial. These AEs are, however, also reported for mCRPC (current PI) and regarded to be of relevance for the treating physician and patient.

The adverse events reported in the three Clinical Studies are consistent with the known safety profile of docetaxel. However, literature data indicate possible differences (increase) in frequency of severe adverse reactions as febrile neutropenia in mHSPC patients compared to mCRPC patients.

It should be noted that fatal events related to docetaxel treatment are also part of the known safety profile for docetaxel. Deaths possibly related to docetaxel have been also reported for STAMPED (n=2), CHAARTED (n=1) and GETUG-AFU 15 (n=4). As stated in the SmPC, docetaxel is contraindicated in patients with baseline neutrophil count of < 1,500 cells/mm^3 (SmPC section 4.3) and prophylactic G-CSF may be used to mitigate the risk of haematological toxicities (SmPC section 4.2). In addition, also the warning section of the SmPC (4.4) contains detailed information on neutropenia as most frequent and sometimes severe adverse reaction.

With regard to age dependency, the STAMPEDE study showed that more patients ≥65 years in the docetaxel arm reported hypersensitivity reaction, neutropenia, anemia, fluid retention, dyspnea, and nail changes compared to patients below 65. In addition, more patients ≥65 years in the docetaxel arm reported grade ≥3 neutropenia compared to patients below 65. This is also true for febrile neutropenia in (17% versus 13%). For patients above the age of 75, more patients ≥75 years in the docetaxel arm reported AEs compared to patients below 75 in every AE category.

Regarding time dependency, the breakdown of worst toxicity grade (any grade) for different time points provided shows that docetaxel related toxicity is most obvious during the administration (docetaxel is administered in 6 cycle every 3 weeks). In later time points (after 1 year or 2 years), differences between the treatment arms (SOC vs. SOC + DoC) diminish. This result would have been expected and is in line with what was seen with the detrimental impact on QoL.

As regard to metastatic disease versus non-metastatic disease, there was a general tendency for the M0 patients to experience more frequent AEs compared to the M1 patients, irrespective of the treatment received. However, these differences were often more pronounced for the patients treated with docetaxel, with the exception of diarrhoea and lethargy. Regarding to Grade ≥3 events, no clinically meaningful differences were noted between M0 and M1 patients treated with docetaxel. Severe neutropenia was slightly more frequent in the M0 patients when compared to the M1 patients (15% versus 11%). Severe bone pain was only reported in the M1 patients. There was no difference in the incidence of febrile neutropenia between M0 and M1 patients treated with docetaxel; febrile neutropenia was reported in 15% of the M0 patients treated with docetaxel, and in 16% of the M1 patients treated with docetaxel.

In summary, the summited safety data picture a safety profile of docetaxel in line with what is already known from studies in other malignancies. Safety results, mainly derived from results in the STAMPEDE trial, have been overall adequately covered in the proposed PI including its amendments.

2.5.2. Conclusions on clinical safety

Safety data related to the combination of docetaxel and ADT was derived from a large cohort of 1124 patients and were comprehensively reported.

Addition of docetaxel to ADT treatments provided additional AEs to those classically related to ADT, notably hot-flushes, decreased libido and erectile dysfunction.

Additional AEs of all grades, reported in excess in the docetaxel + ADT arm compared to the ADT arm, were those pertaining to the known safety profile of docetaxel, including alopecia, nail changes, sensory neuropathy, neutropenia, febrile neutropenia, anaemia, stomatitis, nausea, fatigue.

Grade ≥3 AEs reported in excess in the docetaxel + ADT arm compared to the ADT arm were febrile neutropenia, neutropenia, diarrhea and fatigue.

A thorough safety analysis of docetaxel was performed within this submission that showed that the safety profile of docetaxel has been relatively consistent with no major safety concerns. Relevant information is reflected in the SmPC.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The WSA submitted RMP version 1.0 with this variation.

The CHMP was of the opinion that no safety concerns require inclusion in the safety specification of the risk management plan for products containing docetaxel. Furthermore, in line with the PRAC recommendation, it was agreed that no pharmacovigilance activities and additional risk minimisation measures are currently required. However, remaining unresolved issues pertaining to the risk management require further assessment and should be resolved in a separate type II variation.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet has been updated accordingly.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Malta.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the WSA and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

This extension of indication is for the treatment of patients with metastatic hormone-sensitive prostate cancer, in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone.

3.1.2. Available therapies and unmet medical need

Prostate cancer is the second most common cancer and the first cause of death from cancer in men. When the disease becomes metastatic, systemic therapy is the only option and despite castration and ADT, the disease can progress and become resistant to hormonal manipulations. Taxanes are for the time being indicated at these late disease stages, but many oncologists have proposed an earlier use of chemotherapy, when the tumour is metastatic but still sensitive to hormones, and investigated this option in clinical trials that support the present application. These academic studies led to recommendations in academic and institutional guidelines (e.g., ESMO, ASCO).

3.1.3. Main clinical studies

The MAH submitted three main randomized, controlled, open-label studies, of which STAMPEDE was characterised as a main study (n = …), whereas CHAARTED and GETUG-AFU15 were supportive studies, and one meta-analysis of these studies to demonstrate a survival benefit in the claimed indication. In all three studies, docetaxel was randomised to be used in combination with a backbone of ADT+/- glucocorticosteroids and the primary endpoint was OS.

3.2. Favourable effects

In the STAMPEDE study an overall survival difference was shown for all patients (M0 and M1) treated with docetaxel and ADT compared with to ADT (corresponding to a 9-month benefit in median OS and HR 0.78, 95% CI: 0.66-0.93; p = 0.006).

Among M1 patients of the STAMPEDE trial, a difference in OS was shown in a pre-planned subset analysis for the docetaxel + ADT group compared to the ADT-only group. Median survival was 62 months (95% CI: 51-73) and 43 months (95% CI: 40-48) in the docetaxel + ADT and ADT-only groups, respectively (HR 0.76, 95% CI: 0.62-0.92; p = 0.005), reflecting a 19-month longer median survival associated with docetaxel + ADT compared to ADT-only.

A statistically significant FFS benefit was shown for the docetaxel + ADT group compared to the ADT-only group; median FFS was 37 months (95% CI: 33-42) and 21 months (95% CI: 18-23) in the docetaxel + ADT and ADT-only groups, respectively (HR 0.61, 95% CI: 0.53-0.70; p = 0.413 x10-13).

A statistically significant SRE benefit was shown for the docetaxel + ADT group compared to the ADT-only group (HR 0.60, 95% CI: 0.48-0.74; p = 0.127 x10-5), and the 5-year SRE-free rate was 75% and 66% in the docetaxel + ADT and ADT-only groups, respectively.

The provided updated analyses were performed with a median FU time of 6.5 years (vs 3.5 years for the primary analyses) at the data cutoff date and the analysis of OS was based on a total of 719 deaths (66%) (vs 494 deaths (45%) for the primary analyses), with 494 events (68%) (vs 350 events (48%) for the primary analyses) reported in the ADT arm and 225 events (62%) (vs 144 events (40%) for the primary

analyses) reported in the ADT + docetaxel arm. Updated estimated hazard ratio (HR) for OS was 0.81 (95% CI: 0.69 to 0.95), characterizing a statistically significant and clinically meaningful reduction of 19% in risk of death with ADT + docetaxel compared to ADT (p=0.009). Median overall survival (95% CI) in the docetaxel + ADT arm was 58.8 months, compared to 43.2 months in the ADT only arm, corresponding to a 16 months survival benefit for the patients treated with docetaxel.

An overall survival benefit was shown also in the CHAARTED study in the primary analysis (corresponding to a 13.6-month benefit in median OS and HR 0.61, 95% CI: 0.47-0.80; p = 0.0003) and in the long-term analysis (corresponding to a 10.4-month benefit in median OS and HR 0.72, 95% CI: 0.59-0.89; p = 0.0018). Updated analyses were performed with a median FU time of 53.7 months at the data cutoff date and the analysis of OS was based on a total of 399 deaths (51%) (vs 237 deaths (30%) for the primary analyses), with 211 events (54%) (vs 136 events (35%) for the primary analyses) reported in the ADT arm and 188 events (47%) (vs 101 events (25%) for the primary analyses) reported in the ADT + docetaxel arm. In these updated analyses, the estimated HR for OS was 0.72 (95% CI: 0.59 to 0.89), characterizing a statistically significant and clinically meaningful reduction of 28% in risk of death with ADT + docetaxel compared to ADT (p=0.0018). Median overall survival (95% CI) in the docetaxel + ADT arm was 57.6 months (52 to 63.9), compared to 47.2 months (41.8 to 52.8) in the ADT only arm, corresponding to a 10.4 months survival benefit for the patients treated with docetaxel.

In the GETUG-AFU15 study, the main analysis was on a fixed-time assessment of survival at three years. There is no apparent benefit related to docetaxel with a HR close to 1, and K-M curves are quite superimposable.

A survival benefit assessed in the meta-analysis was shown in men with mHSPC with HR 0.77 (95% CI: 0.68-0.87; p <0.0001).

On secondary endpoints, docetaxel shows an undisputable activity in all submitted studies. This was expected.

3.3. Uncertainties and limitations about favourable effects

The neutral effect on survival observed in the GETUG-AFU15 study could be the result of the extensive use of taxanes at progression in the control arm (85% of patients with disease progression in the ADT-only treatment arm received docetaxel as subsequent therapy).

3.4. Unfavourable effects

The adverse events reported in the three Clinical Studies are consistent with the known safety profile of docetaxel. The safety data from the STAMPEDE study formed the main source of safety information for updating the PI.

Addition of docetaxel to ADT treatments provided additional AEs, including serious AEs, to those classically related to ADT. The most frequent AEs (all grades, reported in at least 10% of the patients in the docetaxel + ADT arm of the STAMPEDE study) were lethargy, urinary frequency, impotence, nail changes, diarrhea, anemia, constipation, arthralgia, bone pain, generalized pain, insomnia, nausea, stomatitis, fluid retention, dyspepsia, myalgia, dyspnea, neutropenia, abdominal pain, coughing, asthenia, headache, flatulence, flu-like symptoms, febrile neutropenia, dizziness, upper respiratory tract infection, anorexia, rash, increased ALT, vomiting, hypersensitivity, and fever. AEs related to hormone therapy were reported at similar incidences in the two treatment arms, with the notable exception of all grade hot flashes which were more frequent in the ADT-only arm (63%) compared to the docetaxel + ADT arm (37%). Other frequently (≥5% of the patients) reported Grade ≥3 AEs were decreased libido and erectile dysfunction, which were reported at similar rates in both treatment arms.

Expectedly, those additional AEs were those pertaining to the known safety profile of docetaxel, including alopecia, nail changes, sensory neuropathy, neutropenia, febrile neutropenia, anemia, stomatitis, nausea, fatigue. Several AE were grade ≥3 AEs such as febrile neutropenia, neutropenia, diarrhea and fatigue.

3.5. Uncertainties and limitations about unfavourable effects

Although not statistically significant and based on a limited data set, and cross-study comparisons, there is a trend to a higher incidence of severe neutropenia, febrile neutropenia, and neutropenic sepsis in patients with mHSPC when compared to mCRPC patients.

3.6. Effects Table

Table 2. Effects Table for Taxotere/Docetaxel Zentiva, for mHSPC

Effect	Short description	Unit	ADT + Docetaxel	ADT	Uncertainties/ Strength evidence	References
Favourable Effects (M1)						
OS	Survival (median)	Mths	58.8	43.2	16 mths survival benefit	STAMPEDE
OS	Survival	HR	0.81 (0.69-0.95) p0.009		66% events	
OS	Survival (median)	Mths	57.6 (52-63.9)	47.2 (41.8-52.8)	10.4 mths survival benefit	CHAARTED
OS		HR	0.72 (0.59-0.89) p0.0018		51% events	
OS	Survival (median)	Mths	59 (51-69)	54 (42-NR)	Cross-over>80 %, extensive use of taxanes at progression	GETUG-AFU15
OS		HR	1.01(0.75-1.36) p0.955		Long term maturity 70%	
Unfavourable Effects - grade ⩾3 (M0+M1)						
All		%	36	16	Usual observed safety profile of docetaxel	STAMPEDE
neutropenia		%	12	0		
febrile neutropenia		%	15	0		
diarrhoea		%	3	1		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Docetaxel is active on prostate cancer and this was expected given its efficacy demonstrated years ago at the castration-resistant and metastatic stage. This activity is confirmed by a survival benefit in two of the three studies submitted here (STAMPEDE and CHAARTED), even if in the third study (GETUG-AFU15), docetaxel failed to produce even a positive trend. Overall, updated analyses of these 2 studies, with more mature data, confirmed the primary analyses and, demonstrated a clinically relevant difference in survival for patients treated with docetaxel and ADT by comparison to ADT alone. The STAMPEDE study was retrospectively analysed by subgroups according to metastasis burden at randomization, using the definition that was used for the CHAARTED study. The estimated HR in these 2 subgroups (low and high burden) were, numerically, of similar magnitude and test for interaction between treatment and disease volume was not significant, supporting the absence of evidence for heterogeneity in the treatment effect in these 2 subgroups of patients, in contrast to what was reported in the CHAARTED study. Of note, the ESMO guidelines and EAU guidelines recommended to offer castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy.

The new analysis of the STAMPEDE study, with the largest subgroup of patients with a low metastatic burden, showed a consistent treatment effect irrespective of metastasis burden, providing additional information to support the use of upfront docetaxel for all M1 patients.

Severe neutropenia, febrile neutropenia, and neutropenic sepsis in patients with mHSPC treated with SOC+DOC are an important safety risk. In the STAMPEDE study, a considerable percentage of 13% stopped SOC+Doc treatment due to toxicity. Compared to what is known for mCRPC docetaxel toxicity seems to be more pronounced in mHSPC. Older people (above 65 or 75 years, respectively) reported AEs more frequently, neutropenia, anemia, diarrhea, dyspnea and upper respiratory tract infection were reported with a greater incidence of at least 10% in patients above 75 years. It should be noted that fatal events related to docetaxel treatment are also part of the known safety profile for docetaxel. Fatal events possibly related to docetaxel have been reported for STAMPED (n=2), CHAARTED (n=1) and GETUG-AFU 15 (n=4). Treatment related risks are adequately covered in the PI. As stated in the SmPC, docetaxel is e.g. contraindicated in patients with baseline neutrophil count of < 1,500 cells/mm3 (SmPC section 4.3) and prophylactic G-CSF may be used to mitigate the risk of haematological toxicities (SmPC section 4.2). In addition, also the warning section of the SmPC (4.4) contains detailed information on neutropenia as most frequent and sometimes severe adverse reaction.

3.7.2. Balance of benefits and risks

The updated results provided by MAH for STAMPEDE and CHAARTED studies are mature to support the claimed indication. The benefit of anticipating the treatment of prostate cancer with docetaxel at the hormone sensitive stage is now certain and demonstrated a survival benefit for patients treated with docetaxel and ADT by comparison to ADT alone.

The adverse events reported in the three Clinical Studies are consistent with the known safety profile of docetaxel. Adverse events below grade 3 are regarded to be of minor relevance.

It can be concluded that the overall B/R of TAXOTERE / Docetaxel Zentiva in combination with androgen-deprivation therapy (ADT), with or without prednisone or prednisolone, for the treatment of patients with metastatic hormone-sensitive prostate cancer is considered positive.

3.8. Conclusions

The overall B/R of TAXOTERE / Docetaxel Zentiva is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include the treatment of patients with metastatic hormone-sensitive prostate cancer in combination with androgen-deprivation therapy (ADT), with or without prednisone or

prednisolone, for Taxotere and Docetaxel Zentiva; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated accordingly. The RMP version 1.0 has also been submitted. In addition, the Worksharing applicant took the opportunity to update information on the local representatives in the Package Leaflet.

Amendments to the marketing authorisation

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

This recommendation is subject to the following new condition:

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

In addition, an updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

An updated RMP shall be submitted by 31 October 2019.