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# Treatment of patients with newly diagnosed metastatic hormone sensitive prostate cancer (mHSPC) in Belgium: a real world data analysis

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**ABSTRACT**

**INTRODUCTION:** Abiraterone acetate + prednisone (AAP) and docetaxel have proven their efficacy in the treatment of patients with newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC) in clinical trials. However, real-world data are scarce. The goal of this study is to evaluate real-world data on the efficacy and safety of these therapies in mHSPC patients.

**PATIENTS AND METHODS:** Records of 93 patients from 21 different centres were retrospectively reviewed. Primary and secondary endpoints were radiographic and PSA progression-free survival (RPFS – PSA-PFS) and cancer specific and overall survival (CSS – OS), respectively. Adverse events (AEs) were evaluated according to the Common Terminology Criteria for Adverse Events version 5.0. Differences in oncological outcome and AEs were evaluated between three treatment groups: ADT only (N=26) – ADT + AAP (N=48) – ADT + docetaxel (N=19). Survival analysis was performed using Kaplan–Meier statistics.

**RESULTS:** Median RPFS was 13 months (95% confidence interval [CI]: 9–17) for ADT only, 21 months (95% CI: 19–23) for ADT + AAP and 12 months (95% CI: 11–14) for ADT + docetaxel ($p = 0.004$). The 1-year PSA-PFS, CSS and OS were 73.5%, 90.7% and 88.7%, respectively, with no significant differences between the three groups. Adverse events of grade 3 or higher were not observed more frequently.

**CONCLUSION:** Retrospective real-world data show a significantly longer RPFS for mHSPC patients treated with ADT + AAP compared to ADT only or ADT + docetaxel at short-term follow-up. This can aid in counselling of mHSPC patients in daily clinical practice.

**KEYWORDS**
Abiraterone acetate; androgen deprivation therapy; docetaxel; metastatic hormone sensitive prostate cancer

## Introduction

The treatment of metastatic hormone-sensitive prostate cancer (mHSPC) has radically changed in the last decade, with a shift in the treatment paradigm from androgen deprivation (ADT) monotherapy to early combination treatments. Different randomized controlled trials (RCTs) have shown a significant benefit of combination treatments of ADT with abiraterone acetate + prednisone (AAP) [1,2], docetaxel [3,4], apalutamide [5], enzalutamide [6,7], local radiotherapy [8] or triple therapy (ADT + AAP + Docetaxel) [9] for patients with newly diagnosed mHSPC. As a consequence, these treatments are currently recommended in European Association of Urology, American Urological Association and National Comprehensive Cancer Network guidelines [9–11].

Real-world data on the use, effect and safety of these agents in the mHSPC setting are limited. Clinical trials play a key role in evaluating the safety and efficacy of new treatments, but they are often performed with strict in-and exclusion criteria, not necessarily representative of the real-world patient population. Especially patients with poor performance status or severe comorbidities are often excluded, leading to an under-representation of specific patients groups such as low-income, highly comorbid and elderly patients [12].

To our knowledge, no studies have analysed the real-world efficacy and adverse event (AE) rate of patients with mHSPC treated with a combination treatment. The goal of this article is to determine the

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oncological outcome and AE rate of different mHSPC treatments (ADT only, ADT + AAP and ADT + docetaxel) and indirectly compare these with the results from their phase III trials [1–4]. We report on one of the first real-world mHSPC cohorts treated with ADT + AAP or ADT + docetaxel.

## Patients and methods

### Patients

Physicians from 21 Belgian hospitals provided a list of all consecutive patients who presented with newly diagnosed mHSPC from 1 November 2017 until 31 October 2018. Data of this cohort were retrospectively analysed. This period was taken as it encompassed the abiraterone acetate compassionate use program for mHSPC in Belgium (1 February 2018–31 October 2018). Patients could only start AAP within 3 months after diagnosis, therefore the time window for this analysis was expanded with the 3 prior months. During this time frame, all participating centers had access to treatment with ADT, docetaxel and AAP. Enzalutamide and apalutamide were not yet available in this setting and local radiotherapy was not yet indicated at that time.

Inclusion criteria for the Belgian abiraterone acetate compassionate use program were [1] age ≥18 years old [2], newly diagnosed mHSPC with metastases established on imaging (bone scan, magnetic resonance imaging or conventional tomography) [3] a written informed consent [4], Eastern Cooperative Oncology Group performance status 0–2 and [5] at least 2 of the 3 following high-risk factors: Gleason score of 8 or more; at least 3 bone lesions; the presence of measurable visceral metastasis. Follow-up was at physician's discretion.

Exclusion criteria for the Belgian abiraterone compassionate use program were [1] previous treatment with chemotherapy, radiotherapy or surgery with curative intent (with exception of those patients treated with 3 months or less of ADT with or without concurrent first-generation androgen-receptor antagonists).

The inclusion criteria for this study were equal to those of the Belgian abiraterone acetate compassionate use program, with the only difference that the number of high-risk factors was not taken into consideration.

The 21 participating centers provided a total number of 114 patients. After critical analysis, 21 patients were excluded because of recurrent disease (N = 19) or diagnosis out of time frame (N = 2). Therefore, 93 patients were enrolled in this study.

Data on patient characteristics, oncological outcome and AEs were collected retrospectively from the patient files by two medical doctors (E.L and S.H.) between January 2019 and January 2020. Data retrieved included all available reports from clinical visits, lab results, imaging and date of death. Follow-up time was defined as the time between start of ADT and date of last follow-up or death. All patients provided written informed consent. The study was approved by the ethics committee (EC/2018/1275).

### Outcomes

The co-primary endpoints were radiographic progression-free survival (RPFS) and PSA progression-free survival (PSA-PFS). Secondary outcomes were cancer-specific survival (CSS) and overall survival (OS). Radiographic progression was defined as the appearance of bone metastasis or 2 or more new bone lesions on bone scan, new soft tissue lesions on CT scan or a relative increase of at least 20% (absolute increase of at least 5 mm) in the sum of the diameters of the measurable lesions (according to Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 criteria [13]). PSA progression was defined as three consecutive PSA rises, at least 1 week apart, resulting in two times a 50% increase of PSA above the nadir, with PSA >2 ng/ml. CSS and OS were, respectively, defined as time from start of treatment for mHSPC to death caused by prostate cancer (PC) or death by any cause.

Adverse events were evaluated and graded according to the Common Terminology Criteria for Adverse Events version 5.0 [14]. Skeletal related events (SRE) were defined as any pathological bone fracture, spinal cord compression, palliative radiation to the bone or surgery to the bone because of bone metastasis.

Differences in oncological outcome and AEs were evaluated between different treatment regimens: ADT only versus ADT + AAP versus ADT + docetaxel. The relationship between several patient, tumor and treatment characteristics (see Table 2) and RPFS was analysed. Table 1

The predictive value for radiographic progression of different variables (WHO prognostic grade group, TNM stage, amount of high-risk factors, volume of disease, type of ADT, type of systemic treatment, PSA (dynamics) and neutrophil-to-lymphocyte ratio) was analysed.

In order to compare the disease characteristics of our patient cohort with those of phase 3 trials, different factors for poor prognosis were compared. We selected age, Gleason ≥8, ≥3 bone metastases, high volume disease according to CHAARTED [3], M1c and PSA at start of ADT as factors for poor prognosis.

### Statistical analysis

Continuous variables are presented as median (interquartile range [IQR]). Non-parametric variables were compared between the 3 treatment groups using the Kruskal–Wallis test. Comparison of two treatment groups was performed by the Fisher's exact test for categorical variables and the independent

student's t-test for continuous variables. Comparison of population proportions was performed by the Z-test for proportions. Survival analysis was performed using Kaplan–Meier statistics. The survival distribution of different factors in Kaplan Meier analysis was analysed by the Log Rank test. Univariate Cox regression analysis (CRA) was performed to identify predictors for RPFS. Statistical analysis was performed in SPSS Statistics v.26 (IBM, NY, USA). A P-value less than 0.05 was considered statistically significant.

## Results

Patient, disease and treatment characteristics are summarized in . Disease characteristics at diagnosis were comparable between the different treatment groups. The ADT + docetaxel treatment group was significantly younger than the ADT only and ADT + AAP group. Median follow-up was 15 months (IQR 11–18).

### *Oncological outcome*

Radiographic progression was documented in 18 (19,4%) patients with a median RPFS of 16,5 months (95% CI: 14,7–18,2).

PSA progression was documented in 20 out of 93 (21,5%) patients. The one-year PSA-PFS was 73,5%. Median PSA-PFS was not reached. Median relative decrease in PSA after start of treatment was 97,7% (IQR 90,3–99,7), 99,9% (99,6–100,0) and 99,6% (99,0–99,8) in the ADT only, ADT + AAP and ADT + docetaxel group, respectively.

Ten patients (10,8%) died, of which 7 (7,5%) due to PC progression and 3 (3,2%) due to other reasons. One-year CSS and OS were 90,7% and 88,7%, respectively. Median CSS and OS were not reached.

### *Stratification by type of treatment*

Radiographic progression was documented in 9 (34,6%) patients on ADT only, in 5 (10,4%) patients on ADT + AAP and in 4 (21,1%) patients on ADT + docetaxel. Median RPFS was significantly different between the three groups (ADT only: 13 months [95% CI 8,9–17,1], ADT + AAP: 21 months [95% CI 19,2–23,2], ADT + docetaxel: 12 months [95% CI 10,5–13,5], p = 0,004; Figure 1(a)). RPFS was significantly longer in patients receiving ADT + AAP compared to ADT + docetaxel (21 vs. 12 months, p = 0,011) and ADT + AAP compared to ADT only (21 vs. 13 months, p = 0,001). No significant difference in RPFS could be observed between the ADT only and the ADT + docetaxel group (13 vs. 12 months, p = 0,618).

PSA progression was documented in 9 (34,6%) patients on ADT only, in 8 (16,7%) on ADT + AAP and in 3 (15,8%) on ADT + docetaxel. Mean PSA-PFS was not significantly different between the three groups (ADT only: 14,4 months [95% CI 11,7–17,0], ADT + AAP: 16,0 months [95% CI 14,8–17,3], ADT + docetaxel: 15,1 months [95% CI 13,2–17,0], p = 0,088; Figure 1(b)).

No significant differences in mean CSS or OS were observed between the three groups (CSS: ADT only: 20,7 months [95% CI 18,9–22,4], ADT + AAP: 20,4 months [95% CI 19,6–21,2], ADT + docetaxel: 17,8 months [95% CI 15,4–20,2], p = 0,298. OS: ADT only: 19,6 months [95% CI 17,4–21,8], ADT + AAP: 20,4 months [95% CI 19,6–21,2], ADT + docetaxel: 17,8 months [95% CI 15,4–20,2], p = 0,201; Figure 1 (c–d)).

In univariate CRA, ADT with bilateral orchiectomy was associated with inferior RPFS (HR 27.505 [95% CI: 2,331–324,477], p = 0,008, LHRH agonist = reference), while prolonged RPFS was found in patients treated with ADT + AAP (HR 0,174 [95% CI: 0,053–0,567], p = 0,004, ADT only = reference) and in patients with N1 disease (HR 0,272 [95% CI: 0,098–0,751], p = 0,012) (Table 2).

N1-stage was observed in a significantly higher proportion of patients with M1a disease (11/11, 100%) compared to patients with M1b or M1c disease (51/81, 63%) (p = 0,048).

### *Adverse events*

Adverse events of different treatments were summarized in Table 4. Overall, 63 (67,6%) patients reported one or more AEs due to treatment with ADT, of which hot flushes were the most frequent (39/93 [41,9%] patients). In patients treated with AAP, one or more AEs occurred in 40 (87,0%) patients, of which the most frequent was hypertension (17/46 (37,0%) patients). Of these patients, 13 (27,1%) had a grade 3 or higher AE. In patients treated with docetaxel, one or more AEs occurred in 18 (94,7%) patients, of which the most frequent was fatigue (12/19 (63,2%) patients). Of these patients, 8 (42,1%) had a grade 3 or higher AE. Grade 3 or higher adverse events were not significantly higher in patients receiving docetaxel compared to those receiving AAP (p = 0,255). The rate of treatment discontinuation due to AEs was similar between treatment groups (ADT + AAP: 5/48 (10,4%) patients vs. ADT + Docetaxel: 1/19 (5,3%) patients; p = 0,447). No deaths occurred due to AEs.Table 3

SREs were observed in 28 (30,1%) patients. In the ADT only group, SREs occurred in 7 (26,9%) patients (4x radiation therapy to the bone, 1x spinal cord compression, 1x pathological bone fracture, 1x surgery to the bone). In the AAP group, SREs occurred in 14 (29,2%) patients (2x pathological bone fracture, 2x surgery to the bone, 9x radiation therapy to the bone, 1x spinal cord compression). Finally, SREs occurred in 7 (36,8%) patients receiving Docetaxel (3x pathological bone fracture, 4x radiation therapy to the bone).

**Table 1.** Patient, disease and treatment characteristics.

| | | | Overall | | ADT only | | ADT + AAP | | ADT + Docetaxel | | P |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | (N = 93) | | (N = 26) | | (N = 48) | | (N = 19) | | |
| Age (years) at time of start treatment | | | 73 (68–79) | | 80 (72–84) | | 72 (68–78) | | 66 (60–72) | | <0,001* |
| PSA at diagnosis | | | 59,5 (24,7–236,8) | | 50,6 (19,0–131,9) | | 80,6 (25,7–325,0) | | 61,4 (26,0–166) | | 0,714* |
| Biopsy results | | | | | | | | | | | 0,375* |
| WHO GG 1 | | | 1 | 1,1% | 0 | 0,0% | 1 | 2,1% | 0 | 0,0% | |
| | WHO GG 2 | | 3 | 3,2% | 2 | 7,7% | 0 | 0,0% | 1 | 5,3% | |
| | WHO GG 3 | | 8 | 8,6% | 3 | 11,5% | 2 | 4,2% | 3 | 15,8% | |
| | WHO GG 4 | | 30 | 32,3% | 6 | 23,1% | 18 | 37,5% | 6 | 31,6% | |
| | WHO GG 5 | | 45 | 48,4% | 12 | 46,2% | 26 | 54,2% | 7 | 36,8% | |
| | Missing | | 6 | 6,5% | 3 | 11,5% | 1 | 2,1% | 2 | 10,5% | |
| Staging results | | | | | | | | | | | |
| T | Clinical | cT1 | 1 | 1,1% | 1 | 3,8% | 0 | 0,0% | 0 | 0,0% | 0,149* |
| | | cT2 | 20 | 21,5% | 9 | 34,6% | 8 | 16,7% | 3 | 15,8% | |
| | | cT3 | 34 | 37,0% | 7 | 26,9% | 23 | 47,9% | 4 | 21,1% | |
| | | cT4 | 13 | 14,1% | 2 | 7,7% | 8 | 16,7% | 3 | 15,8% | |
| | | cTx | 25 | 26,9% | 7 | 26,9% | 9 | 18,8% | 9 | 47,4% | |
| N | Iconographic | iN0 | 29 | 31,2% | 12 | 46,2% | 13 | 27,1% | 4 | 21,1% | 0,179* |
| | | iN1 | 61 | 65,6% | 12 | 46,2% | 34 | 70,8% | 15 | 78,9% | |
| | | iNx | 2 | 2,2% | 1 | 3,8% | 1 | 2,1% | 0 | 0,0% | |
| M | | iM1a | 11 | 11,8% | 3 | 11,5% | 5 | 10,4% | 3 | 15,8% | 0,322* |
| | | iM1b | 65 | 69,9% | 15 | 57,7% | 39 | 81,3% | 11 | 57,9% | |
| | | iM1c | 16 | 17,2% | 7 | 26,9% | 4 | 8,3% | 5 | 26,3% | |
| | | iMx | 1 | 1,1% | 1 | 3,8% | 0 | 0,0% | 0 | 0,0% | |
| Amount of high risk factors (cfr. LATITUDE) | | | | | | | | | | | 0,508* |
| | 0 | | 4 | 4,3% | 2 | 7,7% | 2 | 4,2% | 0 | 0,0% | |
| | 1 | | 17 | 18,3% | 6 | 23,1% | 5 | 10,4% | 6 | 31,6% | |
| | 2 | | 55 | 59,1% | 10 | 38,5% | 35 | 72,9% | 10† | 52,6% | |
| | 3 | | 12 | 12,9% | 5 | 19,2% | 5 | 10,4% | 2 | 10,5% | |
| | Missing | | 5† | 5,4% | 3 | 11,5% | 1 | 2,1% | 1 | 5,3% | |
| Volume of disease (cfr. CHAARTED) | | | | | | | | | | | 0,655* |
| | Low volume | | 27 | 29,0% | 7 | 26,9% | 16 | 33,3% | 4 | 21,1% | |
| | High volume | | 61 | 65,6% | 16 | 61,5% | 31 | 64,6% | 14 | 73,7% | |
| | Missing | | 5 | 5,4% | 3 | 11,5% | 1 | 2,1% | 1 | 5,3% | |
| Androgen deprivation therapy (ADT) | | | | | | | | | | | 0,731* |
| | Bilateral ochiectomy | | 3 | 3,2% | 2 | 7,7% | 0 | 0,0% | 1 | 5,3% | |
| | LHRH Agonist | | 35 | 37,6% | 7 | 26,9% | 20 | 41,7% | 8 | 42,1% | |
| | LHRH Antagonist | | 53 | 57,0% | 15 | 57,7% | 28 | 58,3% | 10 | 52,6% | |
| | Anti-androgen | | 1 | 1,1% | 1 | 3,8% | 0 | 0,0% | 0 | 0,0% | |
| | Missing | | 1 | 1,1% | 1 | 3,8% | 0 | 0,0% | 0 | 0,0% | |
| Local treatment | | | | | | | | | | | 0,699* |
| | None | | 84 | 90,3% | 22 | 84,6% | 45 | 93,8% | 17 | 89,5% | |
| | Radiation Therapy | | 7 | 7,5% | 2 | 7,7% | 3 | 6,3% | 2 | 10,5% | |
| | Radical prostatectomy | | 2 | 2,2% | 2 | 7,7% | 0 | 0,0% | 0 | 0,0% | |
| Disease progression during follow-up | | | | | | | | | | | |
| | PSA progression | | 20 | 21,5% | 9 | 34,6% | 8 | 16,7% | 3 | 15,8% | 0,104* |
| | Radiographic progression | | 18 | 19,4% | 9 | 34,6% | 5 | 10,4% | 4 | 21,1% | 0,033** |
| Subsequent treatment | | | | | | | | | | | 0,651* |
| | None | | 78 | 83,9% | 21 | 80,8% | 41 | 85,4% | 16 | 84,2% | |
| | AAP | | 2 | 2,2% | 1 | 3,8% | | | 1 | 5,3% | |
| | Docetaxel | | 5 | 5,4% | 1 | 3,8% | 4 | 8,3% | | | |
| | Enzalutamide | | 5 | 5,4% | 3 | 11,5% | 0 | 0,0% | 2 | 10,5% | |
| | Radium-223 | | 2 | 2,2% | 0 | 0,0% | 2 | 4,2% | 0 | 0,0% | |
| | Clinical trial | | 1 | 1,1% | 0 | 0,0% | 1 | 2,1% | 0 | 0,0% | |
| Time between first and subsequent treatment (weeks) | | | 44 (21–61) | | 59 (31–67) | | 34 (1–69) | | 42 (25–53) | | 0,513* |
| Death | | | 10 | 10,8% | 4 | 15,4% | 3 | 6,3% | 3 | 15,8% | 0,335* |
| Cause of death | | | | | | | | | | | 0,618* |
| | Prostate cancer | | 7 | 7,5% | 2 | 7,7% | 2 | 4,2% | 3 | 15,8% | |
| | Other | | 1 | 2,2% | 1 | 3,8% | 1 | 2,1% | 0 | 0,0% | |
| | Unknown | | 1 | 1,1% | 1 | 3,8% | 0 | 0,0% | 0 | 0,0% | |
| Follow-up (months) | | | 15 [11–18] | | 16 (5,12–20) | | 15 [11–18] | | 13 [10–15] | | 0,749* |

AAP = Abiraterone acetate + prednisone – ADT: Androgen deprivation therapy – LHRH: Luteinizing hormone releasing hormone – PSA: Prostate specific antigen

† = In one patient treated with Docetaxel the Gleason score was unknown. However, since he had >3 bone metastases and multiple visceral metastases, he was classified as having (at least) 2 high risk factors.

* = Comparison of the three treatment groups and comparison of the ADT + AAP and ADT + Docetaxel group between themselves showed equal statistical significance levels.

** = Comparison of the three treatment groups showed a statistically significant difference, while comparison of the ADT + AAP and ADT + Docetaxel group between themselves did not show a statistically significant difference.

Table 2. Results of univariate cox regression analysis.

| Radiographic Progression – Univariate Cox Regression analysis | | |
|---|---|---|
| Variables | HR (95% CI) | P value |
| WHO 2016 Prognostic Grade Group | | |
| GG1 | Ref | |
| GG2 | 1,197 (0,106–13,581) | 0,884 |
| GG3 | 0,168 (0,010–2,759) | 0,211 |
| GG4 | 0,097 (0,008–1,131) | 0,063 |
| GG5 | 0,227 (0,027–1,894) | 0,171 |
| T stage | | |
| Localised disease (T1-T2) | Ref | |
| Locally advanced disease (T3-T4) | 0,440 (0,141–1,372) | 0,157 |
| N1 stage (vs. N0 stage) | | |
| N0 | Ref | |
| N1 | 0,272 (0,098–0,751) | 0,012 |
| M stage | | |
| M1a | Ref | |
| M1b | 0,705 (0,088–5,655) | 0,742 |
| M1c | 0,407 (0,035–5,760) | 0,473 |
| Amount of high risk factors (cfr. LATITUDE) | | |
| 0 | Ref | |
| 1 | 1,107 (0,122–10,051) | 0,928 |
| 2 | 0,416 (0,050–3,449) | 0,417 |
| 3 | 0,329 (0,028–3,870) | 0,377 |
| High volume disease (vs. low volume, cfr. CHAARTED) | 1,508 (0,429–5,294) | 0,522 |
| Type of ADT | | |
| LHRH Agonist | Ref | |
| LHRH Antagonist | 0,803 (0,289–2,228) | 0,673 |
| Bilateral orchiectomy | 27,505 (2,331–324,477) | 0,008 |
| Type of systemic treatment | | |
| ADT only | Ref | |
| ADT + AAP | 0,174 (0,053–0,567) | 0,004 |
| ADT + Docetaxel | 0,862 (0,254–2,929) | 0,812 |
| PSA at start treatment | 1,000 (0,999–1,000) | 0,412 |
| PSA reduction >50% after 1 m ADT | 0,395 (0,084–1,846) | 0,395 |
| PSA after 1 m ADT | 0,999 (0,992–1,006) | 0,788 |
| Neutrophyl to lymphocyte ratio | 0,980 (0,915–1,050) | 0,568 |

AAP: Abiraterone acetate + prednisone – ADT: Androgen deprivation therapy – HR: Hazard ratio – LHRH: Luteinizing hormone releasing hormone – PSA: Prostate specific antigen

### *Comparison with phase 3 trials*

Patients treated with ADT + AAP showed a median RPFS of 21,4 months (95% CI 13,0–23,3), which is shorter than the 33,0 months (95% CI not reported) reported in LATITUDE [1]. Patients treated with ADT + docetaxel showed a RPFS of 13,0 months (95% CI: 10,3–15,6), which is shorter than the RPFS reported in CHAARTED [3] and GETUG-AFU 15 [15] (, respectively, 20,2 (95% CI: 17,2–23,6) and 23,5 months (95% CI: 20,5–31,9)). Patients treated with ADT only in our study showed a RPFS of 13 months (95% CI 8,9–17,1), which was in line with the RPFS reported in the ADT monotherapy groups of LATITUDE (14,8 months (95% CI not reported) and CHAARTED (11,7 (95% CI: 10,8–14,7 months).

The 1-y OS of 95.8% of the ADT + AAP cohort in this study is comparable to the 1-y OS of 88.6% (p = 0,12) and 93.8% (p = 0,57) of, respectively, the LATITUDE and G-arm of the STAMPEDE study [1,2]. The 1-y OS of 84.2% of the ADT + docetaxel cohort in this study is also in line with the 1-y OS of 83.9% (p = 0,97), 92.1% (p = 0,22) and 91.1% (p = 0,33) of, respectively, the CHAARTED, C-arm of the STAMPEDE and GETUG AFU-15 trials [3,4,15].

A comparison of poor prognostic factors between our patient cohort and corresponding phase 3 trials is summarized in . The ADT + AAP cohort of this study had a significantly higher age compared to the corresponding phase 3 trial (p = 0,003). On the other hand, the patient population of the phase 3 trial had significantly more Gleason ≥8 (p = 0,010), ≥3 bone metastases (p < 0,001) and M1c disease (p = 0,012). The ADT + Docetaxel cohort of this study showed no significant differences in age (p = 0,379), Gleason ≥8 (p = 0,503), high volume disease (p = 0,503) and M1c disease (p = 0,153) with the corresponding phase 3 trial, but showed a significantly higher PSA at start of ADT (p < 0,001).

In the ADT + AAP group of this study, AEs of grade 3 or higher were observed in 27%, which is significantly lower than those reported in the G-arm of the STAMPEDE study (47%, p = 0,008) and in LATITUDE (63%, p < 0,001). Nevertheless, the incidence of anemia, fatigue and increase in ALAT/ASAT was significantly higher in our study population compared to the LATITUDE population (Table 4). Grade 3 or higher AEs were observed in 42,1% of patients treated with ADT + docetaxel in this study. These results are in line with the results of CHAARTED (29,5%, p = 0,242) and STAMPEDE arm C (52%, p = 0,379) [3,4].

## Discussion

Different systemic therapies, including AAP and docetaxel, have proven their efficacy and safety as an add-on therapy to ADT in mHSPC in clinical trials [1–7].

These results, however, must be interpreted against the background of an ageing, less physically fit patient population encountered in daily clinical practice. An important proportion of mHSPC patients have comorbidities, some of which may be life-limiting. These patient profiles are under-represented in clinical trials, and treatment decisions for these patients are complicated by competing risks of cancer, individual comorbidities and potential treatment complications [16]. Rather than blindly extrapolating data of heavily regulated clinical trials, evaluation of real-world data on mHSPC patients is of paramount clinical importance.

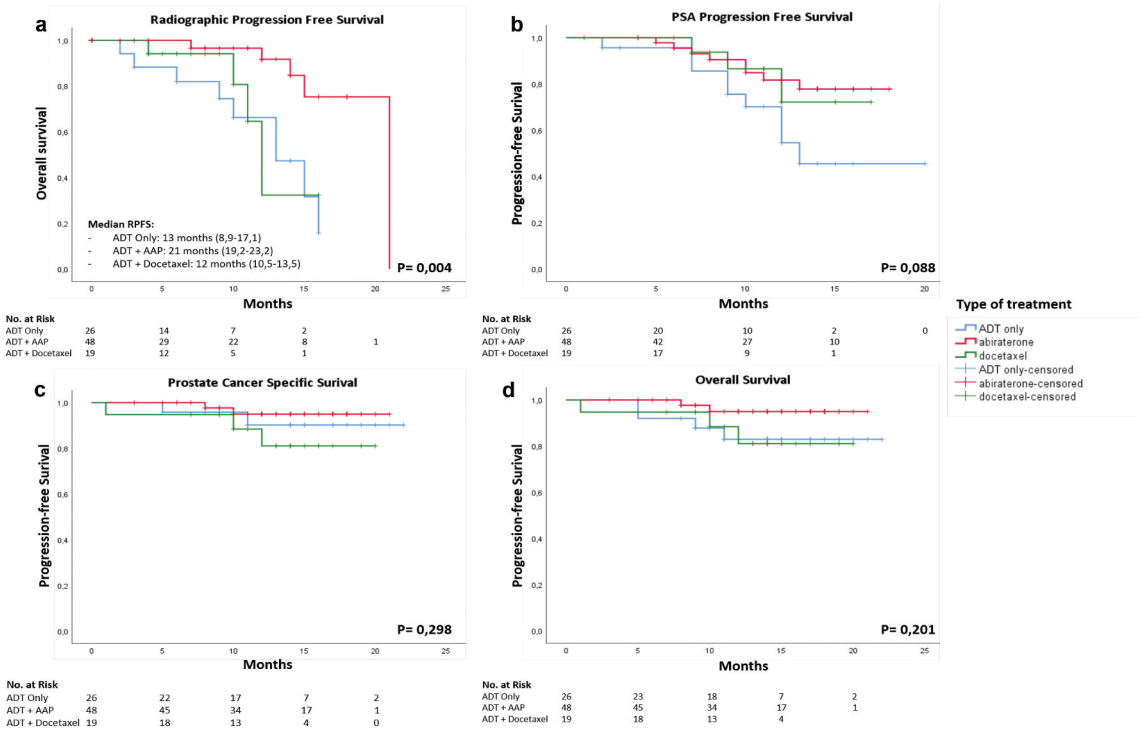


**Figure 1.** Kaplan Meier plots depicting differences in radiographic progression free survival (a), PSA Progression free survival (b), Prostate cancer specific survival (c) and Overall survival (d) between three different treatment groups (ADT only [blue] – ADT + AAP [red] and ADT + Docetaxel [green]). PSA: Prostate Specific Antigen, ADT: Androgen Deprivation Therapy, AAP: Abiraterone Acetate + Prednisone

**Table 3.** Comparison of selected poor prognostic factors between our study cohort and corresponding phase 3 trials for the ADT + AAP and ADT + Docetaxel treatment groups.

| | ADT + AAP | | | ADT + Docetaxel | | |
|---|---|---|---|---|---|---|
| | LATITUDE | Current study | p | CHAARTED | Current study | p |
| Age (median) | 68 | 72 | 0,003 | 64 | 66 | 0,379 |
| Gleason ≥8 | 584/597 (97,8%) | 44/48 (91,7%) | 0,010 | 241/397 (60,7%) | 13/19 (68,4%) | 0,503 |
| ≥3 bone metastases | 586/597 (98,2%) | 38/48 (79,2%) | <0,001 | | | |
| High volume disease | | | | 263/397 (66,2%) | 14/19 (73,7%) | 0,503 |
| M1c disease | 123/597 (20,6%) | 4/48 (8,3%) | 0,012 | 57/397 (14,4%) | 5/19 (26,3%) | 0,153 |
| PSA at start ADT | NR | 97,5 | | 50,9 | 61,4 | <0,001 |

AAP: Abiraterone acetate + prednisone – ADT: Androgen deprivation therapy – NR: Not reported – PSA: Prostate specific antigen

Therefore, we retrospectively assessed the oncological outcome and AEs of 91 mHSPC patients from 21 hospitals in Belgium.

## *Oncological outcome*

In our cohort, patients receiving ADT + AAP had a superior RPFS compared to patients receiving ADT only or ADT + docetaxel. These findings are in line with the results of a post hoc analysis of the STAMPEDE trial with a median follow-up of 4 years, in which patients treated with ADT + AAP had a longer failure-free survival (FFS) (ADT + Docetaxel: 97/189 events vs. ADT + AAP: 122/377 events; FFS HR 0,51 [95% CI: 0,39–0,67], $p < 0,001$), while no statistically significant difference in OS, metastasis-free survival, CSS or SRE was found between patients treated with ADT + AAP or ADT + docetaxel [17].

Different hypotheses may explain this finding. Firstly, the difference in RPFS may be related to the fact that patients treated with AAP received a continuous treatment until progression was observed, whereas patients treated with docetaxel received six cycles of chemotherapy on a 3-weekly basis after which the treatment regimen stopped. Secondly, it is possible that physicians were more likely to start ADT + AAP in patients with a better clinical performance status and docetaxel in patients with more advanced disease or worse prognosis, possibly resulting in worse RPFS. However, no significant differences in disease characteristics were observed between the different treatment groups in our cohort to support this hypothesis. Finally, it is possible that the iconographic follow-up regimen of patients treated with ADT + docetaxel (most often under supervision of a medical oncologist) was different than the

Table 4. Summary of adverse events per treatment.

| Adverse Events | Number of patients with AEs in this study (%) | | Number of patients with AEs in phase III clinical trials (%) | | p | |
|---|---|---|---|---|---|---|
| | All Grades | Grade 3 or higher | All grades | Grade 3 or higher | All grades | Grade 3 or higher |
| AAP | | **N = 48** | **LATITUDE (N = 597)** | | | |
| Any AE | 40 (87%) | 13 (27,1%) | 558 (93,5%) | 374 (62,6%) | 0,009 | <0,001 |
| Hypertension | 17 (37,0%) | 5 (10,9%) | 219 (36,7%) | 121 (20,3%) | 0,857 | 0,100 |
| Anemia | 16 (34,8%) | 2 (4,3%) | 54 (9,0%) | 15 (2,5%) | <0,001 | 0,490 |
| Fatigue | 15 (32,6%) | 1 (2,2%) | 77 (12,9%) | 10 (1,7%) | <0,001 | 0,834 |
| ASAT increase | 15 (32,6%) | 1 (2,2%) | 87 (14,6%) | 26 (4,4%) | <0,001 | 0,447 |
| ALAT increase | 14 (30,4%) | 2 (4,3%) | 98 (16,4%) | 33 (5,5%) | <0,001 | 0,689 |
| Hypokaliemia | 10 (21,7%) | 4 (8,7%) | 75 (12,6%) | 62 (10,4%) | 0,103 | 0,653 |
| Edema | 5 (10,9%) | 0 (0%) | NR | NR | | |
| Cardiac disorders | 4 (8,7%) | | 74 (12,4%) | 20 (3,4%) | 0,08 | |
| Docetaxel | | **N = 19** | **CHAARTED (N = 390)** | | | |
| Any AE | 18 (94,7%) | 8 (42,1%) | NR | 115 (29,5%) | | 0,242 |
| Fatigue | 12 (63,2%) | 3 (15,8%) | NR | 16 (4,1%) | | 0,02 |
| Anemia | 9 (47,4%) | 1 (5,3%) | NR | 5 (1,3%) | | 0,159 |
| Neutropenia | 8 (42,1%) | 4 (21,1%) | NR | 47 (12,1%) | | 0,246 |
| Thrombocytopenia | 3 (15,8%) | 0 (0%) | NR | 1 (0,3%) | | 0,826 |
| Polyneuropathy | 6 (31,6%) | 1 (5,3%) | NR | 4 (1,0%) | | 0,101 |
| Edema | 4 (21,1%) | 0 (0%) | NR | NR | | |
| Hypertension | 3 (15,8%) | 1 (5,3%) | NR | NR | | |
| Stomatitis | 3 (15,8%) | 0 (0%) | NR | 2 (0,5%) | | 0,757 |
| Allergic reaction | 2 (10,5%) | 0 (0%) | NR | 8 (2,1%) | | 0,529 |
| ADT | | **N = 93** | | | | |
| Any AE | 63 (67,7%) | | | | | |
| Hot flushes | 39 (41,9%) | | | | | |
| Energy loss | 24 (25,8%) | | | | | |
| Local reaction | 17 (18,3%) | | | | | |
| Weight increase | 11 (11,8%) | | | | | |
| Edema | 4 (4,3%) | | | | | |
| Mood swings | 3 (3,2%) | | | | | |
| Impotency | 3 (3,2%) | | | | | |
| Osteoporosis | 2 (2,2%) | | | | | |
| Libido loss | 2 (2,2%) | | | | | |

AAP: Abiraterone acetate + prednisone – ADT: Androgen Deprivation Therapy – NR: Not reported

follow-up of patients treated with ADT + AAP (most often under supervision of a urologist) since the iconographic follow-up was at the physician's discretion.

Both the ADT + AAP and ADT + docetaxel treatment groups showed shorter RPFS compared to their respective phase 3 trials, while the ADT only group had similar RPFS compared to phase 3 trials. This finding is remarkable since patients treated with ADT + AAP in our cohort had significantly fewer poor prognostic factors compared to the ADT + AAP group of the LATITUDE trial and patients treated with ADT + docetaxel had similar poor prognostic factors compared to the active treatment arm of the CHAARTED trial. We have no apparent explanation for this, but other unidentified poor prognostic factors or differences in follow-up protocols might contribute to this.

Univariate CRA identified patients with N1 disease to have a shorter RPFS compared to those with N0 disease. This finding might be explained by the fact that N1-stage was observed in a significantly higher proportion of patients with M1a disease compared to patients with M1b or M1c disease. Patients with N0 disease thus had a proportionally higher rate of bone or visceral metastases, which could explain their shorter RPFS. Surgical castration was associated with worse RPFS, but this statistical finding does not seem clinically relevant as this comprised only three patients of whom two received ADT only (aged 86 and 95 years old) and 1 received ADT + docetaxel (aged 69 years old).

No robust conclusions regarding CCS or OS can be made due to short follow-up and few deaths in our cohort. Nonetheless, when comparing the 1-y OS data of the three treatment groups in this study with the 1-y OS data of phase 3 trials, no significant differences were observed.

### *Adverse events*

The safety profile of ADT + docetaxel in real-world patients was in line with published phase 3 trials [3,4], while we saw a significantly lower incidence of grade 3 or higher AEs in our cohort treated with ADT + AAP compared to clinical trials [1,2]. Nevertheless, the incidence of anemia, fatigue and increase in ALAT/ASAT was significantly higher in our study population compared to the LATITUDE population (Table 4). Different hypotheses may explain these differences. First of all, it is possible that these differences reflect the contrast between a real-world patient population that is more frail and the highly selected population of clinical trials. However, we were not able to show proof of this difference in frailty due to the high number of missing values for performance status and

comorbidities in our retrospective analysis. Secondly, selection bias could have occurred. Finally, the observed differences in the ADT + AAP group could be due to the relatively short follow-up period of this study. Patients treated with docetaxel finished their treatment regimen (six cycles of chemotherapy) and thus completed the period in which AEs can occur. Patients treated with AAP on the other hand continue treatment until progression occurs. Therefore, patients on AAP could still develop AEs after the time our observations stopped.

### *Limitations*

This study has several shortcomings. First, this concerns a retrospective study with inherent missing data and attribution bias. However, the prominent outcome variables were based on fixed data such as blood values, radiographic data and survival time points. Another limitation of this study is the relatively small number of included patients and short follow-up. Data on OS and CSS are not mature and cannot lead to robust conclusions. However, mHSPC treatment is rapidly evolving, with apalutamide and enzalutamide demonstrating efficacy in recent trials and several other drugs being tested in phase III trials [5,6]. Given the current lack of real-world data on differential use of ADT + AAP versus ADT + docetaxel, we feel that our data contain meaningful messages for clinicians today. Of course, further follow-up is required.

Finally, as previously discussed, selection bias may have occurred, possibly influencing both the survival and AE data. If the treating physicians were more likely to start ADT + AAP in patients with a better clinical performance status and docetaxel in patients with more advanced disease, this could have resulted in both worse survival outcomes and more AEs in patients receiving docetaxel. Just because patient and tumor characteristics did not differ significantly, does not mean that these groups were similar.

## Conclusion

These retrospective real-world data show a significantly longer RPFS for mHSPC patients treated with ADT + AAP compared to patients treated with ADT only or ADT + docetaxel at short-term follow-up. RPFS was shorter for both the ADT + AAP and ADT + docetaxel treatment groups compared to their corresponding phase 3 trials. Whether these differences are actually treatment related or due to selection bias is not clear. Although further follow-up is required to analyse long-term patient outcomes, our findings highlight the importance of 'real world' data for adequate counselling of mHSPC patients in daily clinical practice. Large-scale real-world data analyses are needed to further evaluate the effect of different treatment regimens to influence clinical decision-making.

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## Data availability statemenT

All data generated or analyzed during this study are included in this article [. Further enquiries can be directed to the corresponding author. https://authoragreement.taylorandfrancisgroup.com/LicenseSummary/Index/1e027452-ec07-4838-8e8d-b990393b95a4

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